TECHNICAL REPORT

for the

AUSTRALIAN ADAPTATION OF THE ESHRE EVIDENCE-BASED GUIDELINE FOR UNEXPLAINED INFERTILITY

2023

For submission to NHMRC for consideration of approval under section 14A of the NHMRC Act 1992.

Please note the following considerations when reading this document:

- We recommend using the 'Bookmarks' function to navigate through this document, or ctrl + click on the relevant section in the contents page.

- PICO questions were addressed using systematic reviews to answer a specific question or set of questions and were prepared by evidence and clinical experts.

- Narrative reviews were prepared by clinical experts in the guideline development group (GDG). Narrative reviews were completed where the clinical question was not well suited to a systematic review.

- Some reviews underwent a systematic review process, however if no evidence was identified, the results were addressed in narrative format.

- The evidence summaries and narrative reviews in this technical report represent the steps after evidence synthesis when GDGs met to discuss and make recommendations, and are a set stage in evolution of the process of evidence synthesis and the development, refinement and consensus of recommendations in various stages of review, discussion and consultation across clinical experts, GDGs and panels. Therefore, the final recommendation (in the guideline) may not be reflected here. Final recommendations in the guideline reflect post GDG meeting follow-up, integration and response to feedback from public consultation and the latest updates in key evidence raised during public consultation, which is not encompassed or documented in these reviews. The table of responses to feedback are available as a separate document. Following these changes and evolution from the technical report to the final document, consensus was again sought with all GDG members across all recommendations.

- GRADE components may be formatted slightly differently across reviews given the varied nature of the questions and evidence derived.

GUIDING PRINCIPLES

In following the ADAPTE process for this ESHRE guideline to the Australian setting, several principles were agreed by the GDG including:

- Access to diagnostic assessments, treatment and monitoring of UI are adversely impacted by regionality and rurality in Australia, which represents an equity issue and needs to be considered in making recommendations and in informing policy on fertility care in Australia (https://doi.org/10.1093/humrep/deac205)

- Australian Aboriginal and Torres Strait Islander people are disproportionately represented in regional settings, acknowledging that most live in urban areas. They are also disproportionately affected by a range of risk factors for infertility warranting education, healthcare models, policy change and further research to ensure accessible, timely and equitable care (https://doi.org/10.1186/s12913-021-06714-8, DOI: 10.1002/ijgo.13920)

- Inadequate or misinformation is common in infertility, with an imperative for evidence-based care, across diagnosis, treatment and monitoring, and with a need for resources, tools, and education to enable informed shared decision making between patients and healthcare professionals

- Cost effectiveness data are limited in the Australian setting on comparisons between expectant management and different fertility options, yet health professionals should be aware of, inform and enable shared decision making encompassing direct and indirect costs to enable shared decision making. https://doi.org/10.1007/s40258-022-00764

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2. CRITERIA AND SEARCH STRATEGIES

ALL SEARCHES WERE UPDATED (USING THE SAME TERMS) ON 24 OCTOBER 2022.

1. DEFINITION OF UNEXPLAINED INFERTILITY

- **NARRATIVE QUESTION I.1 AFTER HOW MANY MONTHS OF UNPROTECTED INTERCOURSE SHOULD A COUPLE BE DEFINED AS INFERTILE?**

- **NARRATIVE QUESTION I.2 SHOULD FREQUENCY OF SEXUAL INTERCOURSE AFFECT THE DEFINITION OF UI?**

- **NARRATIVE QUESTION I.3 SHOULD FEMALE OR MALE PARTNER'S AGE AFFECT THE DEFINITION OF UI?**

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2. DIAGNOSIS OF UNEXPLAINED INFERTILITY

- **QUESTION 2.1 WHICH IS THE RELIABILITY AND CONVENIENCE OF METHODS TO CONFIRM REGULAR OVULATION?**

Patients	Intervention	Comparison	Outcomes
Couples assessed for infertility	- Menstrual history - Menstrual history + 1 Progesterone / USS/ LH urinary measurement in luteal phase (NICE) - LH urinary measurement - Serial basal body temperature (BBT) - Changes in the characteristics of cervical mucus - Follicular growth and rupture monitoring by ultrasound	Compare to each other predictive value of each test	Accurate assessment of ovulation Consider acceptability for patient, reliability, feasibility, costs

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Menstrual history
Comparison:	Compare to each other, predictive value of each test
Outcomes	Accurate assessment of ovulation, acceptability for patient, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
25/06/2021	(ovulation detection OR ovulation prediction OR "Ovulation Detection"[Mesh] OR "Ovulation Prediction"[Mesh]) AND (menstrual cycl* OR menstruation OR menstrual history OR Menstruation[Mesh] OR "Menstrual Cycle"[Mesh] OR tracker app OR Mobile Applications[Mesh])	Pubmed	786	12	718	
25/06/2021	(ovulation detection OR ovulation prediction) AND (menstrual cycl* OR menstruation OR menstrual history OR tracker app)	Cochrane	168			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Menstrual history + 1 Progesterone / USS/ LH urinary measurement in luteal phase (NICE)
Comparison:	Compare to each other, predictive value of each test
Outcomes	Accurate assessment of ovulation, acceptability for patient, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
25/06/2021	(ovulation detection OR ovulation prediction OR "Ovulation Detection"[Mesh] OR "Ovulation Prediction"[Mesh]) AND (menstrual cycl* OR menstruation OR menstrual history OR Menstruation[Mesh] OR "Menstrual Cycle"[Mesh] OR tracker app OR serum progesterone OR "Progesterone/blood"[Mesh] OR urinary luteinizing hormone OR urinary LH OR "Luteinizing Hormone/urine"[Mesh] OR home test OR "Reagent Kits, Diagnostic"[Mesh] OR ultrasound OR sonography OR ultrasonography OR USS OR "Ultrasonography"[Mesh])	Pubmed	1588	44	1089	
25/06/2021	(ovulation detection OR ovulation prediction) AND (menstrual cycl* OR menstruation OR menstrual history OR tracker app OR serum progesterone OR urinary luteinizing hormone OR urinary LH OR home test OR ultrasound OR sonography OR ultrasonography OR USS)	Cochrane	313			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	LH urinary measurement
Comparison:	Compare to each other, predictive value of each test
Outcomes	Accurate assessment of ovulation, acceptability for patient, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
25/06/2021	(ovulation detection OR ovulation prediction OR "Ovulation Detection"[Mesh] OR "Ovulation Prediction"[Mesh]) AND (urinary luteinizing hormone OR urinary LH OR "Luteinizing Hormone/urine"[Mesh] OR home test OR "Reagent Kits, Diagnostic"[Mesh])	Pubmed	301	92	165	
25/06/2021	(ovulation detection OR ovulation prediction) AND (urinary luteinizing hormone OR urinary LH)	Cochrane	27			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Serial basal body temperature (BBT)
Comparison:	Compare to each other, predictive value of each test
Outcomes	Accurate assessment of ovulation, acceptability for patient, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
25/06/2021	(ovulation detection OR ovulation prediction OR "Ovulation Detection"[Mesh] OR "Ovulation Prediction"[Mesh]) AND (basal body temperature OR BBT OR Body Temperature[Mesh])	Pubmed	344	65	201	
25/06/2021	(ovulation detection OR ovulation prediction) AND (basal body temperature OR BBT)	Cochrane	10			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Changes in the characteristics of cervical mucus
Comparison:	Compare to each other, predictive value of each test
Outcomes	Accurate assessment of ovulation, acceptability for patient, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
25/06/2021	(ovulation detection OR ovulation prediction OR "Ovulation Detection"[Mesh] OR "Ovulation Prediction"[Mesh]) AND (cervix mucus OR cervical mucus OR Cervix Mucus[Mesh])	Pubmed	313	56	202	
25/06/2021	(ovulation detection OR ovulation prediction) AND (cervix mucus OR cervical mucus)	Cochrane	18			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Follicular growth and rupture monitoring by ultrasound
Comparison:	Compare to each other, predictive value of each test
Outcomes	Accurate assessment of ovulation, acceptability for patient, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
25/06/2021	(ovulation detection OR ovulation prediction OR "Ovulation Detection"[Mesh] OR "Ovulation Prediction"[Mesh]) AND (ultrasound OR sonography OR ultrasonography OR USS OR "Ultrasonography"[Mesh])	Pubmed	692	64	348	
25/06/2021	(ovulation detection OR ovulation prediction) AND (ultrasound OR sonography OR ultrasonography OR USS)	Cochrane	167			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- ## QUESTION 2.2 WHAT IS THE RELIABILITY OF PARAMETERS DETECTING GOOD OOCYTE/CORPUS LUTEUM QUALITY?

Patients	Intervention	Comparison	Outcomes
Couples assessed for infertility	- Mid luteal phase progesterone levels (threshold?) - Endometrial biopsy - Fertilization failure - Euploid embryo rate with PGT-A	Gold standard: age	Accurate assessment of oocyte/corpus luteum quality Quality of ovulation

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Mid-luteal phase progesterone levels (threshold?)
Comparison:	Age
Outcomes	Accurate assessment of oocyte/copus luteum quality, quality of ovulation

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
18/02/2021	(Infertility OR "Infertility"[Mesh]) AND (mid luteal progesterone level OR mid luteal serum progesterone OR mid luteal progesterone concentration OR progesterone[Mesh]) AND (corpus luteum OR "Corpus Luteum"[Mesh] OR oocyte OR "Oocytes"[Mesh] OR ovulation OR "Ovulation"[Mesh])	Pubmed	1589	18	1317	
18/02/2021	Infertility AND ("progesterone level" OR "serum progesterone" OR "progesterone concentration") AND (corpus luteum OR oocyte OR ovulation)	Cochrane	197			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Endometrial biopsy
Comparison:	Age
Outcomes	Accurate assessment of oocyte/copus luteum quality, quality of ovulation

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
18/02/2021	(Infertility OR "Infertility"[Mesh]) AND ("endometrial biopsy" OR "Endometrium/diagnosis"[Mesh] OR "Endometrium/pathology"[Mesh]) AND (corpus luteum OR "Corpus Luteum"[Mesh] OR oocyte OR "Oocytes"[Mesh] OR ovulation OR "Ovulation"[Mesh])	Pubmed	526	16	419	
18/02/2021	Infertility AND ("endometrial biopsy") AND (corpus luteum OR oocyte OR ovulation)	Cochrane	54			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Fertilization failure
Comparison:	Age
Outcomes	Accurate assessment of oocyte/copus luteum quality, quality of ovulation

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
18/02/2021	(Infertility OR "Infertility"[Mesh]) AND ("fertilization failure" OR "fertilisation failure" OR "Fertilization/physiology"[Mesh]) AND (corpus luteum OR "Corpus Luteum"[Mesh] OR oocyte OR "Oocytes"[Mesh] OR ovulation OR "Ovulation"[Mesh])	Pubmed	680	12	544	
18/02/2021	Infertility AND ("fertilization failure" OR "fertilisation failure") AND (corpus luteum OR oocyte OR ovulation)	Cochrane	54			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Euploid embryo rate with PGT-A
Comparison:	Age
Outcomes	Accurate assessment of oocyte/copus luteum quality, quality of ovulation

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
18/02/2021	(Infertility OR "Infertility"[Mesh]) AND (PGT-A OR Preimplantation Genetic Testing Aneuploidies OR preimplantation diagnosis OR aneuploidy OR "Preimplantation Diagnosis"[Mesh] OR "Aneuploidy"[Mesh]) AND (corpus luteum OR "Corpus Luteum"[Mesh] OR oocyte OR "Oocytes"[Mesh] OR ovulation OR "Ovulation"[Mesh])	Pubmed	530	17	469	
18/02/2021	Infertility AND (PGT-A OR Preimplantation Genetic Testing Aneuploidies OR preimplantation diagnosis OR aneuploidy) AND (corpus luteum OR oocyte OR ovulation)	Cochrane	59			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- ## QUESTION 2.3 SHOULD ONE OR MORE TESTS OF OVARIAN RESERVE BE INCLUDED IN THE DIAGNOSTIC WORK-UP?

Patients	Intervention	Comparison	Outcomes
Couples assessed for infertility	- AMH - AFC - Day 3 FSH and estradiol - Clomiphene Citrate Challenge Test - Ovarian volume, ovarian blood flow, inhibin B (combinations, repetition?) Maybe expand with practical recommendations	Age	Chance of live birth Assessment of ovarian reserve Reliability, feasibility, costs

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	AMH
Comparison:	Age
Outcomes	Chance of live birth, assessment of ovarian reserve, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
13/10/2020	(Infertility OR "Infertility"[Mesh]) AND (AMH OR antimüllerian hormone OR anti Mullerian hormone OR anti-Müllerian hormone OR Müllerian-inhibiting factor OR Müllerian-inhibiting hormone OR Müllerian-inhibiting substance OR müllerian regression factor OR "Anti-Mullerian Hormone"[Mesh])	Pubmed	1440	110	1315	
13/10/2020	Infertility AND (AMH OR antimüllerian hormone OR anti Mullerian hormone OR anti-Müllerian hormone OR Müllerian-inhibiting factor OR Müllerian-inhibiting hormone OR Müllerian-inhibiting substance OR müllerian regression factor)	Cochrane	363			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	AFC
Comparison:	Age
Outcomes	Chance of live birth, assessment of ovarian reserve, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
13/10/2020	(Infertility OR "Infertility"[Mesh]) AND (AFC OR antral follicle count)	Pubmed	909	99	878	
13/10/2020	Infertility AND (AFC OR antral follicle count)	Cochrane	295			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Day 3 FSH and estradiol
Comparison:	Age
Outcomes	Chance of live birth, assessment of ovarian reserve, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
13/10/2020	(Unexplained infertility OR Infertility OR "Infertility"[Mesh]) AND (basal FSH OR basal follicle stimulating hormone OR "Follicle Stimulating Hormone, Human"[Mesh] OR basal estradiol OR basal estrogen)	Pubmed	1214	71	1096	
13/10/2020	Infertility AND (basal FSH or basal follicle stimulating hormone OR basal estradiol OR basal estrogen)	Cochrane	259			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Clomiphene Citrate challenge test
Comparison:	Age
Outcomes	Chance of live birth, assessment of ovarian reserve, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
13/10/2020	(Infertility OR "Infertility"[Mesh]) AND (clomiphene citrate challenge test OR CCCT)	Pubmed	67	27	41	
13/10/2020	Infertility AND (clomiphene citrate challenge test OR CCCT)	Cochrane	9			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Ovarian volume, ovarian blood flow, inhibin B
Comparison:	Age
Outcomes	Chance of live birth, assessment of ovarian reserve, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
	(Infertility OR "Infertility"[Mesh]) AND ("inhibin B" OR Inh B OR "inhibins"[Mesh] OR ovarian volume OR ovarian blood flow OR ovarian vascularity OR "Ovary/blood supply"[Mesh])	Pubmed	1750	93	1429	
	Infertility AND ("inhibin B" OR Inh B OR ovarian volume OR ovarian blood flow OR ovarian vascularity)	Cochrane	271			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- ## QUESTION 2.4 WHAT IS THE ACCURACY OF COMMONLY USED TESTS OF TUBAL PATENCY?

Patients	Intervention	Comparison	Outcomes
Couples assessed for infertility	- Chlamydia antibody testing - Hysterosalpingography (HSG) - Hystero-contrast-sonography (HyCoSy) or SIS (saline infusion sonography)	Gold standard: laparoscopy	Assessment of tubal patency Reliability, feasibility, costs

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Chlamydia antibody testing
Comparison:	Laparascopy
Outcomes	Assessment of tubal patency, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
16/02/2021	(Infertility OR "Infertility"[Mesh]) AND (Chlamydia antibody testing OR Chlamydial antibody OR Chlamydia trachomatis OR "Chlamydia trachomatis"[Mesh] OR "Chlamydia Infections"[Mesh]) AND (laparoscopy OR "Laparoscopy"[Mesh])	Pubmed	174	69	74	
16/02/2021	Infertility AND (Chlamydia antibody testing OR Chlamydial antibody OR Chlamydia trachomatis) AND laparoscopy	Cochrane	2			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Hysterosalpingography (HSG)
Comparison:	Laparascopy
Outcomes	Assessment of tubal patency, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
16/02/2021	(Infertility OR "Infertility"[Mesh]) AND (hysterosalpingography OR HSG OR "Hysterosalpingography"[Mesh]) AND (laparoscopy OR "Laparoscopy"[Mesh])	Pubmed	645	98	426	
16/02/2021	Infertility AND (hysterosalpingography OR HSG) AND laparoscopy	Cochrane	73			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Hystero-contrast-sonography (hycosy) or saline-infusion-sonography (SIS)
Comparison:	Laparascopy
Outcomes	Assessment of tubal patency, reliability, feasibility, costs

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
16/02/2021	(Infertility OR "Infertility"[Mesh]) AND (Hystero-contrast-sonography OR hysterocontrast sonography OR hycosy OR saline-infusion-sonography OR SIS)	Pubmed	176	82	615	
16/02/2021	Infertility AND (Hystero-contrast-sonography OR hysterocontrast sonography OR hycosy OR saline-infusion-sonography OR SIS)	Cochrane	741			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 2.5.1 WHICH DIAGNOSTIC PROCEDURES SHOULD BE PERFORMED TO CONFIRM A NORMAL UTERINE STRUCTURE/ANATOMY, UTERINE WALL/MYOMETRIUM?**

Patients	Intervention	Comparison	Outcomes
Couples assessed for infertility	- 3D US - MRI	Standard 2D USS	Uterine structure/anatomy (fibroids, myometrial pathologies etc) Acquired? Congenital? Uterine malformations

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	3D USS
Comparison:	2D USS
Outcomes	Uterine structure/anatomy (fibroids, myometrial pathologies etc), Acquired? Congenital?, Uterine malformations

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (ultrasound OR sonography OR ultrasonography OR "Ultrasonography"[Mesh]) AND (uterine structure OR uterine anatomy OR uterine malformations OR "Uterus/abnormalities"[Mesh] OR "Uterus/anatomy and histology"[Mesh] OR "Uterus/injuries"[Mesh] OR "Uterus/physiopathology"[Mesh])	Pubmed	1728	25	1467	
24/02/2021	Infertility AND (ultrasound OR sonography OR ultrasonography) AND (uterine structure OR uterine anatomy OR uterine malformations)	Cochrane	28			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	MRI
Comparison:	2D USS
Outcomes	Uterine structure/anatomy (fibroids, myometrial pathologies etc), Acquired? Congenital?, Uterine malformations

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (magnetic resonance imaging OR MRI OR "Magnetic Resonance Imaging"[Mesh]) AND (ultrasound OR sonography OR ultrasonography OR "Ultrasonography"[Mesh])	Pubmed	545	10	470	
24/02/2021	Infertility AND (magnetic resonance imaging OR MRI) AND (ultrasound OR sonography OR ultrasonography)	Cochrane	18			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 2.5.2 WHICH ADDITIONAL DIAGNOSTIC PROCEDURES SHOULD BE PERFORMED TO CONFIRM AN ANATOMICALLY NORMAL UTERINE CAVITY?**

Patients	Intervention	Comparison	Outcomes
Couples assessed for unexplained infertility	- Hysterosalpingography (HSG) - Hystero-contrast-sonography (hycosi) or SIS (saline infusion sonography) - Hysteroscopy - 3D USS - 2D USS - MRI	- No further testing	Anatomic normal uterine cavity as per ESHRE classification

PICO TERMS	
Patients/Population:	women with unexplained infertility and normal uterine ultrasound
Intervention:	Hysterosalpingography (HSG)
Comparison:	no test
Outcomes	Anatomic normal uterine cavity as per ESHRE classification

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/06/2022	(Infertility OR "Infertility"[Mesh]) AND (hysterosalpingography OR HSG OR "Hysterosalpingography"[Mesh]) AND (ultrasound OR USS OR sonography OR ultrasonography OR "Ultrasonography"[Mesh])	Pubmed	969			
15/06/2022	Infertility AND (hysterosalpingography OR HSG) AND (ultrasound OR USS OR sonography OR ultrasonography)	Cochrane	141			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	women with unexplained infertility and normal uterine ultrasound
Intervention:	Hystero-contrast-sonography or SIS (saline infusion sonography)
Comparison:	no test
Outcomes	Anatomic normal uterine cavity as per ESHRE classification

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/06/2022	(Infertility OR "Infertility"[Mesh]) AND (Hystero-contrast-sonography OR hysterocontrast sonography OR hycosy OR saline-infusion-sonography OR SIS)	Pubmed	179			
15/06/2022	Infertility AND (Hystero-contrast-sonography OR hysterocontrast sonography OR hycosy OR saline-infusion-sonography OR SIS)	Cochrane	36			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	women with unexplained infertility and normal uterine ultrasound
Intervention:	hysteroscopy
Comparison:	no test
Outcomes	Anatomic normal uterine cavity as per ESHRE classification

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/06/2022	(Infertility OR "Infertility"[Mesh]) AND (hysteroscopy OR "Hysteroscopy"[Mesh]) AND (ultrasound OR sonography OR ultrasonography OR "Ultrasonography"[Mesh])	Pubmed	590			
15/06/2022	Infertility AND hysteroscopy AND (ultrasound OR USS OR sonography OR ultrasonography)	Cochrane	99			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	women with unexplained infertility and normal uterine ultrasound
Intervention:	3D USS
Comparison:	no test
Outcomes	Anatomic normal uterine cavity as per ESHRE classification

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/06/2022	(Infertility OR "Infertility"[Mesh]) AND (ultrasound OR USS OR sonography OR ultrasonography OR "Ultrasonography"[Mesh]) AND (3D)	Pubmed	215			
15/06/2022	Infertility AND (ultrasound OR USS OR sonography OR ultrasonography) AND (3D)	Cochrane	26			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	women with unexplained infertility and normal uterine ultrasound
Intervention:	MRI
Comparison:	no test
Outcomes	Anatomic normal uterine cavity as per ESHRE classification

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/06/2022	(Infertility OR "Infertility"[Mesh]) AND (magnetic resonance imaging OR MRI OR "Magnetic Resonance Imaging"[Mesh]) AND (ultrasound OR USS OR sonography OR ultrasonography OR "Ultrasonography"[Mesh])	Pubmed	637			
15/06/2022	Infertility AND (magnetic resonance imaging OR MRI) AND (ultrasound OR USS OR sonography OR ultrasonography)	Cochrane	18			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- ## QUESTION 2.6 SHOULD WOMEN UNDERGO A LAPAROSCOPY BEFORE BEING DIAGNOSED WITH UI?

Patients	Intervention	Comparison	Outcomes
Couples assessed for unexplained infertility	(classical) laparoscopy	-No additional laparoscopy	Diagnosis to UI Accuracy for UI diagnosis Factors potentially related to infertility Acceptability costs? value of laparoscopy

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	classical laparascopy
Comparison:	No additional laparascopy
Outcomes	Diagnosis to UI, accuracy for UI diagnosis, factors potentially related to infertility, acceptability, cost, value of laparascopy

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
19/02/2021	(Infertility OR "Infertility"[Mesh]) AND (laparoscopy OR "Laparoscopy"[Mesh]) AND (unexplained Infertility OR idiopathic infertility OR "infertility diagnosis" OR "Infertility/diagnosis"[Mesh])	Pubmed	1073	70	817	
19/02/2021	Infertility AND laparoscopy AND (unexplained Infertility OR idiopathic infertility OR "infertility diagnosis")	Cochrane	67			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- ## QUESTION 2.7 WHAT IS THE NEED FOR FEMALE LOWER GENITAL TRACT INVESTIGATIONS?

Patients	Intervention	Comparison	Outcomes
Couples assessed for unexplained infertility	- Post-coital test - Vaginal microbiota testing	No tests	Assessment of vaginal-cervical factor for UI Cervical hostility towards sperm Chance to predict spontaneous pregnancy/treatment options Accuracy Acceptability Costs?

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Post-coital test
Comparison:	No additional tests
Outcomes	Assessment of vaginal-cervical factor for UI, Cervical hostility towards sperm, Chance to predict spontaneous pregnancy/treatment options, Accuracy, Acceptability, Costs?

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (post-coital test OR postcoital test)	Pubmed	277	33	203	
24/02/2021	Infertility AND (post-coital test OR postcoital test)	Cochrane	28			
12/05/2022	((Infertility OR "Infertility"[Mesh]) AND (post-coital test OR postcoital test)) AND (("2021/02/01"[Date - Publication] : "2022/05/12"[Date - Publication]))	Pubmed	2	0	2	
12/05/2022	Infertility AND (post-coital test OR postcoital test)	Cochrane	0			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	vaginal microbiota testing
Comparison:	No additional tests
Outcomes	Assessment of vaginal-cervical factor for UI, Cervical hostility towards sperm, Chance to predict spontaneous pregnancy/treatment options, Accuracy, Acceptability, Costs?

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	((Infertility OR "Infertility"[Mesh])) AND (vaginal microbiome OR vaginal microbiota testing OR "Vagina/microbiology"[Mesh])	Pubmed	211	35	111	
24/02/2021	Infertility AND (vaginal microbiome OR vaginal microbiota testing)	Cochrane	9			
12/05/2022	(((Infertility OR "Infertility"[Mesh])) AND (vaginal microbiome OR vaginal microbiota testing OR "Vagina/microbiology"[Mesh])) AND (("2021/02/01"[Date - Publication] : "2022/05/12"[Date - Publication]))	Pubmed	40	9	32	
12/05/2022	Infertility AND (vaginal microbiome OR vaginal microbiota testing)	Cochrane	1			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 2.8 SHOULD MEN UNDERGO ADDITIONAL DIAGNOSTIC PROCEDURES TO CONFIRM NORMAL GENITO-URINARY ANATOMY BEFORE BEING DIAGNOSED WITH UI?**

Patients	Intervention	Comparison	Outcomes
Couples assessed for unexplained infertility	- Scrotal Ultrasound, including doppler (anatomical /vascular alterations -varicocele) AND physical examination of male genital anatomy	No investigation	chance to predict live birth/ miscarriage

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Scrotal Ultrasound, including doppler (anatomical /vascular alterations -varicocele) AND physical examination of male genital anatomy
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	(Infertility OR "Infertility"[Mesh]) AND (male OR "Male"[Mesh]) AND (ultrasound OR sonography OR ultrasonography OR "Ultrasonography"[Mesh]) AND (live birth OR "Live Birth"[Mesh] OR miscarriage OR "Abortion, Spontaneous"[Mesh] OR predictive value OR "Predictive Value of Tests"[Mesh])	Pubmed	209	25	428	
26/02/2021	(Infertility AND male) AND (ultrasound OR sonography OR ultrasonography)	Cochrane	296			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 2.9 IS THERE ADDED VALUE OF ADDITIONAL TESTS IN THE MALE WITH NORMAL WHO SEMEN ANALYSIS?**

Patients	Intervention	Comparison	Outcomes
Couples assessed for unexplained infertility	- anti-sperm Abs, - DNA fragmentation test, - sperm chromatin condensation test, - sperm aneuploidy screening, - hormonal panel, - HPV, - microbiology test	No further analysis (other than WHO semen analysis)	chance to predict live birth/ miscarriage

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	anti-sperm antibodies
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (anti-sperm antibodies OR antisperm antibodies OR antispermatozoal antibodies OR ASA)	Pubmed	1045	56	807	
24/02/2021	Infertility AND (anti-sperm antibodies OR antisperm antibodies OR antispermatozoal antibodies OR ASA)	Cochrane	74			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	DNA fragmentation test
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (DNA fragmentation test OR sperm DNA fragmentation OR DNA fragmentation index OR DFI OR "DNA Fragmentation"[Mesh]) AND (live birth OR "Live Birth"[Mesh] OR miscarriage OR "Abortion, Spontaneous"[Mesh] OR predictive value OR "Predictive Value of Tests"[Mesh])	Pubmed	218	68	244	
24/02/2021	Infertility AND (DNA fragmentation test OR sperm DNA fragmentation OR DNA fragmentation index OR DFI)	Cochrane	166			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	sperm chromatin condensation test
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (sperm chromatin condensation OR sperm chromatin integrity)	Pubmed	572	44	393	
24/02/2021	Infertility AND (sperm chromatin condensation OR sperm chromatin integrity)	Cochrane	17			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	sperm aneuploidy screening
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	((Infertility OR "Infertility"[Mesh])) AND ("sperm aneuploidy" OR semen aneuploidy)	Pubmed	358	34	331	
24/02/2021	Infertility AND (sperm aneuploidy OR semen aneuploidy)	Cochrane	48			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	hormonal panel
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (hormonal panel OR serum hormone level OR hormone panel) AND (live birth OR "Live Birth"[Mesh] OR miscarriage OR "Abortion, Spontaneous"[Mesh] OR predictive value OR "Predictive Value of Tests"[Mesh])	Pubmed	591	15	590	
24/02/2021	Infertility AND (hormonal panel OR serum hormone level OR hormone panel) AND (live birth OR miscarriage OR predictive value)	Cochrane	121			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	HPV
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (Human papilloma virus OR HPV OR "Papillomaviridae"[Mesh] OR "Papillomavirus Infections"[Mesh])	Pubmed	211	36	149	
24/02/2021	Infertility AND (Human papilloma virus OR HPV)	Cochrane	7			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	microbiology test
Comparison:	No additional tests
Outcomes	Chance to predict live birth, chance to predict miscarriage

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
24/02/2021	(Infertility OR "Infertility"[Mesh]) AND (sperm OR semen OR seminal) AND (microbiome OR microbiota OR bacteria OR microorganism)	Pubmed	1263	22	841	
24/02/2021	Infertility AND (sperm OR semen OR seminal) AND (microbiome OR microbiota OR bacteria OR microorganism)	Cochrane	14			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 2.10 SHOULD THERE BE ADDITIONAL EVALUATIONS OF POSSIBLE SYSTEMIC CAUSE OF UI IN THE COUPLE?**

Patients	Intervention	Comparison	Outcomes
Couples assessed for unexplained infertility	- Autoimmunity - Thrombophilia - Oxidative stress - Genetic/genomic tests - Vitamin D deficiency - Thyroid hormones - Prolactin - Obesity	No additional evaluations to address	Assessment of cause for infertility

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Autoimmunity
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (autoimmunity OR autoimmune disease OR "Autoimmunity"[Mesh] OR "Autoimmune Diseases"[Mesh]) AND (cause OR diagnosis OR "Infertility/diagnosis"[Mesh])	Pubmed	1489	95	1075	
22/02/2021	Infertility AND (autoimmunity OR autoimmune disease) AND (cause OR diagnosis)	Cochrane	25			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Thrombophilia
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (thrombophilia OR "Thrombophilia"[Mesh])	Pubmed	145	44	97	
22/02/2021	Infertility AND thrombophilia	Cochrane	22			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Oxidative stress
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (oxidative stress OR "Oxidative Stress"[Mesh]) AND (cause OR diagnosis OR "Infertility/diagnosis"[Mesh])	Pubmed	1697	99	993	
22/02/2021	Infertility AND oxidative stress AND (cause OR diagnosis)	Cochrane	60			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Genetic/genomic tests
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (genetic test OR genomic test OR "Genetic Testing"[Mesh]) AND (cause OR diagnosis OR "Infertility/diagnosis"[Mesh])	Pubmed	1895	85	1509	
22/02/2021	Infertility AND (genetic test OR genomic test) AND (cause OR diagnosis)	Cochrane	61			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Vitamin D deficiency
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (vitamin D deficiency OR "Vitamin D Deficiency"[Mesh])	Pubmed	141	32	121	
22/02/2021	Infertility AND Vitamin D deficiency	Cochrane	43			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Thyroid hormones
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (thyroid hormones OR "Thyroid Hormones"[Mesh])	Pubmed	546	39	456	
22/02/2021	Infertility AND thyroid hormones	Cochrane	83			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Prolactin
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (prolactin OR "Prolactin"[Mesh]) AND (cause OR diagnosis OR "Infertility/diagnosis"[Mesh])	Pubmed	1434	42	1017	
22/02/2021	Infertility AND prolactin AND (cause OR diagnosis)	Cochrane	69			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Obesity
Comparison:	No additional tests
Outcomes	Assessment of cause of infertility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
22/02/2021	(Infertility OR "Infertility"[Mesh]) AND (obesity OR "Obesity"[Mesh]) AND (cause OR diagnosis OR "Infertility/diagnosis"[Mesh])	Pubmed	2373	98	1879	
22/02/2021	Infertility AND obesity AND (cause OR diagnosis)	Cochrane				
				listed page "relevant papers"	listed page "list of irrelevant papers"	

3. TREATMENT OF UNEXPLAINED INFERTILITY

- **QUESTION 3.1 WHAT IS THE VALUE OF EXPECTANT MANAGEMENT COMPARED TO ACTIVE TREATMENT FOR PATIENTS WITH UI?**

Patients	Intervention	Comparison	Outcomes
Couples diagnosed with unexplained infertility (female age as factor to be considered)	- Expectant management With and without scoring systems (prognostic indicators/predictive models)	- Natural cycle + Timed Intercourse (+/-hCG trigger) • Frequency of intercourse (calendar days) • Ovulation tests (urine and serum LH tests) • USS • Apps - CC+timed intercourse (+/-hCG trigger) - Ltz+ timed intercourse (+/-hCG trigger) - Gn+ timed intercourse (+/-hCG trigger) - IUI - Ovarian stimulation • OS(oral, gonadotrophin) +IUI • IVF - Surgery (laparoscopy for confirming UI and/or mechanical procedures)	<u>Critical outcomes:</u> - Live full-term singleton birth/ Live birth - ongoing pregnancy rate - Multiple pregnancies/multiple births <u>Important outcomes:</u> - Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life, anxiety and/or depression - COST – effectiveness value <u>Other outcomes</u> - Clinical pregnancy rate - Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery) - Ovarian hyperstimulation syndrome - Fetal abnormalities - Feasibility - Acceptability

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	clomiphene citrate + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND ((clomiphene citrate OR CC OR clomifen OR clomid OR "Clomiphene"[Mesh]))	Pubmed	3795	10	3760	
15/03/2021	infertility AND (clomiphene citrate OR CC OR clomifen OR clomid)	Cochrane	1065			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	letrozole + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND ((letrozole OR "aromatase inhibitor" OR "Letrozole"[Mesh]))	Pubmed	486	2	649	
15/03/2021	infertility AND (letrozole OR aromatase inhibitor)	Cochrane	458			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	gonadotropins + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND (("recombinant follicle stimulating hormone" OR "Recombinant FSH" OR rFSH OR Follitropin OR corifollitropin OR puregon OR Gonal-F OR FSH-CTP OR follistim OR "follitropin alfa" [Supplementary Concept] OR "follitropin beta" [Supplementary Concept] OR "follicle stimulating hormone, human, with HCG C-terminal peptide" [Supplementary Concept] OR "purified FSH" OR "purified urinary FSH" OR "purified follicle stimulating hormone" OR p-FSH OR Urofollitropin OR follegon OR metrodin OR fertinex OR "Urofollitropin"[Mesh] OR "highly purified urinary FSH" OR "highly purified FSH" OR "highly purified follicle stimulating hormone" OR hp-FSH OR fostimon OR "Metrodin HP" OR "Metrodin-HP"OR "Metrodin high purity" OR bravelle OR "Urofollitropin highly purified" OR "urofollitropin HP" OR "Fertinorm HP" OR "fertinorm highly purified" OR neo-fertinorm OR "Human menopausal gonadotropin" OR HMG OR Menotrophin OR menopur OR reprones OR Humegon OR Menogon OR Pergonal OR merional OR folltrin OR meriofert OR fertinorm OR normegon OR "Menotropins"[Mesh] OR "Conifollitropin alfa" OR corifollitropin OR "long-acting FSH" OR FSH-CTP OR "follicle stimulating hormone C-terminal peptide" OR "follicle stimulating hormone, human, with HCG C-terminal peptide" [Supplementary Concept] OR gonadotropin OR "Gonadotropins"[Mesh])) AND (live birth OR pregnancy rate OR multiple pregnanc* OR "Live Birth"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Pregnancy, Multiple"[Mesh]))	Pubmed	3867	2	4290	
15/03/2021	Infertility AND (recombinant follicle stimulating hormone OR Recombinant FSH OR rFSH OR Follitropin OR corifollitropin OR puregon OR Gonal-F OR FSH-CTP OR follistim OR purified FSH OR purified urinary FSH OR purified follicle stimulating hormone OR p-FSH OR Urofollitropin OR follegon OR metrodin OR fertinex OR highly purified urinary FSH OR highly purified FSH OR highly purified follicle stimulating hormone OR hp-FSH OR fostimon OR Metrodin HP OR Metrodin-HP OR Metrodin high purity OR bravelle OR Urofollitropin highly purified OR urofollitropin HP OR Fertinorm HP OR fertinorm highly purified OR neo-fertinorm OR Human menopausal gonadotropin OR HMG OR Menotrophin OR menopur OR reprones OR Humegon OR Menogon OR Pergonal OR merional OR folltrin OR meriofert OR fertinorm OR normegon OR Corifollitropin alfa OR corifollitropin OR long-acting FSH OR FSH-CTP OR follicle stimulating hormone C-terminal peptide OR gonadotropin) AND (live birth OR pregnancy rate OR multiple pregnanc*)	Cochrane	1833			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	natural cycle + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND ("natural cycle" OR unstimulated cycle)	Pubmed	425	2	629	
15/03/2021	infertility AND (natural cycle OR unstimulated cycle)	Cochrane	360			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	IUI
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND (IUI OR "intrauterine insemination" OR "intra-uterine insemination" OR "intra uterine insemination" OR "artificial insemination" OR "insemination, Artificial"[Mesh] OR "Insemination"[Mesh]))	Pubmed	4324	23	3725	
15/03/2021	infertility AND (IUI OR intrauterine insemination OR intra-uterine insemination OR intra uterine insemination OR artificial insemination)	Cochrane	1029			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	ovarian stimulation +IUI
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND (IUI OR "intrauterine insemination" OR "intra-uterine insemination" OR "intra uterine insemination" OR "artificial insemination" OR "insemination, Artificial"[Mesh] OR "Insemination"[Mesh]))	Pubmed	4324	23	3725	
15/03/2021	infertility AND (IUI OR intrauterine insemination OR intra-uterine insemination OR intra uterine insemination OR artificial insemination)	Cochrane	1029			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	ovarian stimulation +IVF
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND ("ovulation induction"[Mesh] OR "ovarian stimulation" OR "ovulation induction") AND (IVF OR "in vitro fertilization" OR "Fertilization in Vitro"[Mesh] OR ICSI OR "intracytoplasmic insemination" OR "intracytoplasmic sperm injection" OR "Sperm Injections, Intracytoplasmic"[Mesh]))	Pubmed	4189	3	4615	
15/03/2021	infertility AND (ovarian stimulation OR ovulation induction) AND (IVF OR in vitro fertilization OR ICSI OR intracytoplasmic insemination OR intracytoplasmic sperm injection)	Cochrane	1567			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Expectant management with and without scoring systems (prognostic indicators/predictive models)
Comparison:	Surgery (laparoscopy for confirming UI and/or mechanical procedures)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatth related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((infertility OR "infertility"[Mesh])) AND (laparoscopy OR "Laparoscopy"[Mesh] OR surgery OR "Surgical Procedures, Operative"[Mesh]) AND (live birth OR pregnancy rate OR multiple pregnanc* OR "Live Birth"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Pregnancy, Multiple"[Mesh])	Pubmed	4587	7	4165	
15/03/2021	Infertility AND (IVF OR in vitro fertilization OR ICSI OR intracytoplasmic insemination OR intracytoplasmic sperm injection) AND (laparoscopy OR surgery) AND (live birth OR pregnancy rate OR multiple pregnanc*)	Cochrane	168			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 3.2.1 IF ACTIVE TREATMENT IS PURSUED, WHICH TYPE OF ACTIVE TREATMENT FOR UI?**

Patients	Intervention	Comparison	Outcomes

Couples diagnosed with unexplained infertility
 	
(female age as factor to be considered)
	Ovarian Stimulation alone (different agents)
	• Clomiphene citrate plus timed intercourse(+/- hCG trigger)
	• Letrozole plus timed intercourse (+/-hCG trigger)
	• Gonadotrophins plus timed intercourse (protocols) (+/- hCG trigger)
	• Natural cycle plus timed Intercourse (+/- hCG trigger)
	• IUI
	• Ovarian stimulation
	  ○ OS (oral, gonadotrophin) +IUI
	  ○ IVF
		Compare to each other	<u>Critical outcomes:</u>
			- Live full-term singleton birth/ Live birth
			- ongoing pregnancy rate
			- Multiple pregnancies/multiple births
			<u>Important outcomes:</u>
			- Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life, anxiety and/or depression
			- COST – effectiveness value
			<u>Other outcomes</u>
			- Clinical pregnancy rate
			- Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery)
			- Ovarian hyperstimulation syndrome
			- Fetal abnormalities
			- Feasibility
			- Acceptability

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	clomiphene citrate + timed intercourse (+/- hCG trigger)
Comparison:	all other interventions
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((Infertility OR "Infertility"[Mesh])) AND ((clomiphene citrate OR CC OR clomifen OR clomid OR "Clomiphene"[Mesh]))	Pubmed	3795	54	3725	
15/03/2021	Infertility AND (clomiphene citrate OR CC OR clomifen OR clomid)	Cochrane	1065			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	letrozole + timed intercourse (+/- hCG trigger)
Comparison:	all other interventions
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((Infertility OR "Infertility"[Mesh])) AND ((letrozole OR "aromatase inhibitor" OR "Letrozole"[Mesh]))	Pubmed	486	37	624	
15/03/2021	Infertility AND (letrozole OR aromatase inhibitor)	Cochrane	458			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	gonadotropins + timed intercourse (+/- hCG trigger)
Comparison:	all other interventions
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	((Infertility OR "Infertility"[Mesh])) AND (("recombinant follicle stimulating hormone" OR "Recombinant FSH" OR rFSH OR Follitropin OR corifollitropin OR puregon OR Gonal-F OR FSH-CTP OR follistim OR "follitropin alfa" [Supplementary Concept] OR "follitropin beta" [Supplementary Concept] OR "follicle stimulating hormone, human, with HCG C-terminal peptide" [Supplementary Concept] OR "purified FSH" OR "purified urinary FSH" OR "purified follicle stimulating hormone" OR p-FSH OR Urofollitropin OR follegon OR metrodin OR fertinex OR "Urofollitropin"[Mesh] OR "highly purified urinary FSH" OR "highly purified FSH" OR "highly purified follicle stimulating hormone" OR hp-FSH OR fostimon OR "Metrodin HP" OR "Metrodin-HP"OR "Metrodin high purity" OR bravelle OR "Urofollitropin highly purified" OR "urofollitropin HP" OR "Fertinorm HP" OR "fertinorm highly purified" OR neo-fertinorm OR "Human menopausal gonadotropin" OR HMG OR Menotrophin OR menopur OR reproner OR Humegon OR Menogon OR Pergonal OR merional OR follitrin OR meriofert OR fertinorm OR normegon OR "Menotropins"[Mesh] OR "Corifollitropin alfa" OR corifollitropin OR "long-acting FSH" OR FSH-CTP OR "follicle stimulating hormone C-terminal peptide" OR "follicle stimulating hormone, human, with HCG C-terminal peptide" [Supplementary Concept] OR gonadotropin OR "Gonadotropins"[Mesh])) AND (live birth OR pregnancy rate OR multiple pregnanc* OR "Live Birth"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Pregnancy, Multiple"[Mesh]))	Pubmed	3867	44	4259	
15/03/2021	Infertility AND (recombinant follicle stimulating hormone OR Recombinant FSH OR rFSH OR Follitropin OR corifollitropin OR puregon OR Gonal-F OR FSH-CTP OR follistim OR purified FSH OR purified urinary FSH OR purified follicle stimulating hormone OR p-FSH OR Urofollitropin OR follegon OR metrodin OR fertinex OR highly purified urinary FSH OR highly purified FSH OR highly purified follicle stimulating hormone OR hp-FSH OR fostimon OR Metrodin HP OR Metrodin-HP OR Metrodin high purity OR bravelle OR Urofollitropin highly purified OR urofollitropin HP OR Fertinorm HP OR fertinorm highly purified OR neo-fertinorm OR Human menopausal gonadotropin OR HMG OR Menotrophin OR menopur OR reproner OR Humegon OR Menogon OR Pergonal OR merional OR follitrin OR meriofert OR fertinorm OR normegon OR Corifollitropin alfa OR corifollitropin OR long-acting FSH OR FSH-CTP OR follicle stimulating hormone C-terminal peptide OR gonadotropin) AND (live birth OR pregnancy rate OR multiple pregnanc*)	Cochrane	1833			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	natural cycle + timed intercourse (+/- hCG trigger)
Comparison:	all other interventions
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	(Infertility OR "Infertility"[Mesh]) AND ("natural cycle" OR unstimulated cycle)	Pubmed	425	17	621	
15/03/2021	Infertility AND (natural cycle OR unstimulated cycle)	Cochrane	360			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	IUI
Comparison:	all other interventions
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	(Infertility OR "Infertility"[Mesh]) AND (IUI OR "intrauterine insemination" OR "intra-uterine insemination" OR "intra uterine insemination" OR "artificial insemination" OR "Insemination, Artificial"[Mesh] OR "insemination"[Mesh])	Pubmed	4324	91	3661	
15/03/2021	Infertility AND (IUI OR intrauterine insemination OR intra-uterine insemination OR intra uterine insemination OR artificial insemination)	Cochrane	1029			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	ovarian stimulation +IUI
Comparison:	all other interventions
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	(Infertility OR "Infertility"[Mesh]) AND (IUI OR "intrauterine insemination" OR "intra-uterine insemination" OR "intra uterine insemination" OR "artificial insemination" OR "Insemination, Artificial"[Mesh] OR "insemination"[Mesh])	Pubmed	4324	208	3544	
15/03/2021	Infertility AND (IUI OR intrauterine insemination OR intra-uterine insemination OR intra uterine insemination OR artificial insemination)	Cochrane	1029			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	ovarian stimulation +IVF
Comparison:	all other interventions
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
15/03/2021	(Infertility OR "Infertility"[Mesh]) AND ("ovulation induction"[Mesh] OR "ovarian stimulation" OR "ovulation induction") AND (IVF OR "in vitro fertilization" OR "Fertilization in Vitro"[Mesh] OR ICSI OR "intracytoplasmic insemination" OR "intracytoplasmic sperm injection" OR "Sperm Injections, Intracytoplasmic"[Mesh])	Pubmed	4189	91	4543	
15/03/2021	Infertility AND (ovarian stimulation OR ovulation induction) AND (IVF OR in vitro fertilization OR ICSI OR intracytoplasmic insemination OR intracytoplasmic sperm injection)	Cochrane	1567			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 3.2.3 WHAT IS THE VALUE OF IVF VERSUS ICSI?**

Patients	Intervention	Comparison	Outcomes
Couples diagnosed with unexplained infertility (female age as factor to be considered) Normal ovarian reserve	ICSI	IVF	<u>Critical outcomes:</u> - Live full-term singleton birth/ Live birth - ongoing pregnancy rate - Multiple pregnancies/multiple births <u>Important outcomes:</u> - Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life, anxiety and/or depression - COST – effectiveness value <u>Other outcomes</u> - Clinical pregnancy rate - Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery) - Ovarian hyperstimulation syndrome - Fetal abnormalities - Feasibility - Acceptability

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	ICSI
Comparison:	IVF
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
19/02/2021	(Infertility OR "Infertility"[Mesh]) AND (IVF OR "in vitro fertilization" OR "Fertilization in Vitro"[Mesh]) AND (ICSI OR "intracytoplasmic insemination" OR "intracytoplasmic sperm injection" OR "Sperm Injections, Intracytoplasmic"[Mesh])	Pubmed	5774	35	5789	
19/02/2021	Infertility AND (IVF OR "in vitro fertilization") AND (ICSI OR "intracytoplasmic insemination" OR "intracytoplasmic sperm injection")	Cochrane	1232			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 3.3 WHAT IS THE VALUE OF MECHANICAL-SURGICAL PROCEDURES?**

Patients	Intervention	Comparison	Outcomes
Couples diagnosed with unexplained infertility (female age as factor to be considered)	Surgery/laparoscopy with different aims: - Tubal flushing - (with and without oil) - Hysteroscopic surgery for minor malformations (removal of polyps, correction of T-shaped uterus) - Endometrial scratching - Minimal to mild endometriosis	No surgical correction	<u>Critical outcomes:</u> - Live full-term singleton birth/ Live birth - ongoing pregnancy rate - Multiple pregnancies/multiple births <u>Important outcomes:</u> - Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life, anxiety and/or depression - COST – effectiveness value <u>Other outcomes</u> - Clinical pregnancy rate

			- Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery) - Ovarian hyperstimulation syndrome - Fetal abnormalities - Feasibility - Acceptability

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Surgery/laparascopy (tubal flushing, with and without oil, hysteroscopic surgery for minor malformations (polyps, T-shaped uterus, ...)
Comparison:	clomiphene citrate + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, health related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
05/03/2021	(((infertility OR "infertility"[Mesh])) AND (laparoscopy OR "Laparoscopy"[Mesh] OR surgery OR "Surgical Procedures, Operative"[Mesh])) AND ((clomiphene citrate OR CC OR clomifen OR clomid OR "Clomiphene"[Mesh]))	Pubmed	711	8	648	
05/03/2021	Infertility AND (laparoscopy OR surgery) AND (clomiphene citrate OR CC OR clomifen OR clomid)	Cochrane	109			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Surgery/laparascopy (tubal flushing, with and without oil, hysteroscopic surgery for minor malformations (polyps, T-shaped uterus, ...)
Comparison:	letrozole + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, health related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
05/03/2021	(((infertility OR "infertility"[Mesh])) AND ((letrozole OR "aromatase inhibitor" OR "Letrozole"[Mesh]))	Pubmed	438	0	677	
05/03/2021	Infertility AND (letrozole OR aromatase inhibitor)	Cochrane	458			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Surgery/laparascopy (tubal flushing, with and without oil, hysteroscopic surgery for minor malformations (polyps, T-shaped uterus, ...)
Comparison:	gonadotropins + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, health related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
05/03/2021	(((infertility OR "infertility"[Mesh])) AND (("recombinant follicle stimulating hormone" OR "Recombinant FSH" OR rFSH OR Follitropin OR corifollitropin OR puregon OR Gonal-F OR FSH-CTP OR follistim OR "follitropin alfa" [Supplementary Concept] OR "follitropin beta" [Supplementary Concept] OR "follicle stimulating hormone, human, with HCG C-terminal peptide" [Supplementary Concept] OR "purified FSH" OR "purified urinary FSH" OR "purified follicle stimulating hormone" OR p-FSH OR Urofollitropin OR follegon OR metrodin OR fertinex OR "Urofollitropin"[Mesh] OR "highly purified urinary FSH" OR "highly purified FSH" OR "highly purified follicle stimulating hormone" OR hp-FSH OR fostimon OR "Metrodin HP" OR "Metrodin-HP"OR "Metrodin high purity" OR bravelle OR "Urofollitropin highly purified" OR "urofollitropin HP" OR "Fertinorm HP" OR "fertinorm highly purified" OR neo-fertinorm OR "Human menopausal gonadotropin" OR HMG OR Menotrophin OR menopur OR reproneX OR Humegon OR Menogon OR Pergonal OR merional OR folltrin OR meriofert OR fertinorm OR normegon OR "Menotropins"[Mesh] OR "Corifollitropin alfa" OR corifollitropin OR "long-acting FSH" OR FSH-CTP OR "follicle stimulating hormone C-terminal peptide" OR "follicle stimulating hormone, human, with HCG C-terminal peptide" [Supplementary Concept] OR gonadotropin OR "Gonadotropins"[Mesh])) AND (laparoscopy OR "Laparoscopy"[Mesh] OR surgery OR "Surgical Procedures, Operative"[Mesh])	Pubmed	2905	5	2487	
05/03/2021	Infertility AND (recombinant follicle stimulating hormone OR Recombinant FSH OR rFSH OR Follitropin OR corifollitropin OR puregon OR Gonal-F OR FSH-CTP OR follistim OR purified FSH OR purified urinary FSH OR purified follicle stimulating hormone OR p-FSH OR Urofollitropin OR follegon OR metrodin OR fertinex OR highly purified urinary FSH OR highly purified FSH OR highly purified follicle stimulating hormone OR hp-FSH OR fostimon OR Metrodin HP OR Metrodin-HP OR Metrodin high purity OR bravelle OR Urofollitropin highly purified OR urofollitropin HP OR Fertinorm HP OR fertinorm highly purified OR neo-fertinorm OR Human menopausal gonadotropin OR HMG OR Menotrophin OR menopur OR reproneX OR Humegon OR Menogon OR Pergonal OR merional OR folltrin OR meriofert OR fertinorm OR normegon OR Corifollitropin alfa OR corifollitropin OR long-acting FSH OR FSH-CTP OR follicle stimulating hormone C-terminal peptide OR gonadotropin) AND (laparoscopy OR surgery)	Cochrane	181			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Surgery/laparascopy (tubal flushing, with and without oil, hysteroscopic surgery for minor malformations (polyps, T-shaped uterus, ...)
Comparison:	natural cycle + timed intercourse (+/- hCG trigger)
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, health related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
05/03/2021	(infertility OR "infertility"[Mesh]) AND ("natural cycle" OR unstimulated cycle) AND (laparoscopy OR "Laparoscopy"[Mesh] OR surgery OR "Surgical Procedures, Operative"[Mesh])	Pubmed	78	0	86	
05/03/2021	Infertility AND (natural cycle OR unstimulated cycle) AND (laparoscopy OR surgery)	Cochrane	23			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Surgery/laparascopy (tubal flushing, with and without oil, hysteroscopic surgery for minor malformations (polyps, T-shaped uterus, ...)
Comparison:	IUI
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, health related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
05/03/2021	(infertility OR "infertility"[Mesh]) AND (IUI OR "intrauterine insemination" OR "intra-uterine insemination" OR "intra uterine insemination" OR "artificial insemination" OR "insemination, Artificial"[Mesh] OR "Insemination"[Mesh]) AND (laparoscopy OR "Laparoscopy"[Mesh] OR surgery OR "Surgical Procedures, Operative"[Mesh])	Pubmed	712	26	617	
05/03/2021	Infertility AND (IUI OR intrauterine insemination OR intra-uterine insemination OR intra uterine insemination OR artificial insemination) AND (laparoscopy OR surgery)	Cochrane	73			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Surgery/laparascopy (tubal flushing, with and without oil, hysteroscopic surgery for minor malformations (polyps, T-shaped uterus, ...)
Comparison:	ovarian stimulation +IUI
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, health related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
05/03/2021	(infertility OR "infertility"[Mesh]) AND (IUI OR "intrauterine insemination" OR "intra-uterine insemination" OR "intra uterine insemination" OR "artificial insemination" OR "insemination, Artificial"[Mesh] OR "Insemination"[Mesh]) AND (laparoscopy OR "Laparoscopy"[Mesh] OR surgery OR "Surgical Procedures, Operative"[Mesh])	Pubmed	712	26	617	
05/03/2021	Infertility AND (IUI OR intrauterine insemination OR intra-uterine insemination OR intra uterine insemination OR artificial insemination) AND (laparoscopy OR surgery)	Cochrane	73			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Surgery/laparascopy (tubal flushing, with and without oil, hysteroscopic surgery for minor malformations (polyps, T-shaped uterus, ...)
Comparison:	ovarian stimulation +IVF
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, health related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
05/03/2021	(infertility OR "infertility"[Mesh]) AND ("ovulation induction"[Mesh] OR "ovarian stimulation" OR "ovulation induction") AND (IVF OR "in vitro fertilization" OR "Fertilization in Vitro"[Mesh] OR ICSI OR "intracytoplasmic insemination" OR "intracytoplasmic sperm injection" OR "Sperm Injections, Intracytoplasmic"[Mesh]) AND (laparoscopy OR "Laparoscopy"[Mesh] OR surgery OR "Surgical Procedures, Operative"[Mesh])	Pubmed	1005	22	970	
05/03/2021	Infertility AND (ovarian stimulation OR ovulation induction) AND (IVF OR in vitro fertilization OR ICSI OR intracytoplasmic insemination OR intracytoplasmic sperm injection) AND (laparoscopy OR surgery)	Cochrane	80			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

- **QUESTION 3.4 WHAT IS THE EFFECTIVENESS OF ALTERNATIVE THERAPEUTIC APPROACHES?**

Patients	Intervention	Comparison	Outcomes
Couples diagnosed with unexplained infertility With expectant management	alternative therapeutic approach - Antioxidant (male – female) - Acupuncture - Nutraceuticals (inositol) - Psychotherapy - TCM - Diet, exercise, behavioural therapy	no additional treatment	Critical outcomes: - Live full-term singleton birth/ Live birth - ongoing pregnancy rate - Multiple pregnancies/multiple births Important outcomes: - Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life, anxiety and/or depression - COST – effectiveness value Other outcomes - Clinical pregnancy rate - Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery) - Ovarian hyperstimulation syndrome - Fetal abnormalities - Feasibility - Acceptability
Couples diagnosed with unexplained infertility With active treatment for UI	Alternative therapeutic approach - Antioxidant (male – female) - Acupuncture - Nutraceuticals (inositol) - Psychotherapy - TCM - Diet, exercise, behavioural therapy	No additional treatment	Critical outcomes: - Live full-term singleton birth/ Live birth - ongoing pregnancy rate - Multiple pregnancies/multiple births Important outcomes: - Patient outcomes: clinical symptoms, patient satisfaction, health-related quality of life, anxiety and/or depression - COST – effectiveness value Other outcomes - Clinical pregnancy rate - Adverse pregnancy outcome (including miscarriage, ectopic, stillbirth, preterm delivery) - Ovarian hyperstimulation syndrome - Fetal abnormalities - Feasibility - Acceptability

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Antioxidant (male-female)
Comparison:	No additional treatment
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	(Infertility OR "Infertility"[Mesh]) AND (antioxidant OR "Antioxidants"[Mesh]) AND (live birth OR pregnancy rate OR multiple pregnanc* OR "Live Birth"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Pregnancy, Multiple"[Mesh])	Pubmed	224	65	269	
26/02/2021	Infertility AND antioxidant	Cochrane	256			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Acupuncture
Comparison:	No additional tests
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	((Infertility OR "Infertility"[Mesh])) AND (acupuncture OR "Acupuncture"[Mesh])	Pubmed	345	49	284	
26/02/2021	Infertility AND acupuncture	Cochrane	184			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Nutraceuticals (inositol)
Comparison:	No additional tests
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	((Infertility OR "Infertility"[Mesh])) AND (nutraceutical OR inositol OR dietary supplement OR "Dietary Supplements"[Mesh] OR "Inositol"[Mesh])	Pubmed	577	48	457	
26/02/2021	Infertility AND (nutraceutical OR inositol OR dietary supplement)	Cochrane	157			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Psychotherapy
Comparison:	No additional tests
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	(Infertility OR "Infertility"[Mesh]) AND (psychotherapy OR psycholog* OR "Psychotherapy"[Mesh]) AND (live birth OR pregnancy rate OR multiple pregnanc* OR "Live Birth"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Pregnancy, Multiple"[Mesh])	Pubmed	592	33	571	
26/02/2021	Infertility AND (psychotherapy OR psycholog*) AND (live birth OR pregnancy rate OR multiple pregnanc*)	Cochrane	121			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	TCM
Comparison:	No additional tests
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	(Infertility OR "Infertility"[Mesh]) AND (traditional chinese medicine OR TCM OR "Medicine, Chinese Traditional"[Mesh])	Pubmed	629	25	386	
26/02/2021	Infertility AND (traditional chinese medicine OR TCM)	Cochrane	136			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

PICO TERMS	
Patients/Population:	Couples assessed for unexplained infertility
Intervention:	Diet, exercise, behavioural therapy
Comparison:	No additional tests
Outcomes	Live birth, ongoing pregnancy rate, multiple pregnancies (births), patient outcomes (clinical symptoms, patient satifaction, heatlh related QoL, anxiety and/or depression), cost-effectiveness, clinical pregnancy rate, adverse pregnancy outcome (miscariage, ectopic, stillbirth, preterm delivery), OHSS, fetal abnormalities, feasibility

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	(((Infertility OR "Infertility"[Mesh])) AND (behavioral counseling OR lifestyle intervention OR behavioral therapy OR diet OR exercise OR "Behavioral Disciplines and Activities"[Mesh] OR "Diet"[Mesh] OR "Exercise"[Mesh])) AND (live birth OR pregnancy rate OR multiple pregnanc* OR "Live Birth"[Mesh] OR "Pregnancy Rate"[Mesh] OR "Pregnancy, Multiple"[Mesh])	Pubmed	583	51	560	
26/02/2021	Infertility AND (behavioral counseling OR lifestyle intervention OR behavioral therapy OR diet OR exercise) AND (live birth OR pregnancy rate OR multiple pregnanc*)	Cochrane	180			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

4. QUALITY OF LIFE

- **QUESTION 4 IS THERE A DIFFERENCE IN QOL FOR PATIENTS WITH UNEXPLAINED VERSUS EXPLAINED INFERTILITY?**

Patients	Intervention	Comparison	Outcomes
Couples diagnosed with infertility	Unexplained	Explained	QOL

PICO TERMS	
Patients/Population:	Couples assessed for infertility
Intervention:	Unexplained
Comparison:	Explained
Outcomes	QoL

Date of search	Search term	Database	Nr of results	Nr of relevant papers (after first check)	Nr of irrelevant papers (after first check)	
26/02/2021	(Infertility OR "Infertility"[Mesh]) AND ("quality of life" OR QoL OR "Quality of Life"[Mesh])	Pubmed	1528	4	1602	
26/02/2021	Infertility AND (quality of life OR QoL)	Cochrane	321			
				listed page "relevant papers"	listed page "list of irrelevant papers"	

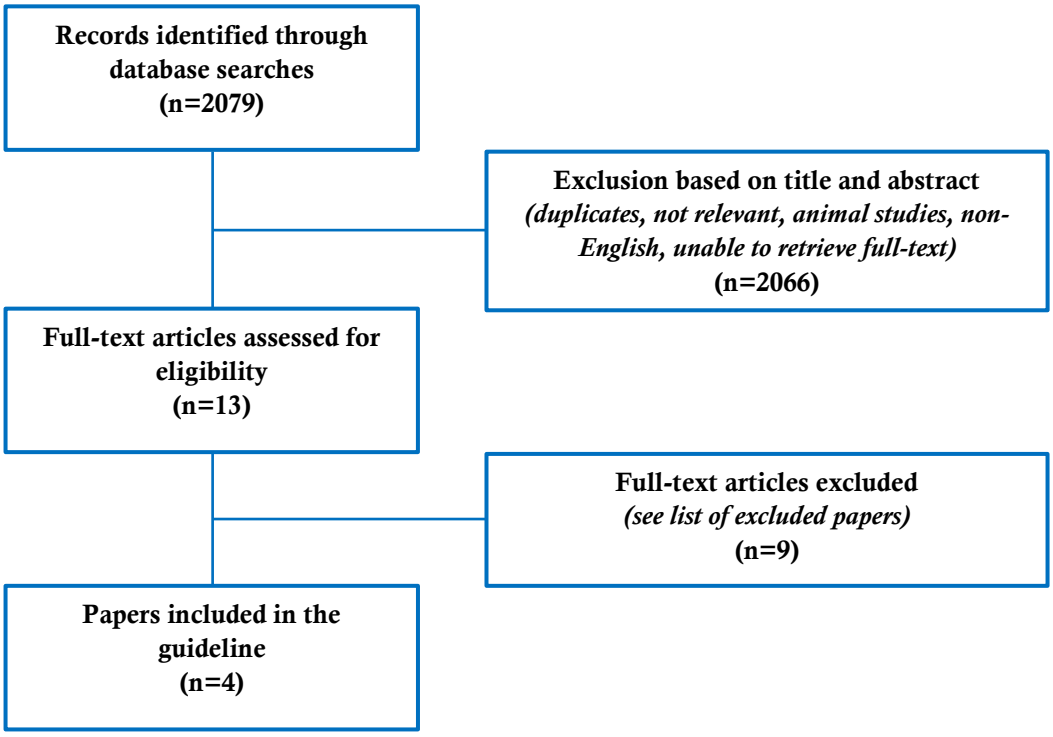
3. SEARCH RESULTS

2. Diagnosis

2.1 Confirmation of ovulation

PICO QUESTION: WHICH IS THE RELIABILITY AND CONVENIENCE OF METHODS TO CONFIRM REGULAR OVULATION?

Flowchart



List of excluded papers

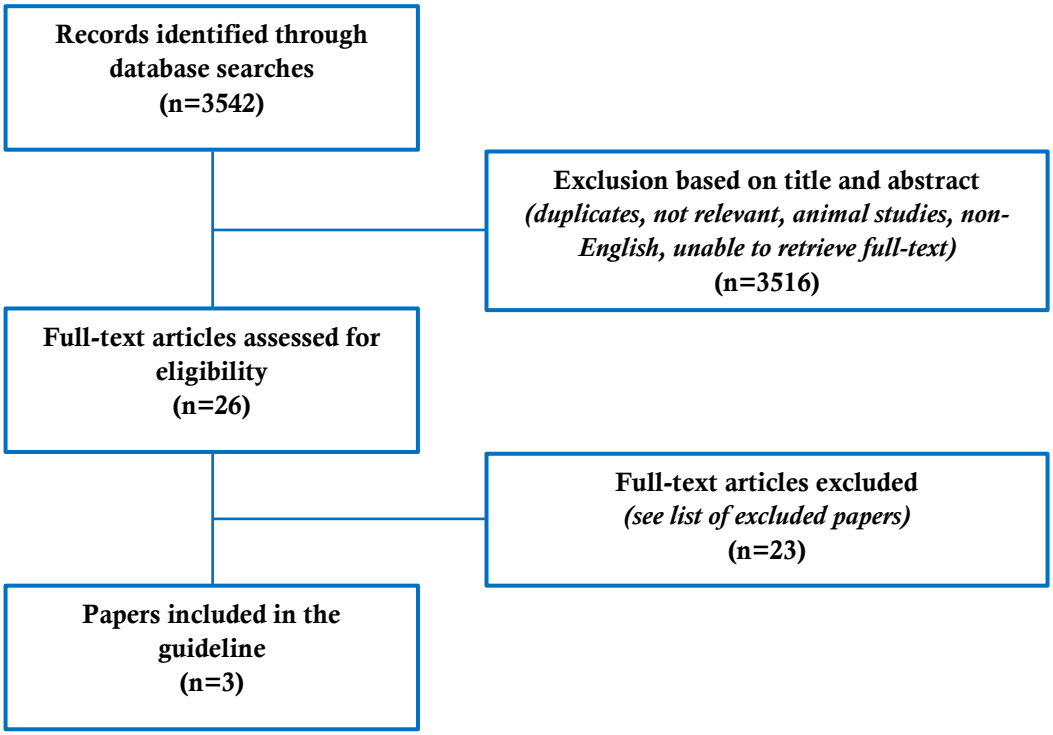
	Exclusion criterion
Broad, A., Biswakarma, R. and Harper, J. C. A survey of women's experiences of using period tracker applications: Attitudes, ovulation prediction and how the accuracy of the app in predicting period start dates affects their feelings and behaviours. Womens Health (Lond). 2022; 18 17455057221095246.	Does not adequately assess the outcome of interest
Graham, F. M., Gosling, L. and France, J. T. An evaluation of teaching cervical mucus symptoms to ovulating infertile women. Aust N Z J Obstet Gynaecol. 1983; 23 (4): 226-30.	Descriptive study only

Lemay, A., Bastide, A., Lambert, R. and Rioux, J. E. Prediction of human ovulation by rapid luteinizing hormone (LH) radioimmunoassay and ovarian ultrasonography. Fertil Steril. 1982; 38 (2): 194-201.	Descriptive study only
Nulsen, J., Wheeler, C., Ausmanas, M. and Blasco, L. Cervical mucus changes in relationship to urinary luteinizing hormone. Fertil Steril. 1987; 48 (5): 783-6.	Non-comparative analysis
Quagliarello, J. and Arny, M. Inaccuracy of basal body temperature charts in predicting urinary luteinizing hormone surges. Fertil Steril. 1986; 45 (3): 334-7.	Descriptive analysis only
Pillet, M. C., Wu, T. F., Adamson, G. D., Subak, L. L. and Lamb, E. J. Improved prediction of postovulatory day using temperature recording, endometrial biopsy, and serum progesterone. Fertil Steril. 1990; 53 (4): 614-9.	Objective was to determine next menses
Rollason, J. C., Outtrim, J. G. and Mathur, R. S. A pilot study comparing the DuoFertility(®) monitor with ultrasound in infertile women. Int J Womens Health. 2014; 6 657-62.	Descriptive analysis of a no longer existant technology
Sasaki, R. S., Approbato, M. S., Maia, M. C., Fleury, E. A., Giviziez, C. R. and Zanluchi, N. Patients' auto report of regularity of their menstrual cycles. Medical history is very reliable to predict ovulation. A cross-sectional study. JBRA Assist Reprod. 2016; 20 (3): 118-22.	Adequate confirmation of ovulation was lacking
Varma, T. R., Patel, R. H. and Everard, D. Determination with Hi-Gonavis of luteinizing hormone levels in urine compared with those in plasma. Br J Obstet Gynaecol. 1982; 89 (1): 87-90.	Non-comparative analysis

2.2 Oocyte/corpus luteum quality

PICO Question: What is the reliability of parameters detecting good oocyte/ corpus luteum quality?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Bassil, R., Casper, R., Samara, N., Hsieh, T. B., Barzilay, E., Orvieto, R. and Haas, J. Does the endometrial receptivity array really provide personalized embryo transfer? J Assist Reprod Genet. 2018; 35 (7): 1301-1305.	Women undergoing frozen blastocyst transfers, comparing agreement between endometrial phase examined by ERA or Noyes criteria. Not about corpus luteum function.
Bongso, A., Chye, N. S., Ratnam, S., Sathananthan, H. and Wong, P. C. Chromosome anomalies in human oocytes failing to fertilize after insemination in vitro. Hum Reprod. 1988; 3 (5): 645-9.	No comparison between age and chromosome status as determinants of oocyte quality.
Bonhoff, A., Johannisson, E. and Bohnet, H. G. Morphometric analysis of the endometrium of infertile patients in relation to peripheral hormone levels. Fertil Steril. 1990; 54 (1): 84-9.	No direct information on corpus luteum function.
Gerhard, I., Bechthold, E., Eggert-Kruse, W., Heberling, D. and Runnebaum, B. Value of endometrial biopsies and serum hormone determinations in women with infertility. Hum Reprod. 1990; 5 (8): 906-14.	Many factors investigated.
Haddad Filho, J., Cedenho, A. P. and de Freitas, V. Correlation between endometrial dating of luteal phase days 6 and 10 of the same menstrual cycle. Sao Paulo Med J. 1998; 116 (3): 1734-7.	Women with low P4 excluded and no direct analysis with P4

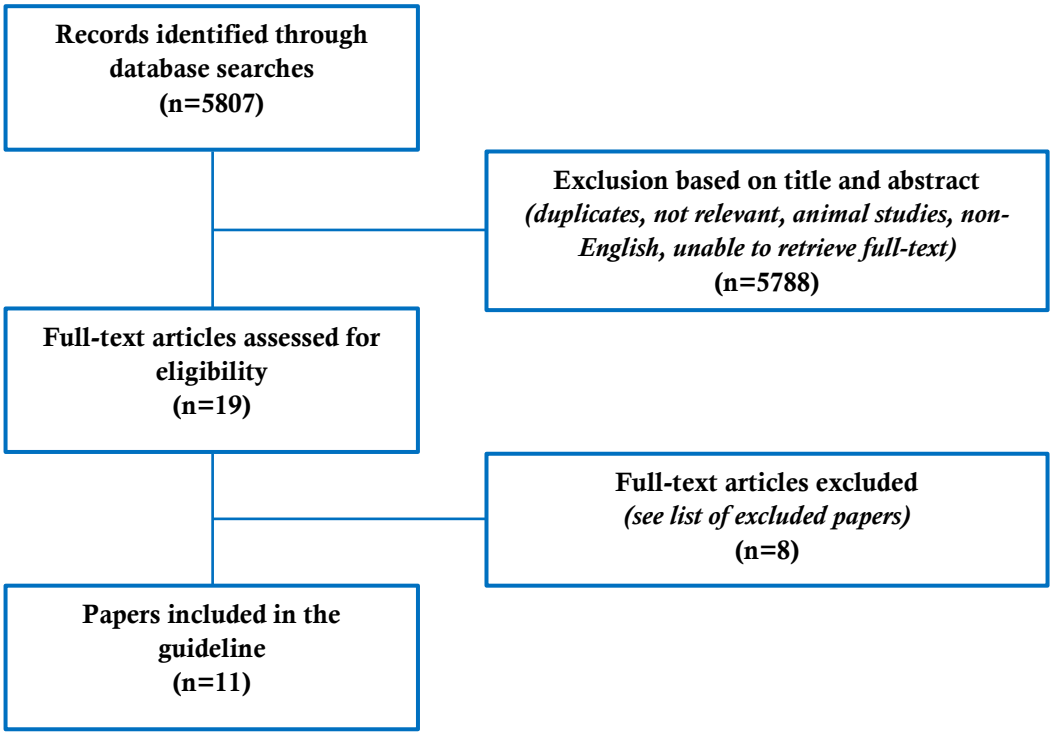
Hansen, K. R., Eisenberg, E., Baker, V., Hill, M. J., Chen, S., Talken, S., Diamond, M. P., Legro, R. S., Coutifaris, C., Alvero, R., Robinson, R. D., Casson, P., Christman, G. M., Santoro, N., Zhang, H. and Wild, R. A. Midluteal Progesterone: A Marker of Treatment Outcomes in Couples With Unexplained Infertility. J Clin Endocrinol Metab. 2018; 103 (7): 2743-2751.	Progesterone measured in stimulated cycles.
Kaye, L., Griffin, D., Thorne, J., Neuber, E., Nulsen, J., Benadiva, C. and Engmann, L. Independent serum markers of corpora lutea function after gonadotropin-releasing hormone agonist trigger and adjuvant low dose human chorionic gonadotropin in in vitro fertilization. Fertil Steril. 2019; 112 (3): 534-544.	Progesterone measured in stimulated cycles.
Kusuhara, K. Clinical importance of endometrial histology and progesterone level assessment in luteal-phase defect. Horm Res. 1992; 37 Suppl 1 53-8.	Endometrial biopsy, not serum progesterone.
Laatikainen, T., Andersson, B., Kärkkäinen, J. and Wahlström, T. Progestin receptor levels in endometria with delayed or incomplete secretory changes. Obstet Gynecol. 1983; 62 (5): 592-5.	Endometrial biopsy
Leiva, R., Bouchard, T., Boehringer, H., Abulla, S. and Ecochard, R. Random serum progesterone threshold to confirm ovulation. Steroids. 2015; 101 125-9.	Progesterone to confirm ovulation
Lim, A. S. and Tsakok, M. F. Age-related decline in fertility: a link to degenerative oocytes? Fertil Steril. 1997; 68 (2): 265-71.	No comparison between age and chromosome status as determinants of oocyte quality.
Ma, S., Kalousek, D. K., Yuen, B. H., Gomel, V., Katagiri, S. and Moon, Y. S. Chromosome investigation in in vitro fertilization failure. J Assist Reprod Genet. 1994; 11 (9): 445-51.	No comparison between age and chromosome status as determinants of oocyte quality.
Macas, E., Floersheim, Y., Hotz, E., Imthurn, B., Keller, P. J. and Walt, H. Abnormal chromosomal arrangements in human oocytes. Hum Reprod. 1990; 5 (6): 703-7.	No comparison between age and chromosome status as determinants of oocyte quality.
Munné, S., Dailey, T., Sultan, K. M., Grifo, J. and Cohen, J. The use of first polar bodies for preimplantation diagnosis of aneuploidy. Hum Reprod. 1995; 10 (4): 1014-20.	No comparison between age and chromosome status as determinants of oocyte quality.
Pellestor, F., Andréo, B., Arnal, F., Humeau, C. and Demaille, J. Maternal aging and chromosomal abnormalities: new data drawn from in vitro unfertilized human oocytes. Hum Genet. 2003; 112 (2): 195-203.	No comparison between age and chromosome status as determinants of oocyte quality.
Perez, R. J., Plurad, A. V. and Palladino, V. S. The relationship of the corpus luteum and the endometrium in infertile patients. Fertil Steril. 1981; 35 (4): 423-7.	Correlation between progesterone and ovulation
Petsos, P., Mamtora, H., Ratcliffe, W. A. and Anderson, D. C. Inadequate luteal phase usually indicates ovulatory dysfunction: observations from serial hormone and ultrasound monitoring of 115 cycles. Gynecol Endocrinol. 1987; 1 (1): 37-45.	Correlation between progesterone and ovulation
Portuondo, J. A., Agustin, A., Herran, C. and Echanojauregui, A. D. The corpus luteum in infertile patients found during laparoscopy. Fertil Steril. 1981; 36 (1): 37-40.	compares whether visualization of ovulatory stigma during laparoscopy is correlated with observation of secretory endometrium in EMB
Shangold, M., Berkeley, A. and Gray, J. Both midluteal serum progesterone levels and late luteal endometrial histology should be assessed in all infertile women. Fertil Steril. 1983; 40 (5): 627-30.	Correlation between serum P and endometrial histology
Staessen, C., Platteau, P., Van Assche, E., Michiels, A., Tournaye, H., Camus, M., Devroey, P., Liebaers, I. and Van Steirteghem, A. Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. Human reproduction (Oxford, England). 2004; 19 (12): 2849-2858.	No comparison between age and chromosome status as determinants of oocyte quality.

Sterzik, K., Abt, M., Grab, D., Schneider, V. and Strehler, E. Predicting the histologic dating of an endometrial biopsy specimen with the use of Doppler ultrasonography and hormone measurements in patients undergoing spontaneous ovulatory cycles. Fertil Steril. 2000; 73 (1): 94-8.	No direct information on corpus luteum function, women with in and out of phase endometrium in the luteal phase of a spontaneous cycle have similar P4 levels.
Vialard, F., Gomes, D. M., Hammoud, I., Bergere, M., Wainer, R., Bailly, M., Lombroso, R. and Selva, J. Stability of aneuploidy rate in polar bodies in two cohorts from the same patient. Reprod Biomed Online. 2008; 17 (2): 213-9.	No comparison between age and chromosome status as determinants of oocyte quality.
Wu, C. H. and Minassian, S. S. The integrated luteal progesterone: an assessment of luteal function. Fertil Steril. 1987; 48 (6): 937-40.	Relies on endometrial dating by histology

2.3 Ovarian reserve

PICO Question: Should one or more tests of ovarian reserve be included in the diagnostic work-up?

Flowchart



List of excluded papers

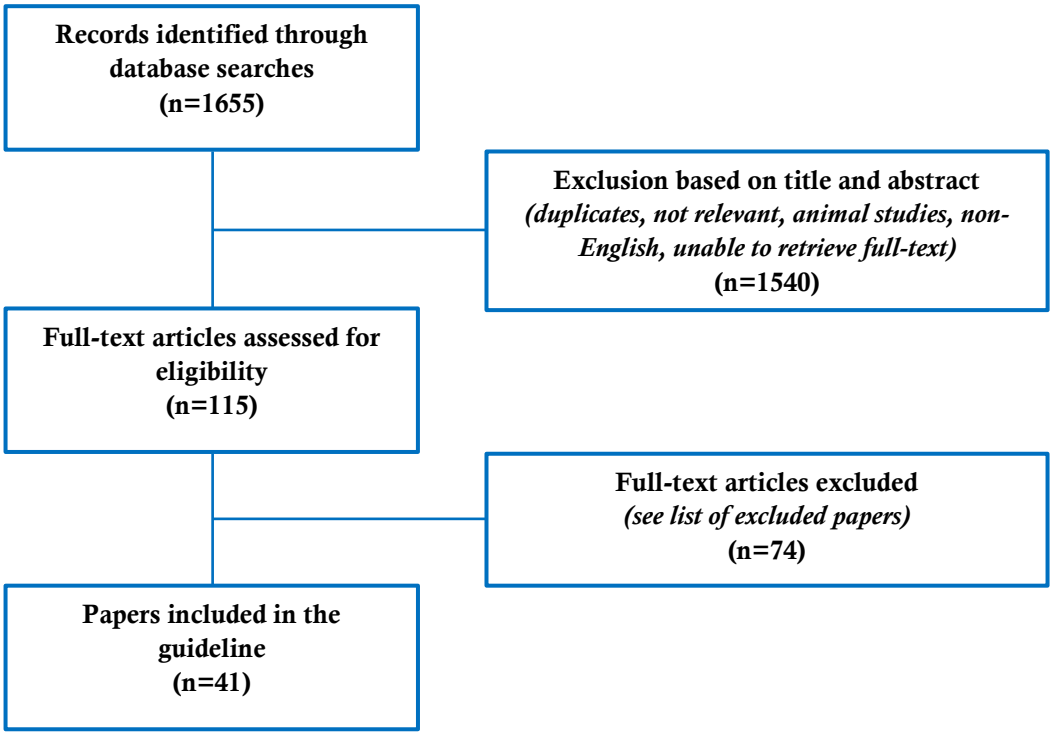
Reference	Exclusion criterion
Erdem, M., Erdem, A., Guler, I. and Atmaca, S. Role of antral follicle count in controlled ovarian hyperstimulation and intrauterine insemination cycles in patients with unexplained subfertility. Fertil Steril. 2008; 90 (2): 360-6.	Difference between AFC in women with UI who got pregnant with IUI and who did not
Leach, R. E., Moghissi, K. S., Randolph, J. F., Reame, N. E., Blacker, C. M., Ginsburg, K. A. and Diamond, M. P. Intensive hormone monitoring in women with unexplained infertility: evidence for subtle abnormalities suggestive of diminished ovarian reserve. Fertil Steril. 1997; 68 (3): 413-20.	Very small sample, inappropriate statistics.
Moro, F., Tropea, A., Scarinci, E., Leoncini, E., Boccia, S., Federico, A., Alesiani, O., Lanzone, A. and Apa, R. Anti-Müllerian hormone concentrations and antral follicle counts for the prediction of pregnancy outcomes after intrauterine insemination. Int J Gynaecol Obstet. 2016; 133 (1): 64-8.	Comparing or markers between women with UI who got an ongoing pregnancy and did not
Ng, E. H., Yeung, W. S. and Ho, P. C. The significance of antral follicle count in controlled ovarian stimulation and intrauterine insemination. J Assist Reprod Genet. 2005; 22 (9-10): 323-8.	Comparing or markers between women with UI who got an ongoing pregnancy and did not
Steiner, A. Z., Herring, A. H., Kesner, J. S., Meadows, J. W., Stanczyk, F. Z., Hoberman, S. and Baird, D. D. Antimüllerian hormone as a predictor of natural fecundability in women aged 30-42 years. Obstet Gynecol. 2011; 117 (4): 798-804.	Small sample, unknown fertility status, those conceived within 3 months excluded

van der Steeg, J. W., Steures, P., Eijkemans, M. J., Habbema, J. D., Hompes, P. G., Broekmans, F. J., Bouckaert, P. X., Bossuyt, P. M., van der Veen, F. and Mol, B. W. Predictive value and clinical impact of Basal follicle-stimulating hormone in subfertile, ovulatory women. J Clin Endocrinol Metab. 2007; 92 (6): 2163-8.	Very complicated design, difficult to draw conclusions on a general association between FSH and pregnancy.
Vagios, S., Hsu, J. Y., Sacha, C. R., Dimitriadis, I., Christou, G., James, K. E., Bormann, C. L. and Souter, I. Pretreatment antimüllerian hormone levels and outcomes of ovarian stimulation with gonadotropins/intrauterine insemination cycles. Fertil Steril. 2021; 116 (2): 422-430.	Not exclusively unexplained infertility
Yarde, F., Voorhuis, M., Dólleman, M., Knauff, E. A., Eijkemans, M. J. and Broekmans, F. J. Antimüllerian hormone as predictor of reproductive outcome in subfertile women with elevated basal follicle-stimulating hormone levels: a follow-up study. Fertil Steril. 2013; 100 (3): 831-8.	Women with FSH >12 included and underwent different treatments

2.4 Tubal factor

PICO Question: What is the accuracy of commonly used tests of tubal patency?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Alborzi, S., Dehbashi, S. and Khodaee, R. Sonohysterosalpingographic screening for infertile patients. Int J Gynaecol Obstet. 2003; 82 (1): 57-62.	No raw data to calculate sensitivity, specificity, PPV, NPV
Alcázar, J. L., Martinez-Astorquiza Corral, T., Orozco, R., Dominguez-Piriz, J., Juez, L. and Errasti, T. Three-Dimensional Hysterosalpingo-Contrast-Sonography for the Assessment of Tubal Patency in Women with Infertility: A Systematic Review with Meta-Analysis. Gynecol Obstet Invest. 2016; 81 (4): 289-95.	More recent systematic review available.
Anestad, G., Lunde, O., Moen, M. and Dalaker, K. Infertility and chlamydial infection. Fertil Steril. 1987; 48 (5): 787-90.	Included in systematic review Mol et al., 1995
Bjercke, S. and Purvis, K. Characteristics of women under fertility investigation with IgA/IgG seropositivity for Chlamydia trachomatis. Eur J Obstet Gynecol Reprod Biol. 1993; 51 (2): 157-61.	Included in systematic review Mol et al., 1995
Chan, C. C., Ng, E. H., Tang, O. S., Chan, K. K. and Ho, P. C. Comparison of three-dimensional hysterosalpingo-contrast-sonography and diagnostic laparoscopy with chromopertubation in the assessment of tubal patency for the investigation of subfertility. Acta Obstet Gynecol Scand. 2005; 84 (9): 909-13.	Included in systematic review Wang et al., 2016
Cheng, Q., Wang, S. S., Zhu, X. S. and Li, F. Evaluation of Tubal Patency with Transvaginal Three-dimensional Hysterosalpingo-contrast Sonography. Chin Med Sci J. 2015; 30 (2): 70-5.	Included in systematic review Wang et al., 2016

Conway, D., Glazener, C. M., Caul, E. O., Hodgson, J., Hull, M. G., Clarke, S. K. and Stirrat, G. M. Chlamydial serology in fertile and infertile women. Lancet. 1984; 1 (8370): 191-3.	No raw data to calculate sensitivity, specificity, PPV, NPV
Coppus, S. F., Land, J. A., Opmeer, B. C., Steures, P., Eijkemans, M. J., Hompes, P. G., Bossuyt, P. M., van der Veen, F., Mol, B. W. and van der Steeg, J. W. Chlamydia trachomatis IgG seropositivity is associated with lower natural conception rates in ovulatory subfertile women without visible tubal pathology. Hum Reprod. 2011; 26 (11): 3061-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Czerwenka, K., Heuss, F., Hosmann, J., Manavi, M., Jelincic, D. and Kubista, E. Salpingitis caused by Chlamydia trachomatis and its significance for infertility. Acta Obstet Gynecol Scand. 1994; 73 (9): 711-5.	No raw data to calculate sensitivity, specificity, PPV, NPV
Darwish, A. M. and Youssef, A. A. Screening sonohysterography in infertility. Gynecol Obstet Invest. 1999; 48 (1): 43-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
den Hartog, J. E., Lardenoije, C. M., Severens, J. L., Land, J. A., Evers, J. L. and Kessels, A. G. Screening strategies for tubal factor subfertility. Hum Reprod. 2008; 23 (8): 1840-8.	Included in systematic review Broeze et al., 2011
Dhaliwal, L. K., Khera, K. R., Gupta, I. and Gupta, A. N. Comparison of hysterosalpingography and laparoscopy in the evaluation of tubal factor. Asia Oceania J Obstet Gynaecol. 1987; 13 (1): 65-7.	very old paper, high risk of bias due to poor methodology, very high detection rate of tubal pathology and very high false-positive rate for HSG.
Dietrich, M., Suren, A., Hinney, B., Osmers, R. and Kuhn, W. Evaluation of tubal patency by hysterocontrast sonography (HyCoSy, Echovist) and its correlation with laparoscopic findings. J Clin Ultrasound. 1996; 24 (9): 523-7.	Included in systematic review Alcazar et al., 2020
Dijkman, A. B., Mol, B. W., van der Veen, F., Bossuyt, P. M. and Hogerzeil, H. V. Can hysterosalpingocontrast-sonography replace hysterosalpingography in the assessment of tubal subfertility? Eur J Radiol. 2000; 35 (1): 44-8.	Included in systematic review Alcazar et al., 2020
Duff, D. E., Fried, A. M., Wilson, E. A. and Haack, D. G. Hysterosalpingography and laparoscopy: a comparative study. AJR Am J Roentgenol. 1983; 141 (4): 761-3.	Inter-observer variance
El Hakim, E. A., Gordon, U. D. and Akande, V. A. The relationship between serum Chlamydia antibody levels and severity of disease in infertile women with tubal damage. Arch Gynecol Obstet. 2010; 281 (4): 727-33.	In the present study only women found to have tubal damage were studied, all other infertile women were excluded.
Exacoustos, C., Zupi, E., Carusotti, C., Lanzi, G., Marconi, D. and Arduini, D. Hysterosalpingo-contrast sonography compared with hysterosalpingography and laparoscopic dye pertubation to evaluate tubal patency. J Am Assoc Gynecol Laparosc. 2003; 10 (3): 367-72.	No raw data to calculate sensitivity, specificity, PPV, NPV
Frost, E., Collet, M., Reniers, J., Leclerc, A., Ivanoff, B. and Meheus, A. Importance of chlamydial antibodies in acute salpingitis in central Africa. Genitourin Med. 1987; 63 (3): 176-8.	All women had acute salpingitis.
Gao, Y. B., Yan, J. H., Yang, Y. D., Sun, J., Dong, J. Y. and Cui, G. H. Diagnostic value of transvaginal four-dimensional hysterosalpingo-contrast sonography combined with recanalization in patients with tubal infertility. Niger J Clin Pract. 2019; 22 (1): 46-50.	Included in systematic review Alcazar et al., 2020
Gijsen, A. P., Land, J. A., Goossens, V. J., Slobbe, M. E. and Bruggeman, C. A. Chlamydia antibody testing in screening for tubal factor subfertility: the significance of IgG antibody decline over time. Hum Reprod. 2002; 17 (3): 699-703.	No raw data to calculate sensitivity, specificity, PPV, NPV
Glatstein, I. Z., Sleeper, L. A., Lavy, Y., Simon, A., Adoni, A., Palti, Z., Hurwitz, A. and Laufer, N. Observer variability in the diagnosis and management of the hysterosalpingogram. Fertil Steril. 1997; 67 (2): 233-7.	No raw data to calculate sensitivity, specificity, PPV, NPV

Guerriero, S., Ajossa, S., Mais, V., Paoletti, A. M. and Melis, G. B. The screening of tubal abnormalities in the infertile couple. J Assist Reprod Genet. 1996; 13 (5): 407-12.	Included in systematic review Alcazar et al., 2020
Gump, D. W., Gibson, M. and Ashikaga, T. Evidence of prior pelvic inflammatory disease and its relationship to Chlamydia trachomatis antibody and intrauterine contraceptive device use in infertile women. Am J Obstet Gynecol. 1983; 146 (2): 153-9.	CAT from biopsies
Guven, M. A., Dilek, U., Pata, O., Dilek, S. and Ciragil, P. Prevalance of Chlamydia trochomatis, Ureaplasma urealyticum and Mycoplasma hominis infections in the unexplained infertile women. Arch Gynecol Obstet. 2007; 276 (3): 219-23.	No raw data to calculate sensitivity, specificity, PPV, NPV
Hamilton, J. A., Larson, A. J., Lower, A. M., Hasnain, S. and Grudzinskas, J. G. Evaluation of the performance of hysterosalpingo contrast sonography in 500 consecutive, unselected, infertile women. Hum Reprod. 1998; 13 (6): 1519-26.	Included in systematic review Alcazar et al., 2020
He, Y., Ma, X., Xu, J., Li, S., Wu, H., Liu, Q., Kong, L., Luo, J. and Liu, H. Comparison of Assessment Methods for Fallopian Tubal Patency and Peritubal Adhesion Between Transvaginal 4-Dimensional Hysterosalpingo-Contrast Sonography and Laparoscopic Chromopertubation. J Ultrasound Med. 2017; 36 (3): 547-556.	Included in systematic review Alcazar et al., 2020
Henry-Suchet, J., Catalan, F., Loffredo, V., Serfaty, D., Siboulet, A., Perol, Y., Sanson, M. J., Debache, C., Pigeau, F., Coppin, R., de Brux, J. and Poynard, T. Microbiology of specimens obtained by laparoscopy from controls and from patients with pelvic inflammatory disease or infertility with tubal obstruction: Chlamydia trachomatis and Ureaplasma urealyticum. Am J Obstet Gynecol. 1980; 138 (7 Pt 2): 1022-5.	No raw data to calculate sensitivity, specificity, PPV, NPV
Henry-Suchet, J., Utzmann, C., De Brux, J., Ardoin, P. and Catalan, F. Microbiologic study of chronic inflammation associated with tubal factor infertility: role of Chlamydia trachomatis. Fertil Steril. 1987; 47 (2): 274-7.	Included in systematic review Mol et al., 1995
Hodgson, R., Driscoll, G. L., Dodd, J. K. and Tyler, J. P. Chlamydia trachomatis: the prevalence, trend and importance in initial infertility management. Aust N Z J Obstet Gynaecol. 1990; 30 (3): 251-4.	Included in systematic review Mol et al., 1995
Holst, N., Abyholm, T. and Borgersen, A. Hysterosalpingography in the evaluation of infertility. Acta Radiol Diagn (Stockh). 1983; 24 (3): 253-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Hubacher, D., Grimes, D., Lara-Ricalde, R., de la Jara, J. and Garcia-Luna, A. The limited clinical usefulness of taking a history in the evaluation of women with tubal factor infertility. Fertil Steril. 2004; 81 (1): 6-10.	No raw data to calculate sensitivity, specificity, PPV, NPV
Inki, P., Palo, P. and Anttila, L. Vaginal sonosalpingography in the evaluation of tubal patency. Acta Obstet Gynecol Scand. 1998; 77 (10): 978-82.	Included in systematic review Alcazar et al., 2020
Jain, M., Gupta, S., Singh, M. and Gulati, A. K. Chlamydial serology and laparoscopic findings in infertile women. J Indian Med Assoc. 1994; 92 (4): 108-9.	Included in systematic review Mol et al., 1995
Kalogeropoulos, A., Frantzidou, F., Klearchou, N., Diza, E., Kyriazopoulou, V. and Karagiannis, V. Chlamydia trachomatis in infertile Greek women. A serologic and laparoscopic study. Eur J Obstet Gynecol Reprod Biol. 1993; 48 (2): 107-10.	Included in systematic review Mol et al., 1995
Kane, J. L., Woodland, R. M., Forsey, T., Darougar, S. and Elder, M. G. Evidence of chlamydial infection in infertile women with and without fallopian tube obstruction. Fertil Steril. 1984; 42 (6): 843-8.	Included in systematic review Mol et al., 1995
Kasby, C. B. Hysterosalpingography: an appraisal of current indications. Br J Radiol. 1980; 53 (628): 279-82.	No raw data to calculate sensitivity, specificity, PPV, NPV
Kelver, M. E. and Nagamani, M. Chlamydial serology in women with tubal infertility. Int J Fertil. 1989; 34 (1): 42-5.	Included in systematic review Mol et al., 1995

Kleinkauf-Houcken, A., Hüneke, B., Lindner, C. and Braendle, W. Combining B-mode ultrasound with pulsed wave Doppler for the assessment of tubal patency. Hum Reprod. 1997; 12 (11): 2457-60.	Included in systematic review Alcazar et al., 2020
Kupesic, S. and Plavsic, B. M. 2D and 3D hysterosalpingo-contrast-sonography in the assessment of uterine cavity and tubal patency. Eur J Obstet Gynecol Reprod Biol. 2007; 133 (1): 64-9.	Included in systematic review Wang et al., 2016
Luciano, D. E., Exacoustos, C., Johns, D. A. and Luciano, A. A. Can hysterosalpingo-contrast sonography replace hysterosalpingography in confirming tubal blockage after hysteroscopic sterilization and in the evaluation of the uterus and tubes in infertile patients? Am J Obstet Gynecol. 2011; 204 (1): 79.e1-5.	Included in systematic review Alcazar et al., 2020
Lucisano, A., Morandotti, G., Marana, R., Leone, F., Branca, G., Dell'Acqua, S. and Sanna, A. Chlamydial genital infections and laparoscopic findings in infertile women. Eur J Epidemiol. 1992; 8 (5): 645-9.	Included in systematic review Mol et al., 1995
Ludwin, I., Ludwin, A., Wiechec, M., Nocun, A., Banas, T., Basta, P. and Pitynski, K. Accuracy of hysterosalpingo-foam sonography in comparison to hysterosalpingo-contrast sonography with air/saline and to laparoscopy with dye. Hum Reprod. 2017; 32 (4): 758-769.	Included in systematic review Alcazar et al., 2020
Maheux-Lacroix, S., Boutin, A., Moore, L., Bergeron, M. E., Bujold, E., Laberge, P., Lemyre, M. and Dodin, S. Hysterosalpingosonography for diagnosing tubal occlusion in subfertile women: a systematic review with meta-analysis. Hum Reprod. 2014; 29 (5): 953-63.	More recent systematic review available.
Martens, M. G., Young, R. L., Uribe, M., Buttram, V. C. and Faro, S. Presence of Chlamydia, Mycoplasma, ureaplasma, and other bacteria in the upper and lower genital tracts of fertile and infertile populations. Infect Dis Obstet Gynecol. 1993; 1 (2): 85-90.	No positive cultures for C. trachomatis found
Martin, D. C., Khare, V. K. and Miller, B. E. Association of Chlamydia trachomatis immunoglobulin gamma titers with dystrophic peritoneal calcification, psammoma bodies, adhesions, and hydrosalpinges. Fertil Steril. 1995; 63 (1): 39-44.	No raw data to calculate sensitivity, specificity, PPV, NPV
Meikle, S. F., Zhang, X., Marine, W. M., Calonge, B. N., Hamman, R. F. and Betz, G. Chlamydia trachomatis antibody titers and hysterosalpingography in predicting tubal disease in infertility patients. Fertil Steril. 1994; 62 (2): 305-12.	Included in systematic review Mol et al., 1995
Minassian, S. S., Wu, C. H., Jungkind, D., Gocial, B., Filer, R. B. and Glassner, M. Chlamydial antibody, as determined with an enzyme-linked immunosorbent assay, in tubal factor infertility. J Reprod Med. 1990; 35 (2): 141-5.	Included in systematic review Mol et al., 1995
Moore, D. E., Spadoni, L. R., Foy, H. M., Wang, S. P., Daling, J. R., Kuo, C. C., Grayston, J. T. and Eschenbach, D. A. Increased frequency of serum antibodies to Chlamydia trachomatis in infertility due to distal tubal disease. Lancet. 1982; 2 (8298): 574-7.	Included in systematic review Mol et al., 1995
Muzii, L., Marana, R. and Mancuso, S. Distal fallopian tube occlusion: false diagnosis with hysterosalpingography in cases of tubal diverticula. Radiology. 1996; 199 (2): 469-71.	No raw data to calculate sensitivity, specificity, PPV, NPV
Okonofua, F. E., Essen, U. I. and Nimalaraj, T. Hysterosalpingography versus laparoscopy in tubal infertility: comparison based on findings at laparatomy. Int J Gynaecol Obstet. 1989; 28 (2): 143-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Patton, D. L., Askienazy-Elbhar, M., Henry-Suchet, J., Campbell, L. A., Cappuccio, A., Tannous, W., Wang, S. P. and Kuo, C. C. Detection of Chlamydia trachomatis in fallopian tube tissue in women with postinfectious tubal infertility. Am J Obstet Gynecol. 1994; 171 (1): 95-101.	No raw data to calculate sensitivity, specificity, PPV, NPV
Piccioni, M. G., Riganelli, L., Filippi, V., Fuggetta, E., Colagiovanni, V., Imperiale, L., Caccetta, J., Panici, P. B. and Porpora, M. G. Sonohysterosalpingography: Comparison of foam and saline solution. J Clin Ultrasound. 2017; 45 (2): 67-71.	Included in systematic review Alcazar et al., 2020
Qu, E., Zhang, M., Ju, J., Chen, Y., Lin, X., Zhang, X. Is Hysterosalpingo-Contrast Sonography (HyCoSy) Using Sulfur Hexafluoride Microbubbles (SonoVue)	Includes only studies using Sonovue contrast medium

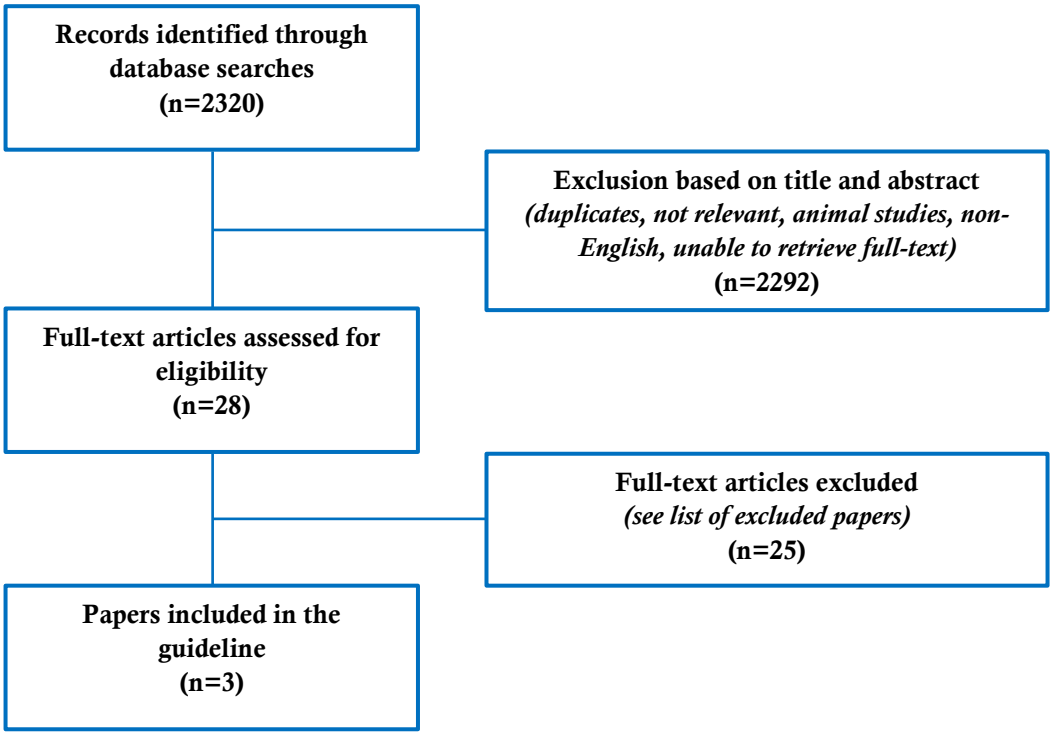
Sufficient for the Assessment of Fallopian Tube Patency? A Systematic Review and Meta-Analysis. J Ultrasound Med 2022; doi 10.1002/jum.15988	
Reis, M. M., Soares, S. R., Cancado, M. L. and Camargos, A. F. Hysterosalpingo contrast sonography (HyCoSy) with SH U 454 (Echovist) for the assessment of tubal patency. Hum Reprod. 1998; 13 (11): 3049-52.	Included in systematic review Alcazar et al., 2020
Reniers, J., Collet, M., Frost, Leclerc, A., Ivanoff, B. and Méheus, A. Chlamydial antibodies and tubal infertility. Int J Epidemiol. 1989; 18 (1): 261-3.	No raw data to calculate sensitivity, specificity, PPV, NPV
Reshef, E., Daniel, W. W., Foster, J. C., Bradley, E. L., Blackwell, R. E. and Younger, J. B. Comparison between 1-hour and 24-hour follow-up radiographs in hysterosalpingography using oil based contrast media. Fertil Steril. 1989; 52 (5): 753-5.	1-hour vs 24-hours follow-up
Rezk, M. and Shawky, M. The safety and acceptability of saline infusion sonography versus hysterosalpingography for evaluation of tubal patency in infertile women. Middle east fertility society journal. 2015; 20 (2): 108-113.	Listed on Retraction Watch with high number of retractions by author(s)
Shibahara, H., Takamizawa, S., Hirano, Y., Ayustawati, Takei, Y., Fujiwara, H., Tamada, S. and Sato, I. Relationships between Chlamydia trachomatis antibody titers and tubal pathology assessed using transvaginal hydrolaparoscopy in infertile women. Am J Reprod Immunol. 2003; 50 (1): 7-12.	All patients CAT positive at baseline.
Siassakos, D., Manley, K., Wardle, P. and Halawa, S. Chlamydia screening or prophylaxis before laparoscopy and dye hydrotubation: no readmissions, no worry, or is that so? Int J STD AIDS. 2007; 18 (12): 861-2.	No raw data to calculate sensitivity, specificity, PPV, NPV
Soliman, A. A., Shaalan, W., Abdel-Dayem, T., Awad, E. E., Elkassar, Y., Lüdders, D., Malik, E. and Sallam, H. N. Power Doppler flow mapping and four-dimensional ultrasound for evaluating tubal patency compared with laparoscopy. Eur J Obstet Gynecol Reprod Biol. 2015; 195 83-7.	No raw data to calculate sensitivity, specificity, PPV, NPV
Strandell, A., Bourne, T., Bergh, C., Granberg, S., Asztely, M. and Thorburn, J. The assessment of endometrial pathology and tubal patency: a comparison between the use of ultrasonography and X-ray hysterosalpingography for the investigation of infertility patients. Ultrasound Obstet Gynecol. 1999; 14 (3): 200-4.	Included in systematic review Broeze et al., 2011
Svenstrup, H. F., Fedder, J., Kristoffersen, S. E., Trolle, B., Birkelund, S. and Christiansen, G. Mycoplasma genitalium, Chlamydia trachomatis, and tubal factor infertility--a prospective study. Fertil Steril. 2008; 90 (3): 513-20.	No raw data to calculate sensitivity, specificity, PPV, NPV
Swart, P., Mol, B. W., van der Veen, F., van Beurden, M., Redekop, W. K. and Bossuyt, P. M. The accuracy of hysterosalpingography in the diagnosis of tubal pathology: a meta-analysis. Fertil Steril. 1995; 64 (3): 486-91.	More recent systematic review available.
Tamási, F., Weidner, A., Domokos, N., Bedros, R. J. and Bagdány, S. ECHOVIST-200 enhanced hystero-sonography: a new technique in the assessment of infertility. Eur J Obstet Gynecol Reprod Biol. 2005; 121 (2): 186-90.	No raw data to calculate sensitivity, specificity, PPV, NPV
Tanawattanacharoen, S., Suwajanakorn, S., Uerpairojkit, B., Boonkasemsanti, W. and Virutamasen, P. Transvaginal hysterosalpingo-contrast sonography (HyCoSy) compared with chromolaparoscopy. J Obstet Gynaecol Res. 2000; 26 (1): 71-5.	Included in systematic review Alcazar et al., 2020
Thejls, H., Gnarpe, J., Lundkvist, O., Heimer, G., Larsson, G. and Victor, A. Diagnosis and prevalence of persistent chlamydia infection in infertile women: tissue culture, direct antigen detection, and serology. Fertil Steril. 1991; 55 (2): 304-10.	Included in systematic review Mol et al., 1995
Thomas, K., Coughlin, L., Mannion, P. T. and Haddad, N. G. The value of Chlamydia trachomatis antibody testing as part of routine infertility investigations. Hum Reprod. 2000; 15 (5): 1079-82.	No raw data to calculate sensitivity, specificity, PPV, NPV
Tjiam, K. H., Zeilmaker, G. H., Alberda, A. T., van Heijst, B. Y., de Roo, J. C., Polak-Vogelzang, A. A., van Joost, T., Stolz, E. and Michel, M. F. Prevalence of antibodies to Chlamydia trachomatis, Neisseria gonorrhoeae, and Mycoplasma hominis in infertile women. Genitourin Med. 1985; 61 (3): 175-8.	Included in systematic review Mol et al., 1995

Tüfekçi, E. C., Girit, S., Bayirli, E., Durmuşoğlu, F. and Yalti, S. Evaluation of tubal patency by transvaginal sonosalpingography. Fertil Steril. 1992; 57 (2): 336-40.	Included in systematic review Alcazar et al., 2020
Van Schoubroeck, D., Van den Bosch, T., Meuleman, C., Tomassetti, C., D'Hooghe, T. and Timmerman, D. The use of a new gel foam for the evaluation of tubal patency. Gynecol Obstet Invest. 2013; 75 (3): 152-6.	Included in systematic review Alcazar et al., 2020
Volpi, E., De Grandis, T., Sismondi, P., Giacardi, M., Rustichelli, S., Patriarca, A. and Bocci, A. Transvaginal salpingo-sonography (TSSG) in the evaluation of tubal patency. Acta Eur Fertil. 1991; 22 (6): 325-8.	No raw data to calculate sensitivity, specificity, PPV, NPV
Wang, J., Li, J., Yu, L., Han, S., Shen, X. and Jia, X. Application of 3D-HyCoSy in the diagnosis of oviduct obstruction. Exp Ther Med. 2017; 13 (3): 966-970.	No raw data to calculate sensitivity, specificity, PPV, NPV
Wang, W., Zhou, Q., Gong, Y., Li, Y., Huang, Y. and Chen, Z. Assessment of Fallopian Tube Fimbria Patency With 4-Dimensional Hysterosalpingo-Contrast Sonography in Infertile Women. J Ultrasound Med. 2017; 36 (10): 2061-2069.	Included in systematic review Alcazar et al., 2020
Woolcott, R., Fisher, S., Thomas, J. and Kable, W. A randomized, prospective, controlled study of laparoscopic dye studies and selective salpingography as diagnostic tests of fallopian tube patency. Fertil Steril. 1999; 72 (5): 879-84.	No raw data to calculate sensitivity, specificity, PPV, NPV

2.5 Uterine factor

PICO Question: Which diagnostic procedures should be performed to confirm a normal uterine structure/anatomy, uterine wall/myometrium?

Flowchart



List of excluded papers

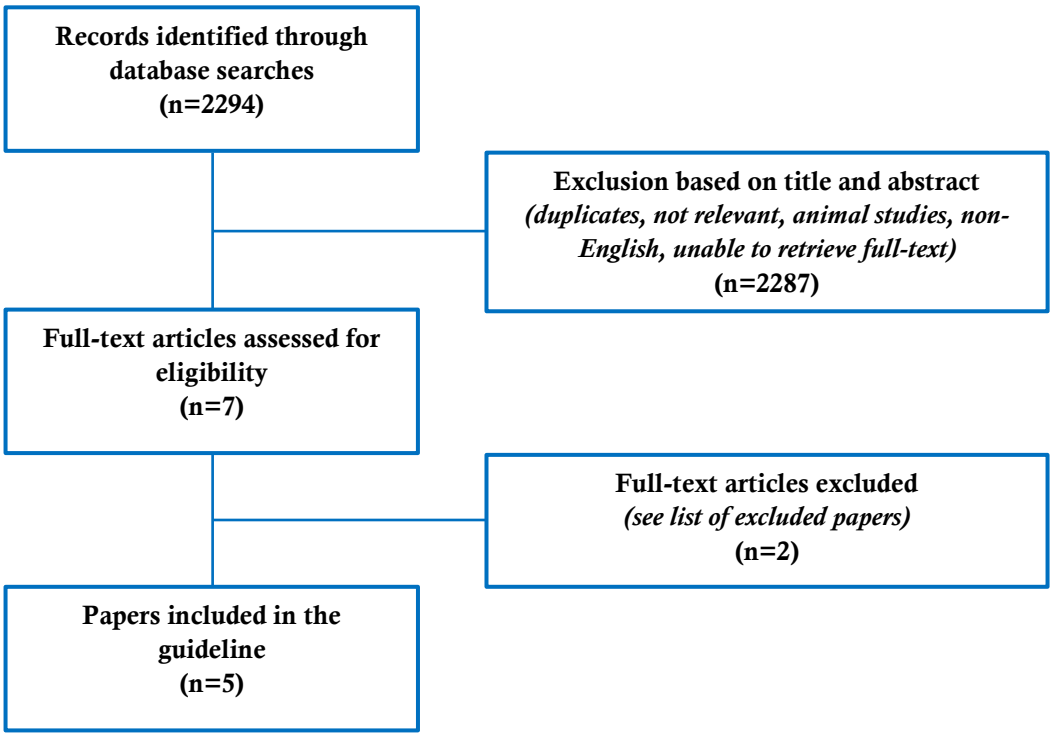
Reference	Exclusion criterion
Aboulghar, M. M., Shoeir, I. K., Momtaz, M., Mohammady, M. E. and Ezzat, H. A comparative study of 2-dimensional sonohysterography versus 3-dimensional sonohysterography in infertile patients with uterine cavity lesions and abnormalities. Middle east fertility society journal. 2011; 16 (1): 67-71.	No comparison between 2D and 3D ultrasound
Apirakviriya, C., Rungruxsirivorn, T., Phupong, V. and Wisawasukmongchol, W. Diagnostic accuracy of 3D-transvaginal ultrasound in detecting uterine cavity abnormalities in infertile patients as compared with hysteroscopy. Eur J Obstet Gynecol Reprod Biol. 2016; 200 24-8.	No comparison between 2D and 3D ultrasound
Armstrong, S. C., Showell, M., Stewart, E. A., Rebar, R. W., Vanderpoel, S. and Farquhar, C. M. Baseline anatomical assessment of the uterus and ovaries in infertile women: a systematic review of the evidence on which assessment methods are the safest and most effective in terms of improving fertility outcomes. Hum Reprod Update. 2017; 23 (5): 533-547.	No comparison between 2D and 3D ultrasound
Bhatt, S., Sumbul, M., Rajpal, R. and Radhakrishnan, G. Value of "Three Dimensional Multidetector CT Hysterosalpingography" in Infertile Patients with Non-Contributory Hysterosalpingography: A Prospective Study. J Reprod Infertil. 2017; 18 (3): 323-332.	No comparison between 2D and 3D ultrasound
Bocca, S. M., Oehninger, S., Stadtmauer, L., Agard, J., Duran, E. H., Sarhan, A., Horton, S. and Abuhamad, A. Z. A study of the cost, accuracy, and benefits of	No comparison between 2D and 3D ultrasound

3-dimensional sonography compared with hysterosalpingography in women with uterine abnormalities. J Ultrasound Med. 2012; 31 (1): 81-5.	
de Souza, N. M., Brosens, J. J., Schwieso, J. E., Paraschos, T. and Winston, R. M. The potential value of magnetic resonance imaging in infertility. Clin Radiol. 1995; 50 (2): 75-9.	No comparison between 2D ultrasound and MRI
El-Sherbiny, W., El-Mazny, A., Abou-Salem, N. and Mostafa, W. S. The diagnostic accuracy of two- vs three-dimensional sonohysterography for evaluation of the uterine cavity in the reproductive age. J Minim Invasive Gynecol. 2015; 22 (1): 127-31.	No comparison between 2D and 3D ultrasound
Grigore, M., Pristavu, A., Iordache, F., Gafitanu, D. and Ursulescu, C. Comparative Study of Hysteroscopy and 3D Ultrasound for Diagnosing Uterine Cavity Abnormalities. Rev Med Chir Soc Med Nat Iasi. 2016; 120 (4): 866-73.	No comparison between 2D and 3D ultrasound
Hamilton, J. A., Larson, A. J., Lower, A. M., Hasnain, S. and Grudzinskas, J. G. Routine use of saline hysterosonography in 500 consecutive, unselected, infertile women. Hum Reprod. 1998; 13 (9): 2463-73.	No comparison between 2D and 3D ultrasound
Inoue, T., Kitajima, M., Taniguchi, K. and Masuzaki, H. Three-dimensional saline-infusion sonohysterography is useful for the identification of endometrial polyp. J Obstet Gynaecol Res. 2016; 42 (7): 855-9.	No comparison between 2D ultrasound and MRI
Kim, M. J., Lee, Y., Lee, C., Chun, S., Kim, A., Kim, H. Y. and Lee, J. Y. Accuracy of three dimensional ultrasound and treatment outcomes of intrauterine adhesion in infertile women. Taiwan J Obstet Gynecol. 2015; 54 (6): 737-41.	No comparison between 2D and 3D ultrasound
Kiyokawa, K., Masuda, H., Fuyuki, T., Koseki, M., Uchida, N., Fukuda, T., Amemiya, K., Shouka, K. and Suzuki, K. Three-dimensional hysterosalpingo-contrast sonography (3D-HyCoSy) as an outpatient procedure to assess infertile women: a pilot study. Ultrasound Obstet Gynecol. 2000; 16 (7): 648-54.	No comparison between 2D and 3D ultrasound
Kupesic, S. and Plavsic, B. M. 2D and 3D hysterosalpingo-contrast-sonography in the assessment of uterine cavity and tubal patency. Eur J Obstet Gynecol Reprod Biol. 2007; 133 (1): 64-9.	No comparison between 2D and 3D ultrasound
Leonhardt, H., Gull, B., Stener-Victorin, E. and Hellström, M. Ovarian volume and antral follicle count assessed by MRI and transvaginal ultrasonography: a methodological study. Acta Radiol. 2014; 55 (2): 248-56.	Only ovarian morphology is assessed
Levaillant, J. M., Pasquier, M. and Massin, N. A novel concept for female infertility exploration: the Fertiliscan©, a dedicated all-in-one 3D ultrasound exploration. J Gynecol Obstet Hum Reprod. 2019; 48 (5): 363-367.	No comparison between 2D and 3D ultrasound
Liu, N. and Ren, Q. Magnetic Resonance Imaging Feature Analysis and Evaluation of Tubal Patency under Convolutional Neural Network in the Diagnosis of Infertility. Contrast Media Mol Imaging. 2021; 2021 5175072.	No comparison between 2D ultrasound and MRI
Ludwin, A., Ludwin, I., Kudla, M., Pitynski, K., Banas, T., Jach, R. and Knafel, A. Diagnostic accuracy of three-dimensional sonohysterography compared with office hysteroscopy and its interrater/intrarater agreement in uterine cavity assessment after hysteroscopic metroplasty. Fertil Steril. 2014; 101 (5): 1392-9.	No comparison between 2D and 3D ultrasound
Maged, A. M., Ramzy, A. M., Ghar, M. A., El Shenoufy, H., Gad Allah, S. H., Wahba, A. H., ElKateb, A. Y. and Hwedi, N. 3D ultrasound assessment of endometrial junctional zone anatomy as a predictor of the outcome of ICSI cycles. Eur J Obstet Gynecol Reprod Biol. 2017; 212 160-165.	No comparison between 2D and 3D ultrasound
Meylaerts, L. J., Wijnen, L., Ombelet, W., Bazot, M. and Vandersteen, M. Uterine junctional zone thickness in infertile women evaluated by MRI. J Magn Reson Imaging. 2017; 45 (3): 926-936.	No comparison between 2D ultrasound and MRI
Ni, J., Han, B., Liang, J. and Wang, F. Three-dimensional 3D ultrasound combined with power Doppler for the differential diagnosis of endometrial lesions among infertile women. Int J Gynaecol Obstet. 2019; 145 (2): 212-218.	No comparison between 2D and 3D ultrasound
Pleş, L., Alexandrescu, C., Ionescu, C. A., Arvătescu, C. A., Vladareanu, S. and Moga, M. A. Three-dimensional scan of the uterine cavity of infertile women	2D and 3D-TVUS were used simultaneously. No

before assisted reproductive technology use. Medicine (Baltimore). 2018; 97 (41): e12764.	comparison between 2D and 3D TVUS
Senoh, D., Tanaka, H., Akiyama, M., Yanagihara, T. and Hata, T. Saline infusion contrast intrauterine sonographic assessment of the endometrium with high-frequency, real-time miniature transducer in normal menstrual cycle: a preliminary report. Hum Reprod. 1999; 14 (10): 2600-3.	No comparison between 2D and 3D ultrasound
Silva, V., Ramos, F. F., Brás, A. F. M., Santos, R. F. S., Xavier, Msdpl and Miguelote, R. F. O. Junctional Zone in Infertile Women: A Three-dimensional Ultrasound Study. Rev Bras Ginecol Obstet. 2020; 42 (3): 152-159.	The interobserver and intraobserver agreements were analyzed (3D TVUS). No comparison between 2D and 3D TVUS
Sylvestre, C., Child, T. J., Tulandi, T. and Tan, S. L. A prospective study to evaluate the efficacy of two- and three-dimensional sonohysterography in women with intrauterine lesions. Fertil Steril. 2003; 79 (5): 1222-5.	No comparison between 2D and 3D ultrasound
Zinther, N. B., Zeuten, A., Marinovskij, E., Haislund, M. and Friis-Andersen, H. Detection of abdominal wall adhesions using visceral slide. Surg Endosc. 2010; 24 (12): 3161-6.	Detection of uterine wall adhesions

PICO QUESTION: WHICH ADDITIONAL DIAGNOSTIC PROCEDURES SHOULD BE PERFORMED TO CONFIRM AN ANATOMICALLY NORMAL UTERINE CAVITY?

Flowchart



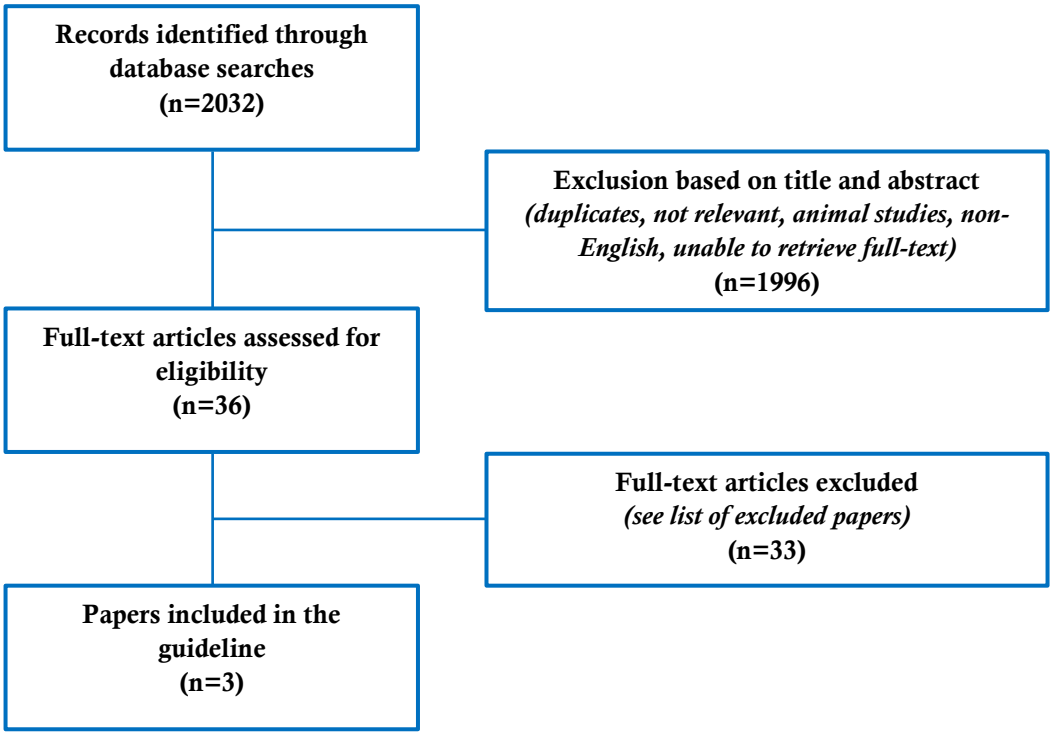
List of excluded papers

Reference	Exclusion criterion
Armstrong, S. C., Showell, M., Stewart, E. A., Rebar, R. W., Vanderpoel, S. and Farquhar, C. M. Baseline anatomical assessment of the uterus and ovaries in infertile women: a systematic review of the evidence on which assessment methods are the safest and most effective in terms of improving fertility outcomes. Hum Reprod Update. 2017; 23 (5): 533-547.	No calculation of accuracy in terms of sensitivity, specificity, PPV, NPV
Kamath, M. S., Bosteels, J., D'Hooghe, T. M., Seshadri, S., Weyers, S., Mol, B. W. J., Broekmans, F. J. and Sunkara, S. K. Screening hysteroscopy in subfertile women and women undergoing assisted reproduction. Cochrane Database Syst Rev. 2019; 4 (4): Cd012856.	No calculation of accuracy in terms of sensitivity, specificity, PPV, NPV

2.6 Laparoscopy

PICO Question: Should women undergo a laparoscopy before being diagnosed with UI?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Badawy, A., Khiary, M., Ragab, A., Hassan, M. and Sherif, L. Laparoscopy--or not--for management of unexplained infertility. J Obstet Gynaecol. 2010; 30 (7): 712-5.	The author has published fraudulent papers (at least 9) and therefore the results of this study can not be taken as reliable
Bonneau, C., Chanelles, O., Sifer, C. and Poncelet, C. Use of laparoscopy in unexplained infertility. Eur J Obstet Gynecol Reprod Biol. 2012; 163 (1): 57-61.	although bilateral tubal patency was an inclusion criterium, 67 % of the patients had a subnormal HSG, including bilateral abnormalities.
Brosens, I., Gordts, S. and Campo, R. Transvaginal hydrolaparoscopy but not standard laparoscopy reveals subtle endometriotic adhesions of the ovary. Fertil Steril. 2001; 75 (5): 1009-12.	compares THL with DL
Campo, R., Gordts, S., Rombauts, L. and Brosens, I. Diagnostic accuracy of transvaginal hydrolaparoscopy in infertility. Fertil Steril. 1999; 71 (6): 1157-60.	compares THL with DL
Casa, A., Sesti, F., Marziali, M. and Piccione, E. Transvaginal hydrolaparoscopy vs. conventional laparoscopy for evaluating unexplained primary infertility in women. J Reprod Med. 2002; 47 (8): 617-20.	compares THL with DL

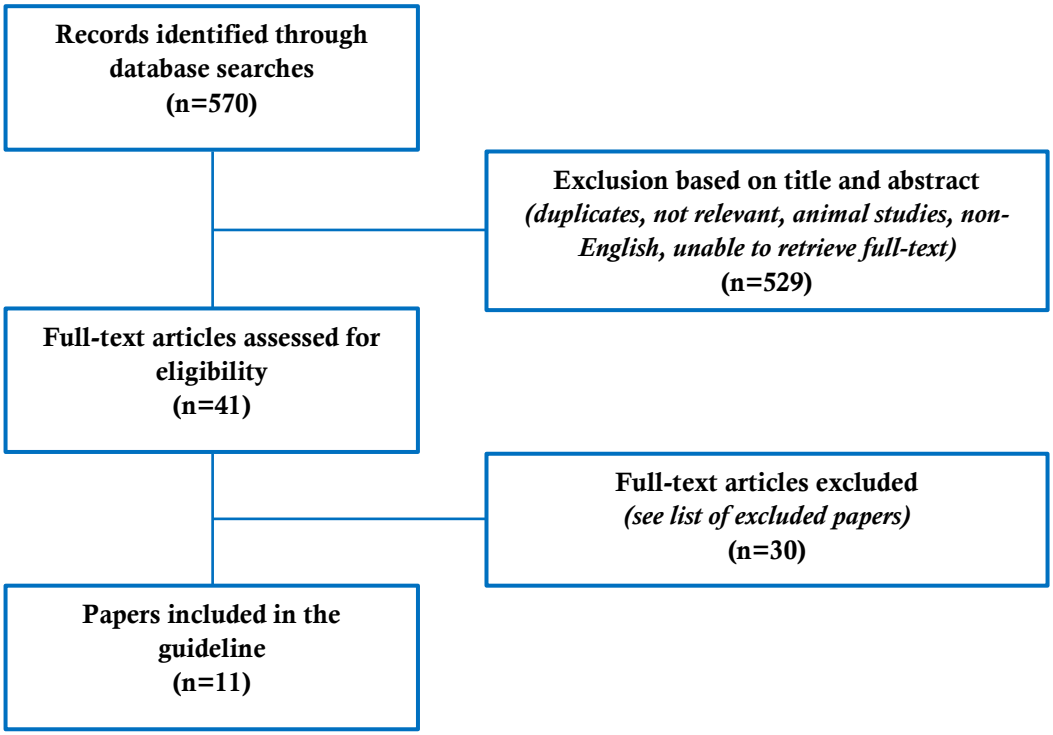
Corson, S. L., Cheng, A. and Gutmann, J. N. Laparoscopy in the "normal" infertile patient: a question revisited. J Am Assoc Gynecol Laparosc. 2000; 7 (3): 317-24.	No controls, publication-, attrition- and selectionbias. Confounding factors and a very small studygroup with no comparison.
Darai, E., Dessolle, L., Lecuru, F. and Soriano, D. Transvaginal hydrolaparoscopy compared with laparoscopy for the evaluation of infertile women: a prospective comparative blind study. Hum Reprod. 2000; 15 (11): 2379-82.	compares THL with DL
Dechaud, H., Ali Ahmed, S. A., Aligier, N., Vergnes, C. and Hedon, B. Does transvaginal hydrolaparoscopy render standard diagnostic laparoscopy obsolete for unexplained infertility investigation? Eur J Obstet Gynecol Reprod Biol. 2001; 94 (1): 97-102.	compares THL with DL
Dunphy, B. C. and Greene, C. A. Falloposcopic cannulation, oviductal appearances and prediction of treatment independent intrauterine pregnancy. Hum Reprod. 1995; 10 (12): 3313-6.	Not only patients with UI
Hauge, K., Flo, K., Riedhart, M. and Granberg, S. Can ultrasound-based investigations replace laparoscopy and hysteroscopy in infertility? Eur J Obstet Gynecol Reprod Biol. 2000; 92 (1): 167-70.	compares HyCoSy to DL
Hovav, Y., Hornstein, E., Almagor, M. and Yaffe, C. Diagnostic laparoscopy in primary and secondary infertility. J Assist Reprod Genet. 1998; 15 (9): 535-7.	compares patients with primary and secondary infertility
Ikechebelu, J. I. and Mbamara, S. U. Should laparoscopy and dye test be a first line evaluation for infertile women in southeast Nigeria? Niger J Med. 2011; 20 (4): 462-5.	Concerns routine DL in infertile women, not only those with normal findings on examination, standard work-up including ultrasound and HSG
Jayakrishnan, K., Koshy, A. K. and Raju, R. Role of laparohysteroscopy in women with normal pelvic imaging and failed ovulation stimulation with intrauterine insemination. J Hum Reprod Sci. 2010; 3 (1): 20-4.	Retrospective cohort after 3 x failed IUI. Selection of patients in whom no abnormalities were found in the work-up. However no mention of tubal patency tests
Kahyaoglu, S., Kahyaoglu, I., Yilmaz, B., Var, T., Ertas, I. E., Mollamahmutoglu, L. and Batioglu, S. Should diagnostic laparoscopy be performed initially or not, during infertility management of primary and secondary infertile women? A cross-sectional study. J Obstet Gynaecol Res. 2009; 35 (1): 139-44.	inclusion of patients with unexplained infertility, however it is not clearly stated that only patients with patient tubes on HSG were included. Table 2 suggests not , because 35 % had an abnormal HSG.
Komori, S., Fukuda, Y., Horiuchi, I., Tanaka, H., Kasumi, H., Shigeta, M., Tuji, Y. and Koyama, K. Diagnostic laparoscopy in infertility: a retrospective study. J Laparoendosc Adv Surg Tech A. 2003; 13 (3): 147-51.	Retrospective study including other causes than UI.
Mahran, A., Abdelraheim, A. R., Eissa, A. and Gadelrab, M. Does laparoscopy still has a role in modern fertility practice? Int J Reprod Biomed. 2017; 15 (12): 787-794.	Mixed population, not only UI
Milingos, S., Protopapas, A., Kallipolitis, G., Drakakis, P., Makrigiannakis, A., Liapi, A., Milingos, D., Antsaklis, A. and Michalas, S. Laparoscopic evaluation of infertile patients with chronic pelvic pain. Reprod Biomed Online. 2006; 12 (3): 347-53.	Cohort of patients with infertility and chronic pelvic pain
Moayeri, S. E., Lee, H. C., Lathi, R. B., Westphal, L. M., Milki, A. A. and Garber, A. M. Laparoscopy in women with unexplained infertility: a cost-effectiveness analysis. Fertil Steril. 2009; 92 (2): 471-80.	Does not involve only patients with UI

Nakagawa, K., Ohgi, S., Horikawa, T., Kojima, R., Ito, M. and Saito, H. Laparoscopy should be strongly considered for women with unexplained infertility. J Obstet Gynaecol Res. 2007; 33 (5): 665-70.	Cohort of patients with initially UI who underwent DL and subsequently ART (IVF), not natural conception, were analyzed. Only patients < 35 years old.
Nawroth, F., Foth, D., Schmidt, T. and Römer, T. Results of a prospective comparative study of transvaginal hydrolaparoscopy and chromolaparoscopy in the diagnostics of infertility. Gynecol Obstet Invest. 2001; 52 (3): 184-8.	compares THL with DL
Pantou, A., Simopoulou, M., Sfakianoudis, K., Giannelou, P., Rapani, A., Maziotis, E., Grigoriadis, S., Tsioulou, P., Syrkos, S., Souretis, K., Koutsilieris, M. and Pantos, K. The Role of Laparoscopic Investigation in Enabling Natural Conception and Avoiding in vitro Fertilization Overuse for Infertile Patients of Unidentified Aetiology and Recurrent Implantation Failure Following in vitro Fertilization. J Clin Med. 2019; 8 (4):	Not only patients with UI, also after failed IVF
Park, H., Ramirez, D., Noble, L., Saldivar, J. S. and Mulla, Z. Use of Laparoscopy in Unexplained Infertility in Historically Underserved Area. J Minim Invasive Gynecol. 2015; 22 (6s): S233-s234.	Cohort of patients with UI who underwent DL and treatment of endometriosis , pelvic adhesions and/or Tubal sides (90/100) and pregnancy outcome. No controls. Abstract only
Rapkin, A. J. Adhesions and pelvic pain: a retrospective study. Obstet Gynecol. 1986; 68 (1): 13-5.	Included patients with chronic pelvic pain and patients with infertility, not necessarily UI

2.7 Cervical/ vaginal factor

PICO Question: What is the need for female lower genital tract investigations?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Babu, G., Singaravelu, B. G., Srikumar, R., Reddy, S. V. and Kokan, A. Comparative Study on the Vaginal Flora and Incidence of Asymptomatic Vaginosis among Healthy Women and in Women with Infertility Problems of Reproductive Age. J Clin Diagn Res. 2017; 11 (8): Dc18-dc22.	Not specifically unexplained infertility
Bernabeu, A., Lledo, B., Díaz, M. C., Lozano, F. M., Ruiz, V., Fuentes, A., Lopez-Pineda, A., Moliner, B., Castillo, J. C., Ortiz, J. A., Ten, J., Llacer, J., Carratala-Munuera, C., Orozco-Beltran, D., Quesada, J. A. and Bernabeu, R. Effect of the vaginal microbiome on the pregnancy rate in women receiving assisted reproductive treatment. J Assist Reprod Genet. 2019; 36 (10): 2111-2119.	women with infertility diagnosis, no stratification of infertility
Bracewell-Milnes, T., Saso, S., Nikolaou, D., Norman-Taylor, J., Johnson, M. and Thum, M. Y. Investigating the effect of an abnormal cervico-vaginal and endometrial microbiome on assisted reproductive technologies: A systematic review. Am J Reprod Immunol. 2018; 80 (5): e13037.	systematic review without meta-analysis
Brandão, P. and Gonçalves-Henriques, M. The Impact of Female Genital Microbiota on Fertility and Assisted Reproductive Treatments. J Family Reprod Health. 2020; 14 (3): 131-149.	systematic review without meta-analysis
Bush, M. R., Walmer, D. K., Couchman, G. M. and Haney, A. F. Evaluation of the postcoital test in cycles involving exogenous gonadotropins. Obstet Gynecol. 1997; 89 (5 Pt 1): 780-4.	no seperate analysis of data by cause of infertility

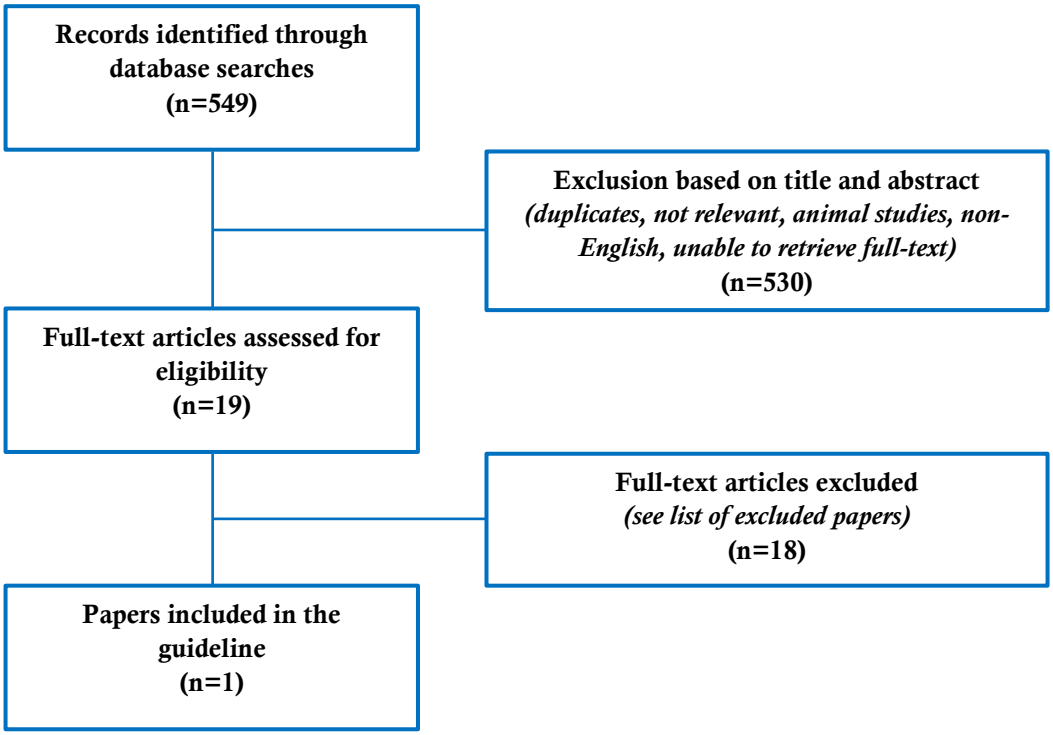
Chen, C., Song, X., Wei, W., Zhong, H., Dai, J., Lan, Z., Li, F., Yu, X., Feng, Q., Wang, Z., Xie, H., Chen, X., Zeng, C., Wen, B., Zeng, L., Du, H., Tang, H., Xu, C., Xia, Y., Xia, H., Yang, H., Wang, J., Wang, J., Madsen, L., Brix, S., Kristiansen, K., Xu, X., Li, J., Wu, R. and Jia, H. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat Commun. 2017; 8 (1): 875.	samples of vagina, cervical canal, uterus, fallopian tubes and peritoneal fluid were included in the study
Collins, J. A., So, Y., Wilson, E. H., Wrixon, W. and Casper, R. F. The postcoital test as a predictor of pregnancy among 355 infertile couples. Fertil Steril. 1984; 41 (5): 703-8.	included in systematic review by Oei et al., 1995
Daru, J., Williamson, H. O., Rust, P. F., Homm, R. J. and Mathur, S. A computerized postcoital test sperm motility: comparison with clinical postcoital test and correlations with sperm antibodies. Arch Androl. 1988; 21 (3): 189-203.	PCT vs. computerized PCT
Dunphy, B. C., Barratt, C. L., Kay, R., Jones, D. E. and Cooke, I. D. Postcoital test: which form of spermatozoal motility is associated with a good fertility outcome? Andrologia. 1990; 22 (3): 269-73.	Reproducibility: all conceptions were treatment independent
Eggert-Kruse, W., Gerhard, I., Tilgen, W. and Runnebaum, B. Clinical significance of crossed in vitro sperm-cervical mucus penetration test in infertility investigation. Fertil Steril. 1989; 52 (6): 1032-40.	in vitro testing of sperm ability to penetrate cervical mucus (CM) vs. PCT parameter, as a parameter of sperm function
Eimers, J. M., te Velde, E. R., Gerritse, R., van Kooy, R. J., Kremer, J. and Habbema, J. D. The validity of the postcoital test for estimating the probability of conceiving. Am J Obstet Gynecol. 1994; 171 (1): 65-70.	excluded from systematic review by Oei et al., 1995 because pregnancy rates could not be calculated for women with normal and abnormal PCT seperately.
Haahr, T., Humaidan, P., Elbaek, H. O., Alsbjerg, B., Laursen, R. J., Rygaard, K., Johannesen, T. B., Andersen, P. S., Ng, K. L. and Jensen, J. S. Vaginal Microbiota and In Vitro Fertilization Outcomes: Development of a Simple Diagnostic Tool to Predict Patients at Risk of a Poor Reproductive Outcome. J Infect Dis. 2019; 219 (11): 1809-1817.	Not specifically unexplained infertility
Haahr, T., Zacho, J., Bräuner, M., Shathmigha, K., Skov Jensen, J. and Humaidan, P. Reproductive outcome of patients undergoing in vitro fertilisation treatment and diagnosed with bacterial vaginosis or abnormal vaginal microbiota: a systematic PRISMA review and meta-analysis. Bjog. 2019; 126 (2): 200-207.	Not specifically unexplained infertility
Harrison, R. F. The diagnostic and therapeutic potential of the postcoital test. Fertil Steril. 1981; 36 (1): 71-5.	included in systematic review by Oei et al., 1995
Hong, X., Ma, J., Yin, J., Fang, S., Geng, J., Zhao, H., Zhu, M., Ye, M., Zhu, X., Xuan, Y. and Wang, B. The association between vaginal microbiota and female infertility: a systematic review and meta-analysis. Arch Gynecol Obstet. 2020; 302 (3): 569-578.	Not specifically unexplained infertility
Hyman, R. W., Herndon, C. N., Jiang, H., Palm, C., Fukushima, M., Bernstein, D., Vo, K. C., Zelenko, Z., Davis, R. W. and Giudice, L. C. The dynamics of the vaginal microbiome during infertility therapy with in vitro fertilization-embryo transfer. J Assist Reprod Genet. 2012; 29 (2): 105-15.	Not specifically unexplained infertility
Kim, S. M., Won, K. H., Hong, Y. H., Kim, S. K., Lee, J. R., Jee, B. C., Suh, C. S. Microbiology of Human Follicular Fluid and the Vagina and Its Impact on in Vitro Fertilization Outcomes. Yonsei Med J. 2022; 63(10): 941-47	Results not stratified according to infertility diagnosis.
Koedooder, R., Singer, M., Schoenmakers, S., Savelkoul, P. H. M., Morré, S. A., de Jonge, J. D., Poort, L., Cuypers, Wjss, Beckers, N. G. M., Broekmans, F. J. M., Cohlen, B. J., den Hartog, J. E., Fleischer, K., Lambalk, C. B., Smeenk, Jmjs, Budding, A. E. and Laven, J. S. E. The vaginal microbiome as a predictor for outcome of in vitro fertilization with or without intracytoplasmic sperm injection: a prospective study. Hum Reprod. 2019; 34 (6): 1042-1054.	Not specifically unexplained infertility

Kong, Y., Liu, Z., Shang, Q., Gao, Y., Li, X., Zheng, C., Deng, X. and Chen, T. The Disordered Vaginal Microbiota Is a Potential Indicator for a Higher Failure of in vitro Fertilization. Front Med (Lausanne). 2020; 7 217.	Not specifically unexplained infertility
Kyono, K., Hashimoto, T., Nagai, Y. and Sakuraba, Y. Analysis of endometrial microbiota by 16S ribosomal RNA gene sequencing among infertile patients: a single-center pilot study. Reprod Med Biol. 2018; 17 (3): 297-306.	Not specifically unexplained infertility
Liversedge, N. H., Turner, A., Horner, P. J., Keay, S. D., Jenkins, J. M. and Hull, M. G. The influence of bacterial vaginosis on in-vitro fertilization and embryo implantation during assisted reproduction treatment. Hum Reprod. 1999; 14 (9): 2411-5.	Not specifically unexplained infertility
Lokken, E. M., Manhart, L. E., Kinuthia, J., Hughes, J. P., Jisuvei, C., Mwinyikai, K., Muller, C. H., Mandaliya, K., Jaoko, W. and McClelland, R. S. Association between bacterial vaginosis and fecundability in Kenyan women planning pregnancies: a prospective preconception cohort study. Hum Reprod. 2021;	non-infertility population
Matson, P. L., Tuvik, A. I., O'Halloran, F. and Yovich, J. L. The value of the postcoital test in predicting the fertilization of human oocytes. J In Vitro Fert Embryo Transf. 1986; 3 (2): 110-3.	Comparison between the fertilization rates of oocytes and the results of the PCT
Miron, N. D., Socolov, D., Mareş, M., Anton, G., Nastasa, V., Moraru, R. F., Virág, K., Anghelache-Lupaşcu, I. and Deák, J. Bacteriological agents which play a role in the development of infertility. Acta Microbiol Immunol Hung. 2013; 60 (1): 41-53.	Prevalence study
Ricci, S., De Giorgi, S., Lazzeri, E., Luddi, A., Rossi, S., Piomboni, P., De Leo, V. and Pozzi, G. Impact of asymptomatic genital tract infections on in vitro Fertilization (IVF) outcome. PLoS One. 2018; 13 (11): e0207684.	Not specifically unexplained infertility
Riganelli, L., Iebba, V., Piccioni, M., Illuminati, I., Bonfiglio, G., Neroni, B., Calvo, L., Gagliardi, A., Levrero, M., Merlino, L., Mariani, M., Capri, O., Pietrangeli, D., Schippa, S. and Guerrieri, F. Structural Variations of Vaginal and Endometrial Microbiota: Hints on Female Infertility. Front Cell Infect Microbiol. 2020; 10 350.	Not specifically unexplained infertility
Sabour, S., Arzanlou, M., Vaez, H., Rahimi, G., Sahebkar, A. and Khademi, F. Prevalence of bacterial vaginosis in pregnant and non-pregnant Iranian women: a systematic review and meta-analysis. Arch Gynecol Obstet. 2018; 297 (5): 1101-1113.	comparing BV in pregnant vs non-pregnant women, no stratification according to MAR or non-MAR or cause of infertility (not UI)
Steures, P., van der Steeg, J. W., Hompes, P. G., Bossuyt, P. M., Habbema, J. D., Eijkemans, M. J., Koks, C. A., Boudrez, P., van der Veen, F. and Mol, B. W. The additional value of ovarian hyperstimulation in intrauterine insemination for couples with an abnormal postcoital test and a poor prognosis: a randomized clinical trial. Fertil Steril. 2007; 88 (6): 1618-24.	subfertile couples with an abnormal postcoital test and a poor prognosis, were randomly allocated to three cycles of IUI with COH or three cycles of IUI without COH.
van Oostrum, N., De Sutter, P., Meys, J. and Verstraelen, H. Risks associated with bacterial vaginosis in infertility patients: a systematic review and meta-analysis. Hum Reprod. 2013; 28 (7): 1809-15.	Not specifically unexplained infertility
Wee, B. A., Thomas, M., Sweeney, E. L., Frentiu, F. D., Samios, M., Ravel, J., Gajer, P., Myers, G., Timms, P., Allan, J. A. and Huston, W. M. A retrospective pilot study to determine whether the reproductive tract microbiota differs between women with a history of infertility and fertile women. Aust N Z J Obstet Gynaecol. 2018; 58 (3): 341-348.	Not specifically unexplained infertility

2.8 Male genito-urinary anatomy

PICO Question: Should men undergo additional diagnostic procedures to confirm normal genito-urinary anatomy before being diagnosed with UI?

Flowchart



List of excluded papers

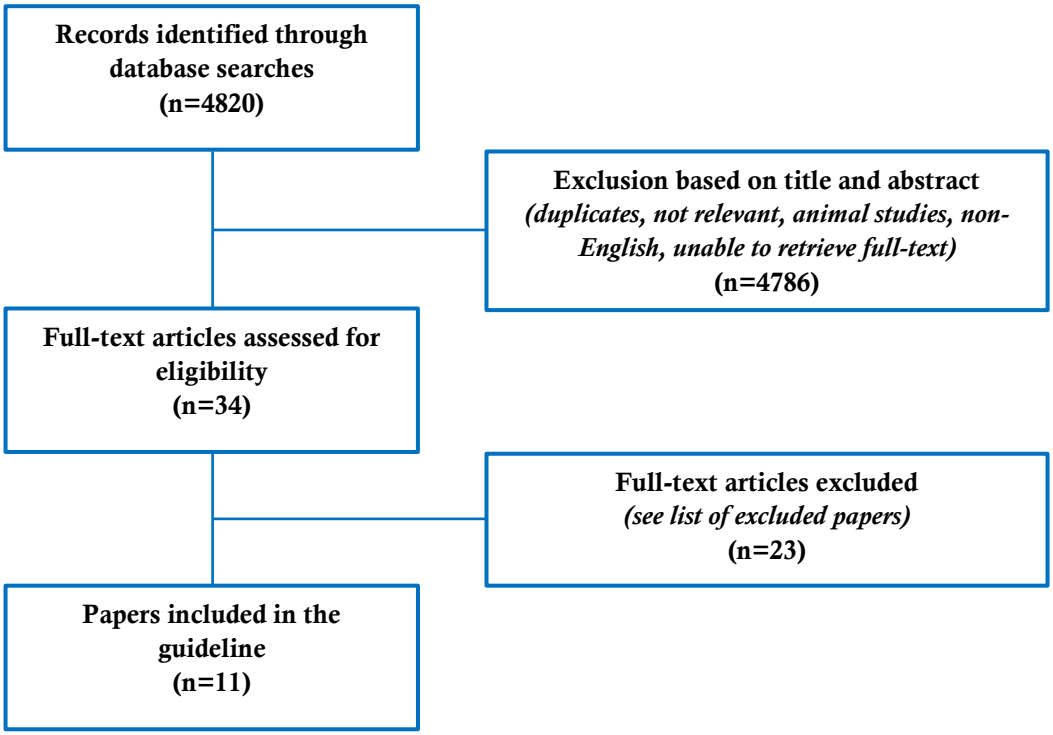
Reference	Exclusion criterion
Abdelwahab, K., Eliwa, A. M., Seleem, M. M., El Galaly, H., Ragab, A., Desoky, E. A., Naguib, M., Ali, M. M., Saber, S. and Kamel, H. Role of Preoperative Testicular Shear Wave Elastography in Predicting Improvement of Semen Parameters After Varicocelectomy for Male Patients With Primary Infertility. Urology. 2017; 107 103-106.	Patients with clinically detectable varicocele and abnormal pre-operative semen parameters
Chen, S. S., Huang, W. J., Chang, L. S. and Wei, Y. H. 8-hydroxy-2'-deoxyguanosine in leukocyte DNA of spermatic vein as a biomarker of oxidative stress in patients with varicocele. J Urol. 2004; 172 (4 Pt 1): 1418-21.	Predictive value of Doppler ultrasound to detect varicocele
Cocuzza, M. S., Tiseo, B. C., Srougi, V., Wood, G. J. A., Cardoso, Jpgf, Esteves, S. C. and Srougi, M. Diagnostic accuracy of physical examination compared with color Doppler ultrasound in the determination of varicocele diagnosis and grading: Impact of urologists' experience. Andrology. 2020; 8 (5): 1160-1166.	Predictive value of Doppler ultrasound to detect varicocele
D'Andrea, S., Barbonetti, A., Castellini, C., Martorella, A., Minaldi, E., Viktor Giordano, A., Carducci, S., Necozione, S., Francavilla, F. and Francavilla, S. Reproductive hormones and sperm parameters after varicocele repair: An observational study. Andrologia. 2018; 50 (10): e13118.	Varicocele, abnormal semen analysis
D'Andrea, S., Barbonetti, A., Castellini, C., Nolletti, L., Martorella, A., Minaldi, E., Giordano, A. V., Carducci, S., Necozione, S., Francavilla, F. and Francavilla, S. Left spermatic vein reflux after varicocele repair predicts pregnancies and live births in subfertile couples. J Endocrinol Invest. 2019; 42 (10): 1215-1221.	Varicocele, abnormal semen analysis

D'Andrea, S., Micillo, A., Barbonetti, A., Giordano, A. V., Carducci, S., Mancini, A., Necozione, S., Francavilla, F. and Francavilla, S. Determination of spermatic vein reflux after varicocele repair helps to define the efficacy of treatment in improving sperm parameters of subfertile men. J Endocrinol Invest. 2017; 40 (10): 1145-1153.	Varicocele, abnormal semen analysis
Erdoğan, H., Durmaz, M. S., Özbakır, B., Cebeci, H., Özkan, D. and Gökmen, İE. Experience of using shear wave elastography in evaluation of testicular stiffness in cases of male infertility. Journal of ultrasound. 2020; 23 (4): 529-534.	No semen parameters provided but seems that infertile men included in the study have at least some abnormal parameters
Eskew, L. A., Watson, N. E., Wolfman, N., Bechtold, R., Scharling, E. and Jarow, J. P. Ultrasonographic diagnosis of varicoceles. Fertil Steril. 1993; 60 (4): 693-7.	Predictive value of Doppler ultrasound to detect varicocele
Gomaa MD, Motawaa MA, Al-Nashar AM, El-Sakka AI. Impact of Subinguinal Varicocelectomy on Serum Testosterone to Estradiol Ratio in Male Patients With Infertility. Urology. 2018 Jul;117:70-77.	Study and control groups are not comparable (varicocele with/without surgical removal vs fertile men)
Hussein, A. F. The role of color Doppler ultrasound in prediction of the outcome of microsurgical subinguinal varicocelectomy. J Urol. 2006; 176 (5): 2141-5.	Varicocele, abnormal semen analysis
Lenz, S., Thomsen, J. K., Giwercman, A., Hertel, N. T., Hertz, J. and Skakkebaek, N. E. Ultrasonic texture and volume of testicles in infertile men. Human reproduction (Oxford, England). 1994; 9 (5): 878-881.	Varicocele, abnormal semen analysis
Lund, L. and Nielsen, A. H. Color Doppler sonography in the assessment of varicocele testis. Scand J Urol Nephrol. 1994; 28 (3): 281-5.	Predictive value of Doppler ultrasound to detect varicocele
Nieschlag, E., Hertle, L., Fischedick, A. and Behre, H. M. Treatment of varicocele: counselling as effective as occlusion of the vena spermatica. Human reproduction (Oxford, England). 1995; 10 (2): 347-353.	Left sided varicocele, abnormal semen analysis
Ortapamuk, H., Tekdogan, U. Y., Naldoken, S., Bulut, S. and Atan, A. Hemodynamic evaluation of varicocele: the role of scrotal scintigraphy and Doppler ultrasonography in the prediction of postoperative seminal improvement. Ann Nucl Med. 2005; 19 (7): 529-34.	Left sided varicocele and abnormal pre-operative semen parameters
Pezzella, A., Barbonetti, A., Micillo, A., D'Andrea, S., Necozione, S., Gandini, L., Lenzi, A., Francavilla, F. and Francavilla, S. Ultrasonographic determination of caput epididymis diameter is strongly predictive of obstruction in the genital tract in azoospermic men with normal serum FSH. Andrology. 2013; 1 (1): 133-8.	Patient population of interest is only a subgroup and the focus of predictive value of the intervention was not on that subgroup
Preutthipan, S. and Nicholas, O. A. Comparative study between scrotal physical examination and scrotal ultrasonography in the detection of varicocele in men with infertility. J Med Assoc Thai. 1995; 78 (3): 135-9.	Varicocele, abnormal semen analysis
Rodriguez Peña, M., Alescio, L., Russell, A., Lourenco da Cunha, J., Alzu, G. and Bardoneschi, E. Predictors of improved seminal parameters and fertility after varicocele repair in young adults. Andrologia. 2009; 41 (5): 277-81.	Varicocoele and semen parameters reported inadequately
Teixeira, T. A., Pariz, J. R., Dutra, R. T., Saldiva, P. H., Costa, E. and Hallak, J. Cut-off values of the Johnsen score and Copenhagen index as histopathological prognostic factors for postoperative semen quality in selected infertile patients undergoing microsurgical correction of bilateral subclinical varicocele. Transl Androl Urol. 2019; 8 (4): 346-355.	Patients who underwent microsurgical correction of subclinical bilateral varicocele; no data on semen parameters though methods state it was performed

2.9 Male additional tests

PICO Question: Is there added value of additional tests in the male with normal WHO semen analysis?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Bibi, R., Jahan, S., Razak, S., Hammadeh, M. E., Almajwal, A. and Amor, H. Protamines and DNA integrity as a biomarkers of sperm quality and assisted conception outcome. Andrologia. 2022; e14418.	Clinical outcomes calculated on pooled data from all patient groups
Bungum, M., Humaidan, P., Axmon, A., Spano, M., Bungum, L., Erenpreiss, J. and Giwercman, A. Sperm DNA integrity assessment in prediction of assisted reproduction technology outcome. Hum Reprod. 2007; 22 (1): 174-9.	Includes patients with mild male factor without stratification of results
Collins, J. A., Barnhart, K. T. and Schlegel, P. N. Do sperm DNA integrity tests predict pregnancy with in vitro fertilization? Fertil Steril. 2008; 89 (4): 823-31.	More recent systematic review available
Cui, D., Han, G., Shang, Y., Liu, C., Xia, L., Li, L. and Yi, S. Antisperm antibodies in infertile men and their effect on semen parameters: a systematic review and meta-analysis. Clin Chim Acta. 2015; 444 29-36.	At least half of the studies includes men with abnormal semen parameters.
Culligan, P. J., Crane, M. M., Boone, W. R., Allen, T. C., Price, T. M. and Blauer, K. L. Validity and cost-effectiveness of antisperm antibody testing before in vitro fertilization. Fertil Steril. 1998; 69 (5): 894-8.	Only fertilisation rates reported, no pregnancy outcomes
Depuydt, C., Donders, G., Verstraete, L., Beert, J., Salembier, G., Bosmans, E., Dhont, N., Kerkhofs, C. and Ombelet, W. Negative Impact of Elevated DNA Fragmentation and Human Papillomavirus (HPV) Presence in Sperm on the Outcome of Intra-Uterine Insemination (IUI). J Clin Med. 2021; 10 (4):	Includes patients with mild male factor without stratification of results

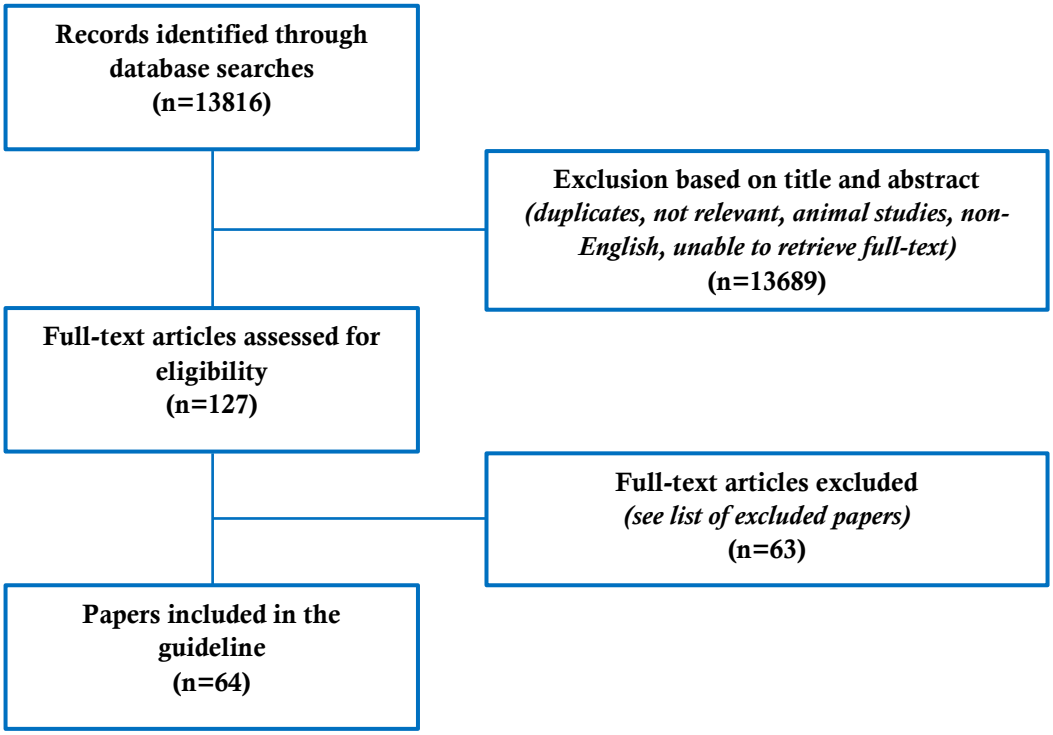
Ford, W. C., Williams, K. M., McLaughlin, E. A., Harrison, S., Ray, B. and Hull, M. G. The indirect immunobead test for seminal antisperm antibodies and fertilization rates at in-vitro fertilization. Hum Reprod. 1996; 11 (7): 1418-22.	Only fertilisation rates reported, no pregnancy outcomes
Garcia, P. C., Rubio, E. M. and Pereira, O. C. M. Antisperm antibodies in infertile men and their correlation with seminal parameters. Reprod Med Biol. 2007; 6 (1): 33-38.	No reproductive outcomes reported.
Henkel, R., Morris, A., Vogiatzi, P., Saleh, R., Sallam, H., Boitrelle, F., Garrido, N., Arafa, M., Gül, M., Rambhatla, A., Maldonado Rosas, I., Agarwal, A., Leisegang, K., Siebert, T. I. Predictive value of seminal oxidation-reduction potential analysis for reproductive outcomes of ICSI. Reprod Biomed Online 2022	No stratification of results according to infertility diagnosis
Jaworek, H., Koudelakova, V., Oborna, I., Zborilova, B., Brezinova, J., Ruzickova, D., Vrbkova, J., Kourilova, P. and Hajduch, M. Impact of human papillomavirus infection on semen parameters and reproductive outcomes. Reprod Biol Endocrinol. 2021; 19 (1): 156.	Includes patients with mild male factor without stratification of results
Junk, S. M., Matson, P. L., Yovich, J. M., Bootsma, B. and Yovich, J. L. The fertilization of human oocytes by spermatozoa from men with antispermatozoal antibodies in semen. J In Vitro Fert Embryo Transf. 1986; 3 (6): 350-2.	Only fertilisation rates reported, no pregnancy outcomes
Malić Vončina, S., Golob, B., Ihan, A., Kopitar, A. N., Kolbezen, M. and Zorn, B. Sperm DNA fragmentation and mitochondrial membrane potential combined are better for predicting natural conception than standard sperm parameters. Fertil Steril. 2016; 105 (3): 637-644.e1.	Included male in the study cohort with abnormal semen parameters.
Moreno-Sepulveda, J. and Rajmil, O. Seminal human papillomavirus infection and reproduction: a systematic review and meta-analysis. Andrology. 2021; 9 (2): 478-502.	Includes studies with males with abnormal sperm parameters.
Nicopoullos, J., Vicens-Morton, A., Lewis, S. E. M., Lee, K., Larsen, P., Ramsay, J., Yap, T. and Minhas, S. Novel use of COMET parameters of sperm DNA damage may increase its utility to diagnose male infertility and predict live births following both IVF and ICSI. Hum Reprod. 2019; 34 (10): 1915-1923.	1 year of regular unprotected intercourse without pregnancy and no genetic abnormalities leading to male infertility other than anomalies in semen parameters
Osman, A., Alsomait, H., Seshadri, S., El-Toukhy, T. and Khalaf, Y. The effect of sperm DNA fragmentation on live birth rate after IVF or ICSI: a systematic review and meta-analysis. Reprod Biomed Online. 2015; 30 (2): 120-7.	Includes studies with abnormal sperm parameters without stratification of results
Rex, A. S., Wu, C., Aagaard, J. and Fedder, J. DNA Fragmentation in Human Spermatozoa and Pregnancy Rates after Intrauterine Insemination. Should the DFI Threshold Be Lowered? J Clin Med. 2021; 10 (6):	Includes patients with mild male factor without stratification of results
Ribas-Maynou, J., Yeste, M., Becerra-Tomás, N., Aston, K. I., James, E. R. and Salas-Huetos, A. Clinical implications of sperm DNA damage in IVF and ICSI: updated systematic review and meta-analysis. Biol Rev Camb Philos Soc. 2021; 96 (4): 1284-1300.	Includes patients with mild male factor without stratification of results
Rossato, M., Galeazzi, C., Ferigo, M., Foresta, C. Antisperm antibodies modify plasma membrane functional integrity and inhibit osmosensitive calcium influx in human sperm. Hum Reprod. 2004; 19(8): 1816-20.	No reproductive outcomes reported.
Sugihara, A., Van Avermaete, F., Roelant, E., Punjabi, U. and De Neubourg, D. The role of sperm DNA fragmentation testing in predicting intra-uterine insemination outcome: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020; 244 8-15.	Includes studies with abnormal sperm parameters without stratification of results
Verheyen, G., Tournaye, H., Laurier, K., Devroey, P. and Van Steirteghem, A. Auto-controlled study on in-vitro fertilization performance with 'antibody-free' spermatozoa selected by immunobead adsorption from semen of patients with anti-sperm antibodies. Hum Reprod. 1994; 9 (6): 1119-26.	Study and control interventions are mixed in the outcomes

Vujisić, S., Lepej, S. Z., Jerković, L., Emedi, I. and Sokolić, B. Antisperm antibodies in semen, sera and follicular fluids of infertile patients: relation to reproductive outcome after in vitro fertilization. Am J Reprod Immunol. 2005; 54 (1): 13-20.	Included male in the study cohort with abnormal semen parameters.
Weinberg, M., Sar-Shalom Nahshon, C., Feferkorn, I. and Bornstein, J. Evaluation of human papilloma virus in semen as a risk factor for low sperm quality and poor in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil Steril. 2020; 113 (5): 955-969.e4.	Descriptive for clinical outcomes
Zhao, J., Zhang, Q., Wang, Y. and Li, Y. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. Fertil Steril. 2014; 102 (4): 998-1005.e8.	Does not report on the critical outcomes of the guideline, i.e. LBR/OPR or multiple PR

2.10 Additional tests for systemic conditions

PICO QUESTION: SHOULD THERE BE ADDITIONAL EVALUATIONS OF POSSIBLE SYSTEMIC CAUSE OF UI IN THE COUPLE?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Abalovich, M., Mitelberg, L., Allami, C., Gutierrez, S., Alcaraz, G., Otero, P. and Levalle, O. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol. 2007; 23 (5): 279-83.	No control group
Andrisani, A., Sabbadin, C., Marin, L., Ragazzi, E., Dessole, F., Armanini, D., Donà, G., Bordin, L. and Ambrosini, G. The influence of thyroid autoimmunity on embryo quality in women undergoing assisted reproductive technology. Gynecol Endocrinol. 2018; 34 (9): 752-755.	No subdivision of UI in the results
Appasamy, M., Jauniaux, E., Serhal, P., Al-Qahtani, A., Groome, N. P. and Muttukrishna, S. Evaluation of the relationship between follicular fluid oxidative stress, ovarian hormones, and response to gonadotropin stimulation. Fertil Steril. 2008; 89 (4): 912-21.	No (fertile) controls
Ashrafi, M., Jahanian Sadatmahalleh, S., Akhoond, M. R., Ghaffari, F. and Zolfaghari, Z. ICSI Outcome in Infertile Couples with Different Causes of Infertility: A Cross-Sectional Study. Int J Fertil Steril. 2013; 7 (2): 88-95.	Subgroup of 34 were unexplained but groups were not identified seperately in results
Aydemir, B., Kiziler, A. R., Onaran, I., Alici, B., Ozkara, H. and Akyolcu, M. C. Impact of Cu and Fe concentrations on oxidative damage in male infertility. Biol Trace Elem Res. 2006; 112 (3): 193-203.	UI but no sperm results not clearly stated as normal.

Ayvaliotis, B., Bronson, R., Rosenfeld, D. and Cooper, G. Conception rates in couples where autoimmunity to sperm is detected. Fertil Steril. 1985; 43 (5): 739-42.	No seperate analysis for UI couples
Azem, F., Many, A., Ben Ami, I., Yovel, I., Amit, A., Lessing, J. B. and Kupferminc, M. J. Increased rates of thrombophilia in women with repeated IVF failures. Hum Reprod. 2004; 19 (2): 368-70.	No seperate analysis for UI couples
Bassey, I. E., Udoh, A. E., Essien, O. E., Isong, I. K., Gali, R. M. and Archibong, E. E. Thyroid hormones and prolactin levels in infertile women in southern Nigeria. J Clin Diagn Res. 2015; 9 (3): Oc13-5.	No seperate analysis for UI couples
Belan, M., Carranza-Mamane, B., Pesant, M. H., AinMelk, Y., Duval, K., Jean-Denis, F., Langlois, M. F. and Baillargeon, J. P. Male partners of subfertile couples in which the spouse is obese display adverse weight and lifestyle associated with reduced sperm quality. Obes Res Clin Pract. 2019; 13 (3): 226-232.	No control group
Bianca, S., Barrano, B., Cutuli, N., Indaco, L., Cataliotti, A., Milana, G., Barone, C. and Ettore, G. Unexplained infertility and inherited thrombophilia. Fertil Steril. 2009; 92 (1): e4; author reply e5.	No seperate analysis for UI couples
Chai, J., Yeung, W. Y., Lee, C. Y., Li, H. W., Ho, P. C. and Ng, H. Y. Live birth rates following in vitro fertilization in women with thyroid autoimmunity and/or subclinical hypothyroidism. Clin Endocrinol (Oxf). 2014; 80 (1): 122-7.	Very small subgroup of UI patients
Ciftci, H., Verit, A., Savas, M., Yeni, E. and Erel, O. Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. Urology. 2009; 74 (1): 73-6.	UI in males, however, no data on the females.
Conway, D. I., Glazener, C. M., Kelly, N. and Hull, M. G. Routine measurement of thyroid hormones and FSH in infertility not worthwhile. Lancet. 1985; 1 (8435): 977-8.	No seperate analysis for UI couples
Cramer, D. W., Sluss, P. M., Powers, R. D., McShane, P., Ginsburgs, E. S., Hornstein, M. D., Vitonis, A. F. and Barbieri, R. L. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? J Assist Reprod Genet. 2003; 20 (6): 210-5.	166 patients had unexplained infertility but no subdivison of results
Dechaud, H., Anahory, T., Reyftmann, L., Loup, V., Hamamah, S. and Hedon, B. Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. Eur J Obstet Gynecol Reprod Biol. 2006; 127 (1): 88-93.	UI but no separation of results
Del Porto, F., Ferrero, S., Cifani, N., Sesti, G. and Proietta, M. Antiphospholipid antibodies and idiopathic infertility. Lupus. 2022; 31 (3): 347-353.	Chose patients with UI who had a positive aPL and we are not told what percentage that was. They recommend testing for aPL but cannot use this as no prevalence or comparison
Deroux, A., Dumestre-Perard, C., Dunand-Faure, C., Bouillet, L. and Hoffmann, P. Female Infertility and Serum Auto-antibodies: a Systematic Review. Clin Rev Allergy Immunol. 2017; 53 (1): 78-86.	UI selection unclear
Dhillon-Smith, R. K., Tobias, A., Smith, P. P., Middleton, L. J., Sunner, K. K., Baker, K., Farrell-Carver, S., Bender-Atik, R., Agrawal, R., Bhatia, K., Chu, J. J., Edi-Osagie, E., Ewies, A., Ghobara, T., Gupta, P., Jurkovic, D., Khalaf, Y., Mulbagal, K., Nunes, N., Overton, C., Quenby, S., Rai, R., Raine-Fenning, N., Robinson, L., Ross, J., Sizer, A., Small, R., Underwood, M., Kilby, M. D., Daniels, J., Thangaratinam, S., Chan, S., Boelaert, K. and Coomarasamy, A. The Prevalence of Thyroid Dysfunction and Autoimmunity in Women With History of Miscarriage or Subfertility. J Clin Endocrinol Metab. 2020; 105 (8):	No subdivision of UI in the results
Di Rosa, R., Ferrero, S., Cifani, N., Ferri, L., Proietta, M., Picchianti Diamanti, A. and Del Porto, F. In vitro fertilization and autoimmunity: Evidence from an observational study. Eur J Obstet Gynecol Reprod Biol. 2019; 234 137-142.	No subdivision of UI in the results

Dressler, N., Chandra, A., Aguirre Dávila, L., Spineli, L. M., Schippert, C. and von Versen-Höynck, F. BMI and season are associated with vitamin D deficiency in women with impaired fertility: a two-centre analysis. Arch Gynecol Obstet. 2016; 293 (4): 907-14.	No control group, no seperate analysis for UI and no clinical outcomes
Eggert-Kruse, W., Batschulat, K., Demirakca, T. and Strowitzki, T. Male immunity to the chlamydial 60 kDa heat shock protein (HSP 60) - associated with semen quality? Andrologia. 2015; 47 (1): 66-76.	No subdivision of UI in the results
Eldar-Geva, T., Shoham, M., Rösler, A., Margalioth, E. J., Livne, K. and Meirow, D. Subclinical hypothyroidism in infertile women: the importance of continuous monitoring and the role of the thyrotropin-releasing hormone stimulation test. Gynecol Endocrinol. 2007; 23 (6): 332-7.	No subdivision of UI in the results
Esteves, S. C., Schneider, D. T. and Verza, S., Jr. Influence of antisperm antibodies in the semen on intracytoplasmic sperm injection outcome. Int Braz J Urol. 2007; 33 (6): 795-802.	No subdivision of UI in the results
Feldthusen, A. D., Pedersen, P. L., Larsen, J., Toft Kristensen, T., Ellervik, C. and Kvetny, J. Impaired Fertility Associated with Subclinical Hypothyroidism and Thyroid Autoimmunity: The Danish General Suburban Population Study. J Pregnancy. 2015; 2015 132718.	No subdivision of UI in the results
Freischem, C. W., Knuth, U. A., Langer, K., Schneider, H. P. and Nieschlag, E. The lack of discriminant seminal and endocrine variables in the partners of fertile and infertile women. Arch Gynecol. 1984; 236 (1): 1-12.	UI but difficult to separate
Fumarola, A., Grani, G., Romanzi, D., Del Sordo, M., Bianchini, M., Aragona, A., Tranquilli, D. and Aragona, C. Thyroid function in infertile patients undergoing assisted reproduction. Am J Reprod Immunol. 2013; 70 (4): 336-41.	No subdivision of UI in the results
Garcia-Segura, S., Ribas-Maynou, J., Lara-Cerrillo, S., Garcia-Peiró, A., Castel, A. B., Benet, J. and Oliver-Bonet, M. Relationship of Seminal Oxidation-Reduction Potential with Sperm DNA Integrity and pH in Idiopathic Infertile Patients. Biology (Basel). 2020; 9 (9):	Males and no information on females
Genco, P. V., Mathur, S., Williamson, H. O., Rust, P. F., Glassman, A. B. and Fudenberg, H. H. Antibodies to A19 and Bw35 complexes of human leukocyte antigens are present in infertile subjects with sperm antibodies. Fertil Steril. 1984; 42 (4): 554-60.	No control subjects so no background rate
Gerhard, I., Lenhard, H. K., Eggert-Kruse, W. and Runnebaum, B. Routine hormone load tests are unnecessary in infertile men. Andrologia. 1992; 24 (4): 219-26.	30% of males had UI. No subdivision of infertility cause
Gracia, C. R., Morse, C. B., Chan, G., Schilling, S., Prewitt, M., Sammel, M. D. and Mandel, S. J. Thyroid function during controlled ovarian hyperstimulation as part of in vitro fertilization. Fertil Steril. 2012; 97 (3): 585-91.	No subdivision of UI in the results
Grassi, G., Balsamo, A., Ansaldi, C., Balbo, A., Massobrio, M. and Benedetto, C. Thyroid autoimmunity and infertility. Gynecol Endocrinol. 2001; 15 (5): 389-96.	No control group, no subdivision of UI in the results
Green, K. A., Werner, M. D., Franasiak, J. M., Juneau, C. R., Hong, K. H. and Scott, R. T., Jr. Investigating the optimal preconception TSH range for patients undergoing IVF when controlling for embryo quality. J Assist Reprod Genet. 2015; 32 (10): 1469-76.	No subdivision of UI in the results
Janssen, H. J., Bastiaans, B. A., Goverde, H. J., Hollanders, H. M., Wetzels, A. A. and Schellekens, L. A. Antisperm antibodies and in vitro fertilization. J Assist Reprod Genet. 1992; 9 (4): 345-9.	males with abnormal sperm parameters in the male and female positive groups
Hosen, M. B., Islam, M. R., Begum, F., Kabir, Y. and Howlader, M. Z. Oxidative stress induced sperm DNA damage, a possible reason for male infertility. Iran J Reprod Med. 2015; 13 (9): 525-32.	UI but vague information regarding female and male SA
Khan, H. L., Bhatti, S., Abbas, S., Kaloglu, C., Qurat-Ul-Ain Zahra, S., Khan, Y. L., Hassan, Z., Turhan, NÖ and Aydin, H. H. Melatonin levels and microRNA (miRNA) relative expression profile in the follicular ambient microenvironment in patients undergoing in vitro fertilization process. J Assist Reprod Genet. 2021; 38 (2): 443-459.	No controls and only follicular fluid measured

Kim, N. Y., Cho, H. J., Kim, H. Y., Yang, K. M., Ahn, H. K., Thornton, S., Park, J. C., Beaman, K., Gilman-Sachs, A. and Kwak-Kim, J. Thyroid autoimmunity and its association with cellular and humoral immunity in women with reproductive failures. Am J Reprod Immunol. 2011; 65 (1): 78-87.	UI but mixed results with RSA and no controls
Lasa, J. S., Zubiaurre, I. and Soifer, L. O. Risk of infertility in patients with celiac disease: a meta-analysis of observational studies. Arq Gastroenterol. 2014; 51 (2): 144-50.	replaced by a more comprehensive systematic review
Li, Y., Yang, D. and Zhang, Q. Impact of overweight and underweight on IVF treatment in Chinese women. Gynecol Endocrinol. 2010; 26 (6): 416-22.	No subdivision of UI in the results
Liu, Y., Kong, X. D., Wu, Q. H., Li, G., Song, L. and Sun, Y. P. Karyotype analysis in large-sample infertile couples living in Central China: a study of 14965 couples. J Assist Reprod Genet. 2013; 30 (4): 547-53.	Not able to determine unexplained infertility. Males with normal count had prevalence of 1.69% which was less than other groups
Ludwig, M., Banz, C., Katalinic, A., Jacobeit, J. W., Epe, M., Von Zur Mühlen, A. and Schulte, H. M. The usefulness of a thyrotropin-releasing hormone stimulation test in subfertile female patients. Gynecol Endocrinol. 2007; 23 (4): 226-30.	No subdivision of UI in the results
Magri, F., Capelli, V., Gaiti, M., Brambilla, E., Montesion, L., Rotondi, M., Spinillo, A., Nappi, R. E. and Chiovato, L. Impaired outcome of controlled ovarian hyperstimulation in women with thyroid autoimmune disease. Thyroid. 2013; 23 (10): 1312-8.	No clear subdivision of UI in the results
Mansuri, T., Jadeja, S. H. D., Singh, M., Begum, R. and Robin, P. Phosphodiesterase 8B Polymorphism rs4704397 Is Associated with Infertility in Subclinical Hypothyroid Females: A Case-Control Study. Int J Fertil Steril. 2020; 14 (2): 122-128.	UI but hypothyroid and no controls
Micoogullari, U., Cakici, M. C., Kilic, F. U., Kisa, E., Ozcift, B., Caglayan, A., Neselioglu, S., Karatas, O. F. and Erel, O. Evaluation of the role of thiol / disulfide homeostasis in the etiology of idiopathic male infertility with a novel and automated assay. Syst Biol Reprod Med. 2022; 68 (2): 162-168.	No female data to establish UI
Mukheef, M. A., Ali, R. A. and Alheidery, H. H. A. Follicular fluid 8-Hydroxy-2-Deoxyguanosine (8-OHdG) as biomarker for oxidative stress in intracytoplasmic sperm injection. J Med Invest. 2022; 69 (1.2): 112-116.	No subdivision of UI in the results
Murakami, N., Kitajima, M., Ohyama, K., Aibara, N., Taniguchi, K., Wei, M., Kitajima, Y., Miura, K. and Masuzaki, H. Comprehensive immune complexome analysis detects disease-specific immune complex antigens in seminal plasma and follicular fluids derived from infertile men and women. Clin Chim Acta. 2019; 495 545-551.	Some UI but no control group
Olszak-Wąsik, K., Bednarska-Czerwińska, A., Olejek, A. and Tukiendorf, A. From "Every Day" Hormonal to Oxidative Stress Biomarkers in Blood and Follicular Fluid, to Embryo Quality and Pregnancy Success? Oxid Med Cell Longev. 2019; 2019 1092415.	No (fertile) controls
Orvieto, R., Meltcer, S., Nahum, R., Rabinson, J., Anteby, E. Y. and Ashkenazi, J. The influence of body mass index on in vitro fertilization outcome. Int J Gynaecol Obstet. 2009; 104 (1): 53-5.	UI at entry but no results
Paffoni, A., Ferrari, S., Mangiarini, A., Noli, S., Bulfoni, A., Vigano, P., Parazzini, F. and Somigliana, E. Concordance of vitamin D peripheral levels in infertile couples' partners. Gynecol Endocrinol. 2017; 33 (8): 649-652.	UI not defined and lumped with POI
Pagidas, K., Hemmings, R., Falcone, T. and Miron, P. The effect of antisperm autoantibodies in male or female partners undergoing in vitro fertilization-embryo transfer. Fertil Steril. 1994; 62 (2): 363-9.	comparison is with patients with antibodies and not against those without antibodies
Papanikolaou, E. G., Vernaeve, V., Kolibianakis, E., Assche, E. V., Bonduelle, M., Liebaers, I., Van Steirteghem, A. and Devroey, P. Is chromosome analysis	No clear definition into UI in tables

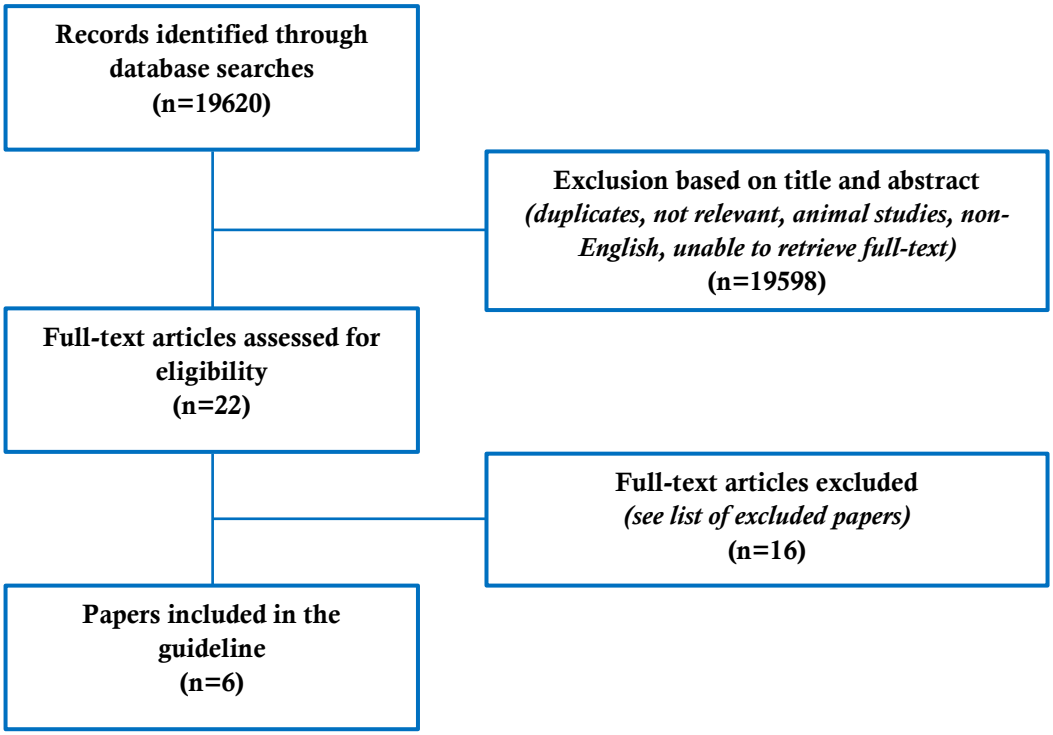
mandatory in the initial investigation of normovulatory women seeking infertility treatment? Hum Reprod. 2005; 20 (10): 2899-903.	
Pasqualotto, F. F., Sharma, R. K., Nelson, D. R., Thomas, A. J. and Agarwal, A. Relationship between oxidative stress, semen characteristics, and clinical diagnosis in men undergoing infertility investigation. Fertil Steril. 2000; 73 (3): 459-64.	Subgroup of male idiopathic infertility but no female data
Pasqualotto, F. F., Sharma, R. K., Pasqualotto, E. B. and Agarwal, A. Poor semen quality and ROS-TAC scores in patients with idiopathic infertility. Urol Int. 2008; 81 (3): 263-70.	Idiopathic infertility but little detail
Rajah, S. V., Parslow, J. M., Howell, R. J. and Hendry, W. F. The effects on in-vitro fertilization of autoantibodies to spermatozoa in subfertile men. Hum Reprod. 1993; 8 (7): 1079-82.	potential selection bias: no clear inclusion criteria applied; groups are expected to not be comparable at clinical baseline level because of aetiology of infertility; no adjustment for confounders; small sample size in both groups
Rashad, N. M., El Shabrawy, R. M., Radwan, A. M., Allam, R. M., Abdul-Maksoud, R. S. and Sherif, M. M. Interferon-gamma Expression Profile as Diagnostic Signatures of Unexplained Infertility in Female Patients Suffer from Hashimoto's Thyroiditis. Iran J Allergy Asthma Immunol. 2021; 20 (4): 465-472.	Patients with Hasimotos thyroiditis were chosen and then fertility looked at . Doesn't tell us if more common than other causes or controls
Rijal, B., Shrestha, R. and Jha, B. Association of thyroid dysfunction among infertile women visiting infertility center of Om Hospital, Kathmandu, Nepal. Nepal Med Coll J. 2011; 13 (4): 247-9.	No comparison to fertile controls
Selva, J., Martin-Pont, B., Hugues, J. N., Rince, P., Fillion, C., Herve, F., Tamboise, A. and Tamboise, E. Cytogenetic study of human oocytes uncleaved after in-vitro fertilization. Hum Reprod. 1991; 6 (5): 709-13.	Oocytes only and does not give information on the karyotype of the woman
Shah, D. K., Missmer, S. A., Berry, K. F., Racowsky, C. and Ginsburg, E. S. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. Obstet Gynecol. 2011; 118 (1): 63-70.	UI at entry but no results
Signorini, C., Moretti, E., Noto, D., Micheli, L., Ponchia, R. and Collodel, G. Fatty Acid Oxidation and Pro-Resolving Lipid Mediators Are Related to Male Infertility. Antioxidants (Basel). 2022; 11 (1):	Unable to ascertain whether UI or not due to lack of female data
Skowronek, M. F., Velazquez, T., Mut, P., Figueiro, G., Sans, M., Bertoni, B. and Sapiro, R. Associations between male infertility and ancestry in South Americans: a case control study. BMC Med Genet. 2017; 18 (1): 78.	No fertile data
Tanacan, A. and Beksac, M. S. Spontaneous pregnancies in patients with at least one failed IVF cycle after the management of autoimmune disorders, hereditary thrombophilia, and methylation disorders. JBRA Assist Reprod. 2019; 23 (4): 361-366.	No controls
Unuane, D., Velkeniers, B., Anckaert, E., Schiettecatte, J., Tournaye, H., Haentjens, P. and Poppe, K. Thyroglobulin autoantibodies: is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? Thyroid. 2013; 23 (8): 1022-8.	Subgroup of possible UI but not defined
Yilmaz, N., Ersoy, E., Tokmak, A., Sargin, A., Ozgu-Erdinc, A. S., Erkaya, S. and Ibrahim Yakut, H. Do Serum Vitamin D Levels Have Any Effect on Intrauterine Insemination Success? Int J Fertil Steril. 2018; 12 (2): 164-168.	No subdivision of UI in the results
Yusuf, I. and Emokpae, M. A. Association between a marker of sperm DNA damage and sperm indices in infertile males in Benin City, Nigeria: A cross-sectional study. Int J Reprod Biomed. 2021; 19 (2): 137-146.	Unable to ascertain whether UI or not due to lack of female data

3. Treatment

3.1 Expectant management

PICO Question: What is the value of expectant management compared to active treatment for patients with UI?

Flowchart



List of excluded papers

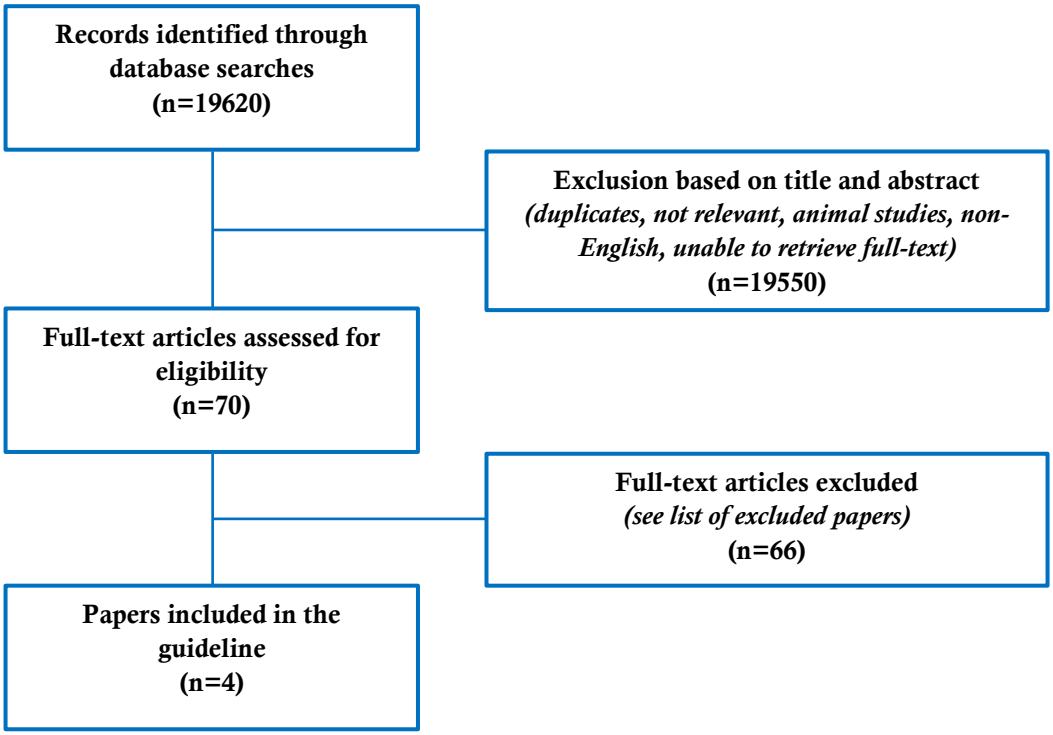
Reference	Exclusion criterion
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Amin, Y., Abbas, A. M. and Salah, I. M. Ovarian superstimulation and intrauterine insemination for the treatment of unexplained infertility. Fertil Steril. 1993; 60 (2): 303-6.	Cohort study in the presence of higher quality evidence
Brandes, M., Hamilton, C. J., van der Steen, J. O., de Bruin, J. P., Bots, R. S., Nelen, W. L. and Kremer, J. A. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. Hum Reprod. 2011; 26 (2): 360-8.	Not a direct comparison. Treatment selected according to prognosis
Custers, I. M., van Rumste, M. M., van der Steeg, J. W., van Wely, M., Hompes, P. G., Bossuyt, P., Broekmans, F. J., Renckens, C. N., Eijkemans, M. J., van Dessel, T. J., van der Veen, F., Mol, B. W. and Steures, P. Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. Hum Reprod. 2012; 27 (2): 444-50.	Included in SR Ayeleke 2020
Deaton, J. L., Gibson, M., Blackmer, K. M., Nakajima, S. T., Badger, G. J. and Brumsted, J. R. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. Fertil Steril. 1990; 54 (6): 1083-8.	Included in SR Ayeleke 2020

Farquhar, C. M., Liu, E., Armstrong, S., Arroll, N., Lensen, S. and Brown, J. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. Lancet. 2018; 391 (10119): 441-450.	Included in SR Ayeleke 2020
Fisch, P., Casper, R. F., Brown, S. E., Wrixon, W., Collins, J. A., Reid, R. L. and Simpson, C. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. Fertil Steril. 1989; 51 (5): 828-33.	No mention of expectant treatment
Glazener, C. M., Coulson, C., Lambert, P. A., Watt, E. M., Hinton, R. A., Kelly, N. G. and Hull, M. G. Clomiphene treatment for women with unexplained infertility: placebo-controlled study of hormonal responses and conception rates. Gynecol Endocrinol. 1990; 4 (2): 75-83.	unable to seerate data for first arm of crossover
Godart, E. S., Shin, D. H., Christensen, E., Thompson, E. R. and Turek, P. J. A study of pregnancy rates in "cleared" male factor couples. Transl Androl Urol. 2021; 10 (2): 620-625.	female not examined, not UI
Helmerhorst, F. M., Van Vliet, Haam, Gornas, T., Finken, M. J. and Grimes, D. A. Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples. Cochrane Database of Systematic Reviews. 2005; (4):	more recent SR on the topic available
Kersten, F. A. M., Nelen, Wldm, van den Boogaard, N. M., van Rumste, M. M., Koks, C. A., IntHout, J., Verhoeve, H. R., Pelinck, M. J., Boks, D. E. S., Gianotten, J., Broekmans, F. J. M., Goddijn, M., Braat, D. D. M., Mol, B. W. J. and Hermens, Rpgm. Implementing targeted expectant management in fertility care using prognostic modelling: a cluster randomized trial with a multifaceted strategy. Hum Reprod. 2017; 32 (8): 1648-1657.	Randomization not on patient level; inclusion criteria also include couples with mild known infertility factor + clinical outcomes are not analysed by type of treatment
Pandian, Z., Bhattacharya, S., Nikolaou, D., Vale, L. and Templeton, A. The effectiveness of IVF in unexplained infertility: a systematic Cochrane review. 2002. Hum Reprod. 2003; 18 (10): 2001-7.	more recent SR on the topic available
Pandian, Z., Gibreel, A. and Bhattacharya, S. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev. 2015; 2015 (11): Cd003357.	More recent IPD-SR available
Peterson, C. M., Hatasaka, H. H., Jones, K. P., Poulson, A. M., Jr., Carrell, D. T. and Urry, R. L. Ovulation induction with gonadotropins and intrauterine insemination compared with in vitro fertilization and no therapy: a prospective, nonrandomized, cohort study and meta-analysis. Fertil Steril. 1994; 62 (3): 535-44.	no true comparison with expectant
Scholten, I., van Zijl, M., Custers, I. M., Brandes, M., Gianotten, J., van der Linden, P. J. Q., Hompes, P. G. A., van der Veen, F. and Mol, B. W. J. The effectiveness of intrauterine insemination: A matched cohort study. Eur J Obstet Gynecol Reprod Biol. 2017; 212 91-95.	no stratification according to infertility diagnosis
Steures, P., Berkhout, J. C., Hompes, P. G., van der Steeg, J. W., Bossuyt, P. M., van der Veen, F., Habbema, J. D., Eijkemans, M. J. and Mol, B. W. Patients' preferences in deciding between intrauterine insemination and expectant management. Hum Reprod. 2005; 20 (3): 752-5.	patient preference was guided by the physician providing prognosis and the recommended treatment for that.
Steures, P., van der Steeg, J. W., Hompes, P. G., Habbema, J. D., Eijkemans, M. J., Broekmans, F. J., Verhoeve, H. R., Bossuyt, P. M., van der Veen, F. and Mol, B. W. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. Lancet. 2006; 368 (9531): 216-21.	Included in SR Ayeleke 2020
van Eekelen, R., van Geloven, N., van Wely, M., McLernon, D. J., Mol, F., Custers, I. M., Steures, P., Bhattacharya, S., Mol, B. W., van der Veen, F. and Eijkemans, M. J. Is IUI with ovarian stimulation effective in couples with unexplained subfertility? Hum Reprod. 2019; 34 (1): 84-91.	Cohort study in the presence of higher quality evidence

3.2 Active treatment

PICO Question: If active treatment is pursued, which type of active treatment for UI?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Amin, Y., Ramzy, A. M., Sattar, M. A. and Kamal, A. Management of long-standing unexplained infertility: A prospective study. Am J Obstet Gynecol. 1999; 181 (2): 371-5.	Cohort study in the presence of higher quality evidence
Aboulghar, M., Mansour, R., Serour, G., Abdrazek, A., Amin, Y. and Rhodes, C. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. Fertil Steril. 2001; 75 (1): 88-91.	Cohort study in the presence of higher quality evidence
Abu-Heija, A. and Yates, R. Comparison of controlled ovarian superstimulation with or without intrauterine insemination for the treatment of unexplained infertility. Ann Saudi Med. 1995; 15 (5): 464-5.	Cohort study in the presence of higher quality evidence
Akbari Sene, A., Ghorbani, S. and Ashrafi, M. Comparison of the pregnancy outcomes and the incidence of fetal congenital abnormalities in infertile women treated with letrozole and clomiphene citrate. J Obstet Gynaecol Res. 2018; 44 (6): 1036-1041.	Cohort study in the presence of higher quality evidence
Arici, A., Byrd, W., Bradshaw, K., Kutteh, W. H., Marshburn, P. and Carr, B. R. Evaluation of clomiphene citrate and human chorionic gonadotropin treatment: a prospective, randomized, crossover study during intrauterine insemination cycles. Fertil Steril. 1994; 61 (2): 314-8.	Included in systematic review Ayeleke et al., 2020

Begum, M. R., Quadir, E., Begum, A., Begum, R. A. and Begum, M. Role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate. J Obstet Gynaecol Res. 2006; 32 (5): 502-6.	Included women with anovulation
Bensdorp, A. J., Tjon-Kon-Fat, R. I., Bossuyt, P. M., Koks, C. A., Oosterhuis, G. J., Hoek, A., Hompes, P. G., Broekmans, F. J., Verhoeve, H. R., de Bruin, J. P., van Golde, R., Repping, S., Cohlen, B. J., Lambers, M. D., van Bommel, P. F., Slappendel, E., Perquin, D., Smeenk, J. M., Pelinck, M. J., Gianotten, J., Hoozemans, D. A., Maas, J. W., Eijkemans, M. J., van der Veen, F., Mol, B. W., van Wely, M. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. Bmj. 2015; 350: g7771	Included in systematic review Nandi et al., 2022
Bhattacharya, S., Harrild, K., Mollison, J., Wordsworth, S., Tay, C., Harrold, A., McQueen, D., Lyall, H., Johnston, L., Burrage, J., Grossett, S., Walton, H., Lynch, J., Johnstone, A., Kini, S., Raja, A. and Templeton, A. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. Bmj. 2008; 337 a716.	Included in systematic review Ayeleke et al., 2020
Brandes, M., Hamilton, C. J., van der Steen, J. O., de Bruin, J. P., Bots, R. S., Nelen, W. L. and Kremer, J. A. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. Hum Reprod. 2011; 26 (2): 360-8.	Cohort study in the presence of higher quality evidence
Chaffkin, L. M., Nulsen, J. C., Luciano, A. A. and Metzger, D. A. A comparative analysis of the cycle fecundity rates associated with combined human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) versus either hMG or IUI alone. Fertil Steril. 1991; 55 (2): 252-7.	Cohort study in the presence of higher quality evidence
Chambers, G. M., Sullivan, E. A., Shanahan, M., Ho, M. T., Priester, K. and Chapman, M. G. Is in vitro fertilisation more effective than stimulated intrauterine insemination as a first-line therapy for subfertility? A cohort analysis. Aust N Z J Obstet Gynaecol. 2010; 50 (3): 280-8.	Cohort study in the presence of higher quality evidence
Chung, C. C., Fleming, R., Jamieson, M. E., Yates, R. W. and Coutts, J. R. Randomized comparison of ovulation induction with and without intrauterine insemination in the treatment of unexplained infertility. Hum Reprod. 1995; 10 (12): 3139-41.	Included in systematic review Ayeleke et al., 2020
Costello, M. F. Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination. Aust N Z J Obstet Gynaecol. 2004; 44 (2): 93-102.	More recent systematic review available
Crosignani, P. G., Walters, D. E. and Soliani, A. The ESHRE multicentre trial on the treatment of unexplained infertility: a preliminary report. European Society of Human Reproduction and Embryology. Hum Reprod. 1991; 6 (7): 953-8.	Included in systematic review Ayeleke et al., 2020 and Nandi et al., 2022
Custers, I. M., König, T. E., Broekmans, F. J., Hompes, P. G., Kaaijk, E., Oosterhuis, J., Mochtar, M. H., Repping, S., van Wely, M., Steures, P., van der Veen, F. and Mol, B. W. Couples with unexplained subfertility and unfavorable prognosis: a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. Fertil Steril. 2011; 96 (5): 1107-11.e1.	Included in systematic review Nandi et al., 2022
Danhof, N. A., van Wely, M., Repping, S., Koks, C., Verhoeve, H. R., de Bruin, J. P., Verberg, M. F. G., van Hooff, M. H. A., Cohlen, B. J., van Heteren, C. F., Fleischer, K., Gianotten, J., van Disseldorp, J., Visser, J., Broekmans, F. J. M., Mol, B. W. J., van der Veen, F. and Mochtar, M. H. Follicle stimulating hormone versus clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial. Hum Reprod. 2018; 33 (10): 1866-1874.	Not within scope: comparison of stimulation protocol for IUI

Danhof, N. A., van Wely, M., Repping, S., van der Ham, D. P., Klijn, N., Janssen, Icah, Rijn-van Weert, J. M., Twisk, M., Traas, M. A. F., Pelinck, M. J., Perquin, D. A. M., Boks, D. E. S., Sluijmer, A., Mol, B. W. J., van der Veen, F. and Mochtar, M. H. Gonadotrophins or clomiphene citrate in couples with unexplained infertility undergoing intrauterine insemination: a cost-effectiveness analysis. Reprod Biomed Online. 2020; 40 (1): 99-104.	Not within scope: comparison of stimulation protocol for IUI
Danhof, N. A., Wang, R., van Wely, M., van der Veen, F., Mol, B. W. J. and Mochtar, M. H. IUI for unexplained infertility-a network meta-analysis. Hum Reprod Update. 2020; 26 (1): 1-15.	Includes Martinez 1990, which does not allow extraction of data on UI alone
DiMarzo, S. J., Kennedy, J. F., Young, P. E., Hebert, S. A., Rosenberg, D. C. and Villanueva, B. Effect of controlled ovarian hyperstimulation on pregnancy rates after intrauterine insemination. Am J Obstet Gynecol. 1992; 166 (6 Pt 1): 1607-12; discussion 1612-3.	Cohort study in the presence of higher quality evidence
Elzeiny, H., Garrett, C., Toledo, M., Stern, K., McBain, J. and Baker, H. W. A randomised controlled trial of intra-uterine insemination versus in vitro fertilisation in patients with idiopathic or mild male infertility. Aust N Z J Obstet Gynaecol. 2014; 54 (2): 156-61.	Included in systematic review Nandi et al., 2022 and Pandian et al., 2015
Evans, J., Wells, C., Gregory, L. and Walker, S. A comparison of intrauterine insemination, intraperitoneal insemination, and natural intercourse in superovulated women. Fertil Steril. 1991; 56 (6): 1183-7.	Excluded from systematic review Ayeleke et al., 2020 because no pre-cross-over data available
Goldman, M. B., Thornton, K. L., Ryley, D., Alper, M. M., Fung, J. L., Hornstein, M. D. and Reindollar, R. H. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). Fertil Steril. 2014; 101 (6): 1574-81.e1-2.	Included in systematic review Nandi et al., 2022
Goverde, A. J., McDonnell, J., Vermeiden, J. P., Schats, R., Rutten, F. F. and Schoemaker, J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet. 2000; 355 (9197): 13-8.	Included in systematic review Ayeleke et al., 2020 and Nandi et al., 2022
Gowri, V., Al-Amri, A., Almamari, T. M. A., Al Khaduri, M., Jaju, S. The Success of Ovulation Induction with Letrozole and Gonadotropins in Obese and Nonobese Women: A Study from a Tertiary Center. Int J Reprod Med. 2022; 1931716	Includes mild male infertility in the UI group
Gregoriou, O., Vitoratos, N., Papadias, C., Konidaris, S., Gargaropoulos, A. and Louridas, C. Controlled ovarian hyperstimulation with or without intrauterine insemination for the treatment of unexplained infertility. Int J Gynaecol Obstet. 1995; 48 (1): 55-9.	Excluded from systematic review Ayeleke et al., 2020
Gunn, D. D. and Bates, G. W. Evidence-based approach to unexplained infertility: a systematic review. Fertil Steril. 2016; 105 (6): 1566-1574.e1.	More recent systematic review available
Guzick, D. S., Carson, S. A., Coutifaris, C., Overstreet, J. W., Factor-Litvak, P., Steinkampf, M. P., Hill, J. A., Mastroianni, L., Buster, J. E., Nakajima, S. T., Vogel, D. L. and Canfield, R. E. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. N Engl J Med. 1999; 340 (3): 177-83.	Included in systematic review Ayeleke et al., 2020
Hewitt, J., Cohen, J., Krishnaswamy, V., Fehilly, C. B., Steptoe, P. C. and Walters, D. E. Treatment of idiopathic infertility, cervical mucus hostility, and male infertility: artificial insemination with husband's semen or in vitro fertilization? Fertil Steril. 1985; 44 (3): 350-5.	Cohort study in the presence of higher quality evidence
Harira, M. Use of Letrozole versus clomiphene-estradiol for treating infertile women with unexplained infertility not responding well to clomiphene alone, comparative study. Middle east fertility society journal. 2018; 23 (4): 384-387.	Not included due to integrity risk rating
Huang, S., Wang, R., Li, R., Wang, H., Qiao, J. and Mol, B. W. J. Ovarian stimulation in infertile women treated with the use of intrauterine insemination: a cohort study from China. Fertil Steril. 2018; 109 (5): 872-878.	Cohort study in the presence of higher quality evidence

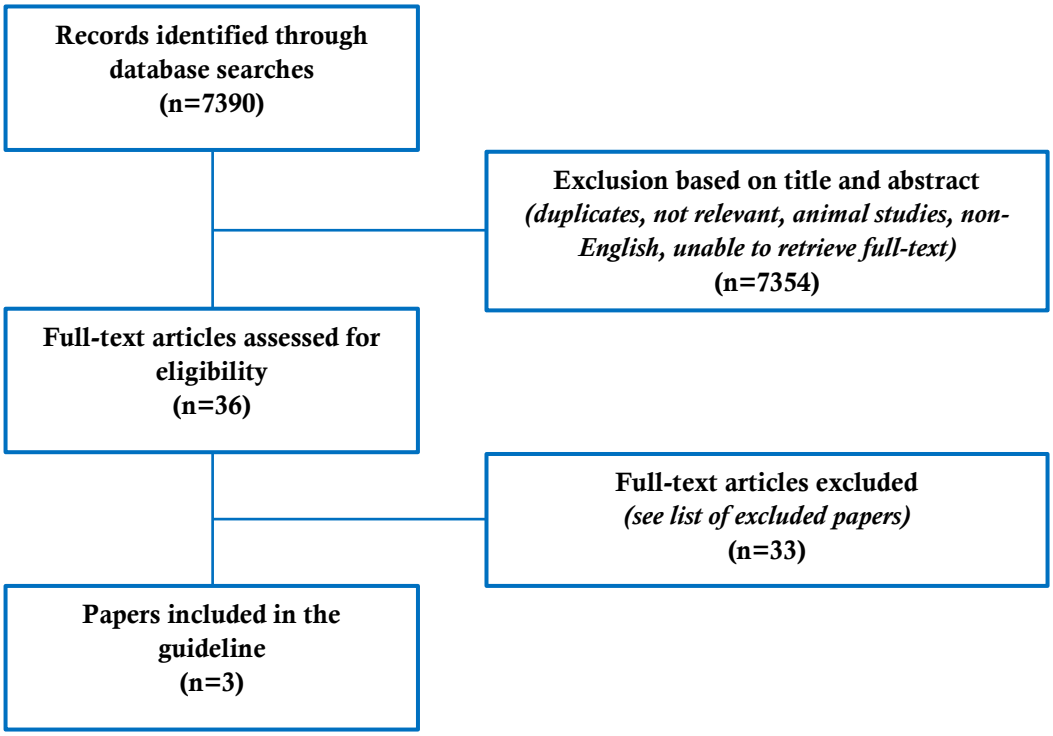
Hughes, E., Brown, J., Collins, J. J. and Vanderkerchove, P. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev. 2010; 2010 (1): Cd000057.	More recent systematic review available
Ibrahim, M. I., Moustafa, R. A. and Abdel-Azeem, A. A. Letrozole versus clomiphene citrate for superovulation in Egyptian women with unexplained infertility: a randomized controlled trial. Arch Gynecol Obstet. 2012; 286 (6): 1581-7.	Not included due to integrity risk rating
Isaksson, R. and Tiitinen, A. Superovulation combined with insemination or timed intercourse in the treatment of couples with unexplained infertility and minimal endometriosis. Acta Obstet Gynecol Scand. 1997; 76 (6): 550-4.	Pseudo-randomised trial
Kalu, E., Thum, M. Y. and Abdalla, H. Intrauterine insemination in natural cycle may give better results in older women. J Assist Reprod Genet. 2007; 24 (2-3): 83-6.	Cohort study in the presence of higher quality evidence
Karlström, P. O., Bergh, T. and Lundkvist, O. A prospective randomized trial of artificial insemination versus intercourse in cycles stimulated with human menopausal gonadotropin or clomiphene citrate. Fertil Steril. 1993; 59 (3): 554-9.	Included in systematic review Ayeleke et al., 2020
Kaur, J., Suri, V., Gainder, S. and Arora, A. Prospective randomized trial comparing efficacy of letrozole step-up protocol with letrozole plus gonadotropins for controlled ovarian stimulation and intrauterine insemination in patients with unexplained infertility. Arch Gynecol Obstet. 2019; 300 (6): 1767-1771.	Not within scope: stimulation protocols for IUI
Kirby, C. A., Flaherty, S. P., Godfrey, B. M., Warnes, G. M. and Matthews, C. D. A prospective trial of intrauterine insemination of motile spermatozoa versus timed intercourse. Fertil Steril. 1991; 56 (1): 102-7.	No pre-cross-over data available
Magsi, S., Lashari, S., Shaikh, R., Magsi, I., Qureshi, S. G. Unexplained Infertility: comparison of Efficacy of Letrozole and Clomiphene Citrate. Pakistan journal of medical and health sciences 2022; 16(3): 109-11	Cohort study in the presence of higher quality evidence
Martinez, A. R., Bernardus, R. E., Voorhorst, F. J., Vermeiden, J. P. and Schoemaker, J. Intrauterine insemination does and clomiphene citrate does not improve fecundity in couples with infertility due to male or idiopathic factors: a prospective, randomized, controlled study. Fertil Steril. 1990; 53 (5): 847-53.	The 4 treatment modalities are not compared according to infertility diagnosis;
Martinez, A. R., Bernardus, R. E., Voorhorst, F. J., Vermeiden, J. P. and Schoemaker, J. Pregnancy rates after timed intercourse or intrauterine insemination after human menopausal gonadotropin stimulation of normal ovulatory cycles: a controlled study. Fertil Steril. 1991; 55 (2): 258-65.	Excluded from systematic review Ayeleke et al., 2020 for no pre-cross-over data available
Marschalek, J., Franz, M., Gonen, Y., Kruessel, J. S., Weichselbaum, A., Kuessel, L., Trofaier, M. L. and Ott, J. The effect of slow release insemination on pregnancy rates: report of two randomized controlled pilot studies and meta-analysis. Arch Gynecol Obstet. 2017; 295 (4): 1025-1032.	Includes only 2 studies with very small sample size
Mascarenhas, L., Khastgir, G., Davies, W. A. and Lee, S. Superovulation and timed intercourse: can it provide a reasonable alternative for those unable to afford assisted conception? Hum Reprod. 1994; 9 (1): 67-70.	Cohort study in the presence of higher quality evidence
Melis, G. B., Paoletti, A. M., Ajossa, S., Guerriero, S., Depau, G. F. and Mais, V. Ovulation induction with gonadotropins as sole treatment in infertile couples with open tubes: a randomized prospective comparison between intrauterine insemination and timed vaginal intercourse. Fertil Steril. 1995; 64 (6): 1088-93.	Included in systematic review Ayeleke et al., 2020
Merviel, P., Labarre, M., James, P., Bouée, S., Chabaud, J. J., Roche, S., Cabry, R., Scheffler, F., Lourdel, E., Benkhalifa, M., Copin, H., Drapier, H. and Beauvillard, D. Should intrauterine inseminations still be proposed in cases of unexplained infertility? Retrospective study and literature review. Arch Gynecol Obstet. 2022; 305 (5): 1241-1254.	Cohort study in the presence of higher quality evidence
Mukherjee, S., Sharma, S. and Chakravarty, B. N. Comparative evaluation of pregnancy outcome in gonadotrophin-clomiphene combination vs clomiphene	Not within scope: CC+/- Gn

alone in polycystic ovarian syndrome and unexplained infertility-A prospective clinical trial. J Hum Reprod Sci. 2010; 3 (2): 80-4.	
Nandi, A., Bhide, P., Hooper, R., Gudi, A., Shah, A., Khan, K. and Homburg, R. Intrauterine insemination with gonadotropin stimulation or in vitro fertilization for the treatment of unexplained subfertility: a randomized controlled trial. Fertil Steril. 2017; 107 (6): 1329-1335.e2.	Included in systematic review Nandi et al., 2022
Nandi, A., Raja, G., White, D. and Tarek, E. T. Intrauterine insemination + controlled ovarian hyperstimulation versus in vitro fertilisation in unexplained infertility: a systematic review and meta-analysis. Arch Gynecol Obstet. 2022; 305 (4): 805-824.	More recent IPD-SR available
Nulsen, J. C., Walsh, S., Dumez, S. and Metzger, D. A. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. Obstet Gynecol. 1993; 82 (5): 780-6.	Not a randomized trial
Pacu, I., Ionescu, C. A., Dimitriu, M., Banacu, M., Tarcomnicu, I., Calin, D., Socea, B., Pantea, A. S., Constantin, V. D., Paunica-Panea, G. and et al. Intrauterine insemination in idiopathic infertility. Archives of the balkan medical union. 2016; 51 (3): 334-339.	Cohort study in the presence of higher quality evidence
Pandian, Z., Gibreel, A. and Bhattacharya, S. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev. 2015; 2015 (11): Cd003357.	More recent IPD-SR available
Qin, F., Zhou, Y., Huan, L. and Gui, W. Comparison of clomiphene and letrozole for superovulation in patients with unexplained infertility undergoing intrauterine insemination: A systematic review and meta-analysis. Medicine (Baltimore). 2020; 99 (31): e21006.	Not within scope: stimulation protocols for IUI
Reindollar, R. H., Regan, M. M., Neumann, P. J., Levine, B. S., Thornton, K. L., Alper, M. M. and Goldman, M. B. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010; 94 (3): 888-99.	Included in systematic review Nandi et al., 2022
Rodriguez-Purata, J., Lee, J., Whitehouse, M., Sandler, B., Copperman, A. and Mukherjee, T. Comparision of Letrozole with Timed Intercourse Versus Clomiphene Citrate with Intrauterine Insemination in Patients with Unexplained Infertility. J Reprod Med. 2016; 61 (9-10): 425-430.	Cohort study in the presence of higher quality evidence
Serhal, P. F., Katz, M., Little, V. and Woronowski, H. Unexplained infertility--the value of Pergonal superovulation combined with intrauterine insemination. Fertil Steril. 1988; 49 (4): 602-6.	Cohort study in the presence of higher quality evidence
Simon, A., Avidan, B., Mordel, N., Lewin, A., Samueloff, A., Zajicek, G., Schenker, J. G. and Laufer, N. The value of menotrophin treatment for unexplained infertility prior to an in-vitro fertilization attempt. Hum Reprod. 1991; 6 (2): 222-6.	Cohort study in the presence of higher quality evidence
Soysal, C. and Ozmen, U. Intrauterine insemination in ovulatory infertile patients. Niger J Clin Pract. 2018; 21 (10): 1374-1379.	Cohort study in the presence of higher quality evidence
Steures, P., Berkhout, J. C., Hompes, P. G., van der Steeg, J. W., Bossuyt, P. M., van der Veen, F., Habbema, J. D., Eijkemans, M. J. and Mol, B. W. Patients' preferences in deciding between intrauterine insemination and expectant management. Hum Reprod. 2005; 20 (3): 752-5.	Cohort study in the presence of higher quality evidence
Tjon-Kon-Fat, R. I., Bensdorp, A. J., Bossuyt, P. M., Koks, C., Oosterhuis, G. J., Hoek, A., Hompes, P., Broekmans, F. J., Verhoeve, H. R., de Bruin, J. P., van Golde, R., Repping, S., Cohlen, B. J., Lambers, M. D., van Bommel, P. F., Slappendel, E., Perquin, D., Smeenk, J., Pelinck, M. J., Gianotten, J., Hoozemans, D. A., Maas, J. W., Groen, H., Eijkemans, M. J., van der Veen, F., Mol, B. W. and van Wely, M. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod. 2015; 30 (10): 2331-9.	Economic evaluation

Tjon-Kon-Fat, R. I., Tajik, P., Zafarmand, M. H., Bensdorp, A. J., Bossuyt, P. M. M., Oosterhuis, G. J. E., van Golde, R., Repping, S., Lambers, M. D. A., Slappendel, E., Perquin, D., Pelinck, M. J., Gianotten, J., Maas, J. W. M., Eijkemans, M. J. C., van der Veen, F., Mol, B. W. and van Wely, M. IVF or IUI as first-line treatment in unexplained subfertility: the conundrum of treatment selection markers. Hum Reprod. 2017; 32 (5): 1028-1032.	Secondary analysis of the RCT by Bensdorp et al., 2015
van Rumste, M. M., Custers, I. M., van Wely, M., Koks, C. A., van Weering, H. G., Beckers, N. G., Scheffer, G. J., Broekmans, F. J., Hompes, P. G., Mochtar, M. H., van der Veen, F. and Mol, B. W. IVF with planned single-embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility: an economic analysis. Reprod Biomed Online. 2014; 28 (3): 336-42.	Economic evaluation
Wang, R., Danhof, N. A., Tjon-Kon-Fat, R. I., Eijkemans, M. J., Bossuyt, P. M., Mochtar, M. H., van der Veen, F., Bhattacharya, S., Mol, B. W. J. and van Wely, M. Interventions for unexplained infertility: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2019; 9 (9): Cd012692.	Replaced by a more recent systematic review
Welner, S., DeCherney, A. H. and Polan, M. L. Human menopausal gonadotropins: a justifiable therapy in ovulatory women with long-standing idiopathic infertility. Am J Obstet Gynecol. 1988; 158 (1): 111-7.	Cohort study in the presence of higher quality evidence
Wiser, A., Shalom-Paz, E., Reinblatt, S. L., Son, W. Y., Das, M., Tulandi, T. and Holzer, H. Ovarian stimulation and intrauterine insemination in women aged 40 years or more. Reprod Biomed Online. 2012; 24 (2): 170-3.	Cohort study in the presence of higher quality evidence
Zikopoulos, K., West, C. P., Thong, P. W., Kacser, E. M., Morrison, J., Wu, F. C. Homologous intra-uterine insemination has no advantage over timed natural intercourse when used in combination with ovulation induction for the treatment of unexplained infertility. Hum Reprod. 1993; 8 (4): 563-7.	excluded from systematic review Ayeleke et al., 2020 for no pre-cross-over data available
Zayed, F. Follow-up of patients with unexplained infertility who previously underwent natural cycle in vitro fertilization. Gynecol Obstet Invest. 2000; 49 (2): 127-31.	Cohort study in the presence of higher quality evidence
Zayed, F., Lenton, E. A. and Cooke, I. D. Comparison between stimulated in-vitro fertilization and stimulated intrauterine insemination for the treatment of unexplained and mild male factor infertility. Hum Reprod. 1997; 12 (11): 2408-13.	Cohort study in the presence of higher quality evidence

PICO QUESTION: WHAT IS THE VALUE OF IVF VERSUS ICSI?

Flowchart



List of excluded papers

	Exclusion criterion
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Amin, Y., Ramzy, A. M., Sattar, M. A. and Kamal, A. Management of long-standing unexplained infertility: A prospective study. Am J Obstet Gynecol. 1999; 181 (2): 371-5.	Not a RCT
Aboulghar, M. A., Mansour, R. T., Serour, G. I., Sattar, M. A. and Amin, Y. M. Intracytoplasmic sperm injection and conventional in vitro fertilization for sibling oocytes in cases of unexplained infertility and borderline semen. J Assist Reprod Genet. 1996; 13 (1): 38-42.	Not a RCT
Biliangady, R., Kinila, P., Pandit, R., Tudu, N. K., Sundhararaj, U. M., Gopal, I. S. T. and Swamy, A. G. Are we Justified Doing Routine Intracytoplasmic Sperm Injection in Nonmale Factor Infertility? A Retrospective Study Comparing Reproductive Outcomes between In vitro Fertilization and Intracytoplasmic Sperm Injection in Nonmale Factor Infertility. J Hum Reprod Sci. 2019; 12 (3): 210-215.	Not a RCT
Bosch, E., Espinós, J. J., Fabregues, F., Fontes, J., García-Velasco, J., Llácer, J., Requena, A., Checa, M. A. and Bellver, J. ALWAYS ICSI? A SWOT analysis. J Assist Reprod Genet. 2020; 37 (9): 2081-2092.	SWOT analysis of IVF vs ICSI for non-male factor. 2 RCTs involving UI are included, these RCTs Bhattacharya 2001 & Foong 2006 are among the list of the 35 studies.
Bungum, L., Bungum, M., Humaidan, P. and Andersen, C. Y. A strategy for treatment of couples with unexplained infertility who failed to conceive after intrauterine insemination. Reprod Biomed Online. 2004; 8 (5): 584-9.	Not a RCT

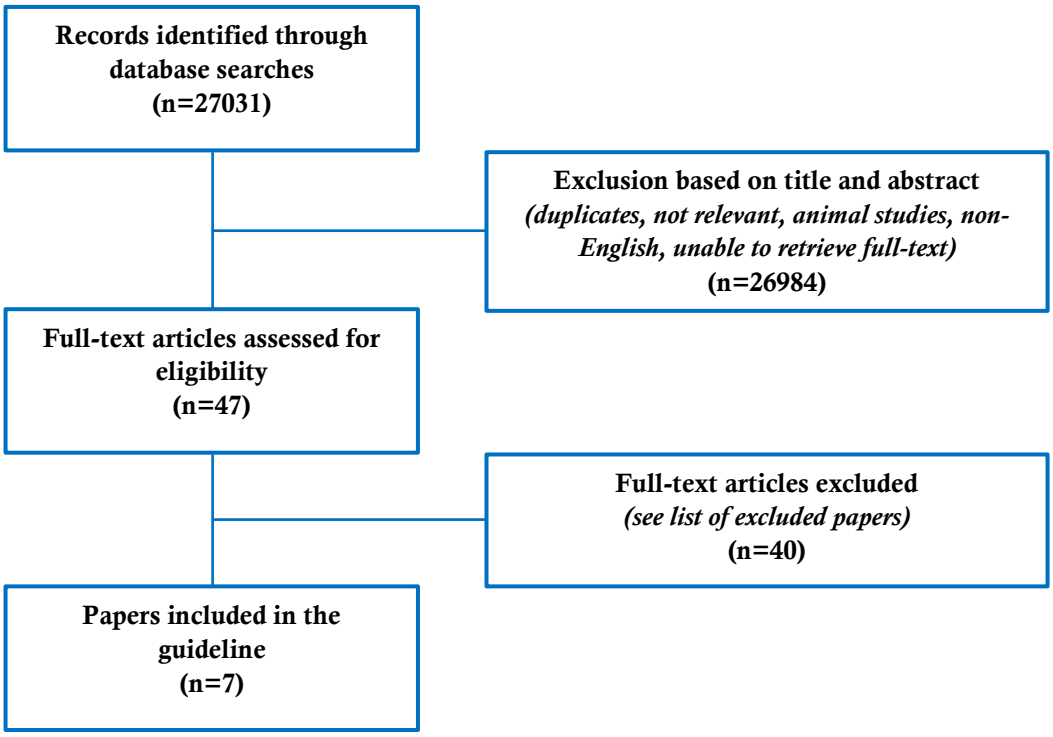
Check, J. H., Bollendorf, A., Dix, E. and Katsoff, D. Effect of fertilization by intracytoplasmic sperm injection versus conventional insemination on embryo cleavage rates. Clin Exp Obstet Gynecol. 2010; 37 (3): 183-4.	Not a RCT
Check, J. H., Bollendorf, A., Summers-Chase, D., Horwath, D. and Hourani, W. Conventional oocyte insemination may result in a better pregnancy outcome than intracytoplasmic sperm injection (ICSI) for unexplained infertility. Clin Exp Obstet Gynecol. 2009; 36 (3): 150-1.	Not a RCT
Chung, C. H. S., Wong, A. W. Y., Yeung, Q. S. Y., Cheung, L. P. and Li, T. C. Is routine intracytoplasmic sperm injection justified in couples with unexplained infertility? A randomized controlled trial using sibling oocytes. Journal of reproductive medicine. 2018; 63 (4): 357-362.	Randomised sibling oocytes to IVF & ICSI
Drakopoulos, P., Garcia-Velasco, J., Bosch, E., Blockeel, C., de Vos, M., Santos-Ribeiro, S., Makrigiannakis, A., Tournaye, H. and Polyzos, N. P. ICSI does not offer any benefit over conventional IVF across different ovarian response categories in non-male factor infertility: a European multicenter analysis. J Assist Reprod Genet. 2019; 36 (10): 2067-2076.	Not a RCT
Eftekhar, M., Mohammadian, F., Yousefnejad, F., Molaei, B. and Aflatoonian, A. Comparison of conventional IVF versus ICSI in non-male factor, normoresponder patients. Iran J Reprod Med. 2012; 10 (2): 131-6.	Not a RCT
Farquhar, C. and Marjoribanks, J. Assisted reproductive technology: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2018; (8): -	Summmary of Cochrane reviews
Gennarelli, G., Carosso, A., Canosa, S., Filippini, C., Cesarano, S., Scarafia, C., Brunod, N., Revelli, A. and Benedetto, C. ICSI Versus Conventional IVF in Women Aged 40 Years or More and Unexplained Infertility: A Retrospective Evaluation of 685 Cycles with Propensity Score Model. J Clin Med. 2019; 8 (10):	Not a RCT
Gunn, D. D. and Bates, G. W. Evidence-based approach to unexplained infertility: a systematic review. Fertil Steril. 2016; 105 (6): 1566-1574.e1.	Systematic review without meta-analysis
Haas, J., Miller, T. E., Nahum, R., Aizer, A., Kirshenbaum, M., Zilberberg, E., Lebovitz, O. and Orvieto, R. The role of ICSI vs. conventional IVF for patients with advanced maternal age-a randomized controlled trial. J Assist Reprod Genet. 2021; 38 (1): 95-100.	Ovaries were randomized in stead of women
Isikoglu, M., Avci, A., Kendirci Ceviren, A., Aydınuraz, B. and Ata, B. Conventional IVF revisited: Is ICSI better for non-male factor infertility? Randomized controlled double blind study. J Gynecol Obstet Hum Reprod. 2020; 50 (7): 101990.	Sibling oocytes were randomised to IVF or ICSI, no separate result for UI cohort
Isikoglu, M., Ceviren, A. K., Cetin, T., Avci, A., Aydinuraz, B., Akgul, O. K. and Karaca, M. Comparison of ICSI and conventional IVF in non-male factor patients with less than four oocytes. Arch Gynecol Obstet. 2022;	Not a RCT
Iwamoto, A., Van Voorhis, B. J., Summers, K. M., Sparks, A., Mancuso, A. C. Intracytoplasmic sperm injection vs. conventional in vitro fertilization in patients with non-male factor infertility. Fertil steril 2022; 118(3): 465-472	No stratification according to infertility diagnosis
Jaroudi, K., Al-Hassan, S., Al-Sufayan, H., Al-Mayman, H., Qeba, M. and Coskun, S. Intracytoplasmic sperm injection and conventional in vitro fertilization are complementary techniques in management of unexplained infertility. J Assist Reprod Genet. 2003; 20 (9): 377-81.	Sibling oocytes were randomised to IVF or ICSI
Khamsi, F., Yavas, Y., Roberge, S., Wong, J. C., Lacanna, I. C. and Endman, M. Intracytoplasmic sperm injection increased fertilization and good-quality embryo formation in patients with non-male factor indications for in vitro fertilization: a prospective randomized study. Fertil Steril. 2001; 75 (2): 342-7.	Randomised sibling oocytes to IVF & ICSI
Kim, J. Y., Kim, J. H., Jee, B. C., Lee, J. R., Suh, C. S. and Kim, S. H. Can intracytoplasmic sperm injection prevent total fertilization failure and enhance embryo quality in patients with non-male factor infertility? Eur J Obstet Gynecol Reprod Biol. 2014; 178 188-91.	Not a RCT

Li, Z., Lin, H., Xiao, W. and Wang, Y. Fertilization of IVF/ICSI using sibling oocytes from couples with subfertile male or unexplained infertility. J Huazhong Univ Sci Technolog Med Sci. 2004; 24 (4): 365-8, 384.	Randomised sibling oocytes to IVF & ICSI
Li, Z., Wang, A. Y., Bowman, M., Hammarberg, K., Farquhar, C., Johnson, L., Safi, N. and Sullivan, E. A. ICSI does not increase the cumulative live birth rate in non-male factor infertility. Hum Reprod. 2018; 33 (7): 1322-1330.	Not a RCT
Liu, L., Wang, H., Li, Z., Niu, J. and Tang, R. Obstetric and perinatal outcomes of intracytoplasmic sperm injection versus conventional in vitro fertilization in couples with nonsevere male infertility. Fertil Steril. 2020; 114 (4): 792-800.	Not a RCT
Miller, K. F., Falcone, T., Goldberg, J. M. and Attaran, M. Previous fertilization failure with conventional in vitro fertilization is associated with poor outcome of intracytoplasmic sperm injection. Fertil Steril. 1998; 69 (2): 242-5.	Not a RCT
Ruiz, A., Remohí, J., Minguez, Y., Guanes, P. P., Simón, C. and Pellicer, A. The role of in vitro fertilization and intracytoplasmic sperm injection in couples with unexplained infertility after failed intrauterine insemination. Fertil Steril. 1997; 68 (1): 171-3.	Randomised sibling oocytes to IVF & ICSI
Song, J., Liao, T., Fu, K. and Xu, J. ICSI Does Not Improve Live Birth Rates but Yields Higher Cancellation Rates Than Conventional IVF in Unexplained Infertility. Front Med (Lausanne). 2020; 7 614118.	Not a RCT
Takeuchi, S., Minoura, H., Shibahara, T., Shen, X., Futamura, N. and Toyoda, N. In vitro fertilization and intracytoplasmic sperm injection for couples with unexplained infertility after failed direct intraperitoneal insemination. J Assist Reprod Genet. 2000; 17 (9): 515-20.	Not a RCT
Sauerbrun-Cutler, M. T., Huber, W. J., 3rd, Has, P., Shen, C., Hackett, R., Alvero, R. and Wang, S. Is intracytoplasmic sperm (ICSI) better than traditional in vitro fertilization (IVF): confirmation of higher blastocyst rates per oocyte using a split insemination design. J Assist Reprod Genet. 2020; 37 (7): 1661-1667.	Not a RCT
van Rumste, M. M., Evers, J. L. and Farquhar, C. M. Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility. Cochrane Database Syst Rev. 2003; (2): Cd001301.	Cochrane review included only 1 RCT of non-male factor infertility, this Bhattacharya 2001 is among the list of the 35 studies.
van Rumste, M. M., Evers, J. L. and Farquhar, C. M. ICSI versus conventional techniques for oocyte insemination during IVF in patients with non-male factor subfertility: a Cochrane review. Hum Reprod. 2004; 19 (2): 223-7.	Paper based on above Cochrane review vam Rumste 2003.
Wyns, C., Vandermonde, J., Pirard, C., Demylle, D., Vanabelle, B. and Donnez, J. IVF and ICSI outcome in couples with unexplained infertility: a randomized study of 60 cases. Jornal brasileiro de reproducao assistida. 2004; 8 (5): 16-24.	Not addressing the specific key question of IVF vs ICSI.
Younes, G., Tannus, S., Son, W. Y. and Dahan, M. H. When to do intracytoplasmic sperm injection: a prospective comparison. Arch Gynecol Obstet. 2019; 300 (5): 1461-1471.	Not a RCT
Yovich, J. L., Conceicao, J. L., Marjanovich, N., Ye, Y., Hinchliffe, P. M., Dhaliwal, S. S. and Keane, K. N. An ICSI rate of 90% minimizes complete failed fertilization and provides satisfactory implantation rates without elevating fetal abnormalities. Reprod Biol. 2018; 18 (3): 301-311.	Not a RCT

3.3 Mechanical-surgical procedures

PICO Question: What is the value of mechanical-surgical procedures?

Flowchart



List of excluded papers

Reference	Exclusion criterion
Abdelhamid, A. M. The success rate of pregnancy in IUI cycles following endometrial sampling. A randomized controlled study: endometrial sampling and pregnancy rates. Arch Gynecol Obstet 2013. 288 (3):673-8	Includes mild male factor infertility patients without stratifying results
Aflatoonian, A., Baradaran Bagheri, R. and Hosseinisadat, R. The effect of endometrial injury on pregnancy rate in frozen-thawed embryo transfer: A randomized control trial. Int J Reprod Biomed. 2016; 14 (7): 453-458.	Not stratifying results according to infertility diagnosis
Al-Fadhli, R., Sylvestre, C., Buckett, W. and Tulandi, T. A randomized study of laparoscopic chromopertubation with lipiodol versus saline in infertile women. Fertil Steril. 2006; 85 (2): 505-7.	Included in systematic review Wang et al., 2020
Alleyassin, A., Abiri, A., Agha-Hosseini, M. and Sarvi, F. The Value of Routine Hysteroscopy before the First Intracytoplasmic Sperm Injection Treatment Cycle. Gynecol Obstet Invest. 2017; 82 (2): 125-130.	Included in systematic review Kamath et al., 2019
Bahaa Eldin, A. M., Abdelmaabud, K. H., Laban, M., Hassanin, A. S., Tharwat, A. A., Aly, T. R., Elbohoty, A. E., Elsayed, H. M., Ibrahim, A. M., Ibrahim, M. E., Sabaa, H. M., Abdelrazik, A. A. and Abdelhady, I. Endometrial Injury May Increase the Pregnancy Rate in Patients Undergoing Intrauterine Insemination: An Interventional Randomized Clinical Trial. Reprod Sci. 2016; 23 (10): 1326-31.	Includes mild male factor infertility patients without stratifying results
Bosteels, J., Weyers, S., Mathieu, C., Mol, B. W. and D'Hooghe, T. The effectiveness of reproductive surgery in the treatment of female infertility: facts, views and vision. Facts Views Vis Obgyn. 2010; 2 (4): 232-52.	Replaced by a more recent systematic review Bafort et al., 2020.

Casini, M. L., Rossi, F., Agostini, R. and Unfer, V. Effects of the position of fibroids on fertility. Gynecol Endocrinol. 2006; 22 (2): 106-9.	Not included due to integrity risk rating
Crosby, D. A., Glover, L. E., Downey, P., Mooney, E. E., McAuliffe, F. M., O'Farrelly, C., Brennan, D. J. and Wingfield, M. The impact of accurately timed mid-luteal endometrial injury in nulligravid women undergoing their first or second embryo transfer. Ir J Med Sci. 2021; 190 (3): 1071-1077.	Cohort study in the presence of higher quality evidence
El-Toukhy, T., Campo, R., Khalaf, Y., Tabanelli, C., Gianaroli, L., Gordts, S. S., Gordts, S., Mestdagh, G., Mardesic, T., Voboril, J., Marchino, G. L., Benedetto, C., Al-Shawaf, T., Sabatini, L., Seed, P. T., Gergolet, M., Grimbizis, G., Harb, H. and Coomarasamy, A. Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. Lancet. 2016; 387 (10038): 2614-2621.	Included in systematic review Kamath et al., 2019
Eskew, A. M., Reschke, L. D., Woolfolk, C., Schulte, M. B., Boots, C. E., Broughton, D. E., Jimenez, P. T., Omurtag, K. R., Keller, S. L., Ratts, V. S., Odem, R. R. and Jungheim, E. S. Effect of endometrial mechanical stimulation in an unselected population undergoing in vitro fertilization: futility analysis of a double-blind randomized controlled trial. J Assist Reprod Genet. 2019; 36 (2): 299-305.	No stratification according to infertility diagnosis
Frantz, S., Parinaud, J., Kret, M., Rocher-Escriva, G., Papaxanthos-Roche, A., Creux, H., Chansel-Debordeaux, L., Bénard, A. and Hocké, C. Decrease in pregnancy rate after endometrial scratch in women undergoing a first or second in vitro fertilization. A multicenter randomized controlled trial. Hum Reprod. 2019; 34 (1): 92-99.	No stratification according to infertility diagnosis
Goel, T., Mahey, R., Bhatla, N., Kalaivani, M., Pant, S. and Kriplani, A. Pregnancy after endometrial scratching in infertile couples undergoing ovulation induction and intrauterine insemination cycles-a randomized controlled trial. J Assist Reprod Genet. 2017; 34 (8): 1051-1058.	Includes mild male factor infertility patients without stratifying results
Hamdi, K., Nia, N. M., Hakimi, P. and Ghasemzadeh, A. The effects of endometrial scratch on pregnancy rate in iui cycles. International journal of women's health and reproduction sciences. 2019; 7 (3): 380-384.	no stratification acc to infertility diagnosis
Hebeisha, S. A., Moiety, F. S., Samir, M. and Hussein, M. Effect of endometrial injury on implantation and pregnancy rates: a randomised controlled trial. Clinical and experimental obstetrics & gynecology. 2018; 45 (1): 105-108.	no stratification acc to infertility diagnosis
Helmy, M. E. E., Maher, M. A., Elkhouly, N. I. and Ramzy, M. A randomized trial of local endometrial injury during ovulation induction cycles. Int J Gynaecol Obstet. 2017; 138 (1): 47-52.	no stratification acc to infertility diagnosis
Hodgson R.M., Hui L.L., Wang R., Mol B.W., Johnson N. Interventions for endometriosis-related infertility: a systematic review and network meat-analysis. Fertil Steril. 2020;113 (2):374-382	Replaced by the Cochrane systematic review Bafort et al., 2020
Jafarabadi, M. N., Bagheri, M., Ebrahimi, Z., Shariat, M. and Haghollahi, F. Endometrial scratching effect on pregnancy rate in intrauterine insemination cycles: a randomized controlled trial. International journal of women's health and reproduction sciences. 2020; 8 (1): 85-89.	Not included due to integrity risk rating
Kamath, M. S., Bosteels, J., D'Hooghe, T. M., Seshadri, S., Weyers, S., Mol, B. W. J., Broekmans, F. J. and Sunkara, S. K. Screening hysteroscopy in subfertile women and women undergoing assisted reproduction. Cochrane Database Syst Rev. 2019; 4 (4): Cd012856.	Fist IVF cycles, not specified unexplained infertility
Kang, Y., Wang, Z., Yang, Y., Liang, H., Duan, X., Gao, Q., Yin, Z. Impact of endometrial scratching on reproductive outcome in patients: A systematic review and meta-analysis. Medicine (Baltimore) 2022; 101(33): e30150	Includes mild male factor infertility patients without stratifying results
Letterie, G. S. and Rose, G. S. Pregnancy rates after the use of oil-based and water-based contrast media to evaluate tubal patency. Southern medical journal. 1990; 83 (12): 1402-1403.	Included in systematic review Wang et al., 2020
Liang, Y., Han, J., Jia, C., Ma, Y., Lan, Y., Li, Y. and Wang, S. Effect of Endometrial Injury on Secretion of Endometrial Cytokines and IVF Outcomes in Women with Unexplained Subfertility. Mediators Inflamm. 2015; 2015 757184.	Cohort study in the presence of higher quality evidence

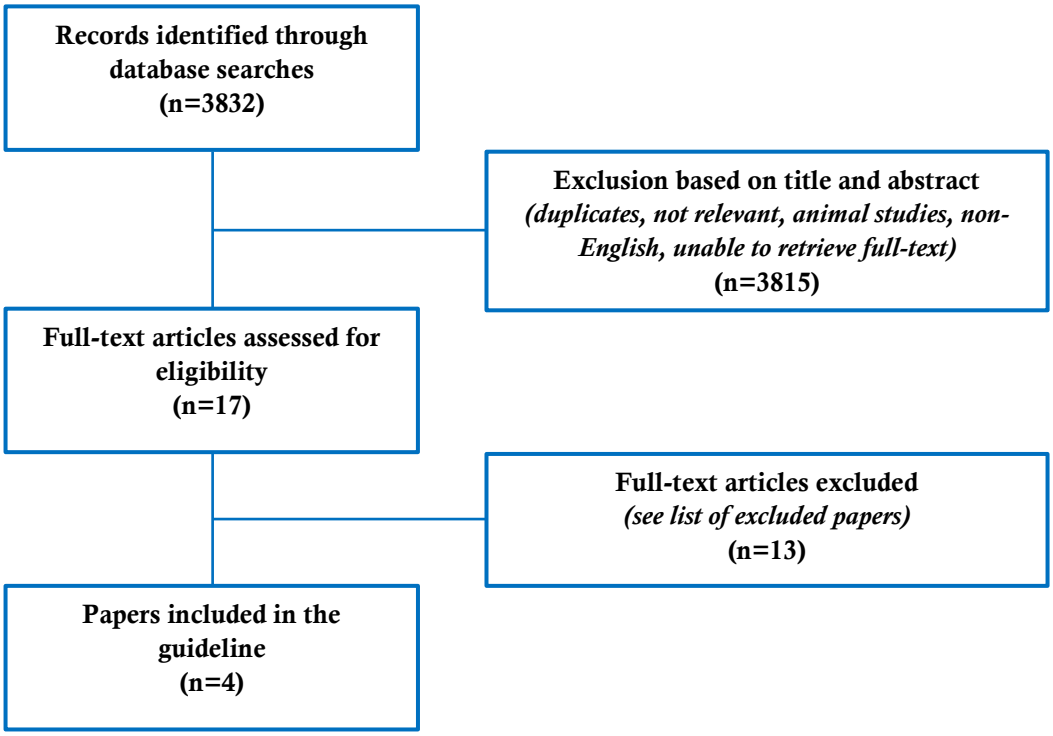
Liu, W., Tal, R., Chao, H., Liu, M. and Liu, Y. Effect of local endometrial injury in proliferative vs. luteal phase on IVF outcomes in unselected subfertile women undergoing in vitro fertilization. Reprod Biol Endocrinol. 2017; 15 (1): 75.	Not stratifying results according to infertility diagnosis
Maged, A. M., Al-Inany, H., Salama, K. M., Souidan, II, Abo Ragab, H. M. and Elnassery, N. Endometrial Scratch Injury Induces Higher Pregnancy Rate for Women With Unexplained Infertility Undergoing IUI With Ovarian Stimulation: A Randomized Controlled Trial. Reprod Sci. 2016; 23 (2): 239-43.	Not included due to integrity risk rating
Mahran, A., Ibrahim, M. and Bahaa, H. The effect of endometrial injury on first cycle IVF/ICSI outcome: a randomized controlled trial. International journal of reproductive biomedicine. 2016; 14 (3): 193-198.	Not stratifying results according to infertility diagnosis
Moramezi, F., Barati, M., Mohammadjafari, R., Barati, S. and Hemadi, M. Effect of hysteroscopy before intra uterine insemination on fertility in infertile couples. Pak J Biol Sci. 2012; 15 (19): 942-6.	Randomisation and allocation concealment not provided. No powercalculation. Not included in the Cochrane review.
Nugent, D., Watson, A. J., Killick, S. R., Balen, A. H. and Rutherford, A. J. A randomized controlled trial of tubal flushing with lipiodol for unexplained infertility. Fertil Steril. 2002; 77 (1): 173-5.	Included in systematic review Wang et al., 2020
Parsanezhad, M. E., Dadras, N., Maharlouei, N., Neghahban, L., Keramati, P. and Amini, M. Pregnancy rate after endometrial injury in couples with unexplained infertility: A randomized clinical trial. Iran J Reprod Med. 2013; 11 (11): 869-74.	Not included due to integrity risk rating
Rama Raju GA, Shashi Kumari G, Krishna KM, Prakash GJ, Madan K. Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome. Archives of Gynecology and Obstetrics 2006;274(3):160-4.	Included in systematic review Kamath et al., 2019
Senocak, G. C., Yapca, O. E. and Borekci, B. Comparison of pregnancy rates between patients with and without local endometrial scratching before intrauterine insemination. J Gynecol Obstet Hum Reprod. 2017; 46 (9): 687-690.	Not included due to integrity risk rating
Seyam, E. M., Hassan, M. M., Mohamed Sayed Gad, M. T., Mahmoud, H. S. and Ibrahim, M. G. Pregnancy Outcome after Office Microhysteroscopy in Women with Unexplained Infertility. Int J Fertil Steril. 2015; 9 (2): 168-75.	Not included due to integrity risk rating
Shawki, H. E., Elmorsy, M. and Eissa, M. K. Routine office hysteroscopy prior to ICSI and its impact on assisted reproduction program outcome: a randomized controlled trial. Middle East Fertility Society journal. 2012; 17 (1): 14-21.	Included in systematic review Kamath et al., 2019
Sherif, A., Abou-Talib, Y., Ibrahim, M. and Arafat, R. The effect of day 6 endometrial injury of the ICSI cycle on pregnancy rate: a randomized controlled trial. Middle East Fertility Society journal. 2018; 23 (4): 292-296.	Not stratifying results according to infertility diagnosis
Shokeir, T., Ebrahim, M. and El - Mogy, H. Hysteroscopic-guided local endometrial injury does not improve natural cycle pregnancy rate in women with unexplained infertility: randomized controlled trial. Journal of obstetrics and gynaecology research. 2016; 42 (11): 1553-1557.	quasi-randomised trial
Smit, J. G., Kasius, J. C., Eijkemans, M. J. C., Koks, C. A. M., van Golde, R., Nap, A. W., Scheffer, G. J., Manger, P. A. P., Hoek, A., Schoot, B. C. and et al. Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. Lancet (london, england). 2016; 387 (10038): 2622-2629.	Included in systematic review Kamath et al., 2019
Soliman, B. S. and Harira, M. Local endometrial scratching under ultrasound-guidance after failed intrauterine insemination and cycle outcome: a randomized controlled trial. Middle East Fertility Society journal. 2017; 22 (1): 60-66.	Includes mild male factor infertility patients without stratifying results
Wadhwa, L. and Mishra, M. Therapeutic Efficacy of Endometrial Scratching in Repeated Controlled Ovarian Stimulation (COS) Failure Cycles. J Hum Reprod Sci. 2018; 11 (1): 59-71.	Not stratifying results according to infertility diagnosis

Wadhwa, L., Pritam, A., Gupta, T., Gupta, S., Arora, S., Chandoke, R. Effect of endometrial biopsy on intrauterine insemination outcome in controlled ovarian stimulation cycle. J Hum Reprod Sci 2015, 8(3): 151-8.	Not stratifying results according to infertility diagnosis
Yavangi, M., Varmaghani, N., Pirdehghan, A., Varmaghani, M. and Faryadras, M. Comparison of pregnancy outcome in intrauterine insemination-candidate women with and without endometrial scratch injury: An RCT. Int J Reprod Biomed. 2021; 19 (5): 457-464.	Not stratifying results according to infertility diagnosis
Yeung, T. W., Chai, J., Li, R. H., Lee, V. C., Ho, P. C. and Ng, E. H. The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing in vitro fertilization: a randomized controlled trial. Hum Reprod. 2014; 29 (11): 2474-81.	Not stratifying results according to infertility diagnosis
Zarei, A., Alborzi, S., Dadras, N. and Azadi, G. The effects of endometrial injury on intrauterine insemination outcome: A randomized clinical trial. Iran J Reprod Med. 2014; 12 (9): 649-52.	Includes mild male factor infertility patients without stratifying results

3.4 Alternative therapeutic approaches

PICO Question: What is the effectiveness of alternative therapeutic approaches?

Flowchart



List of excluded papers

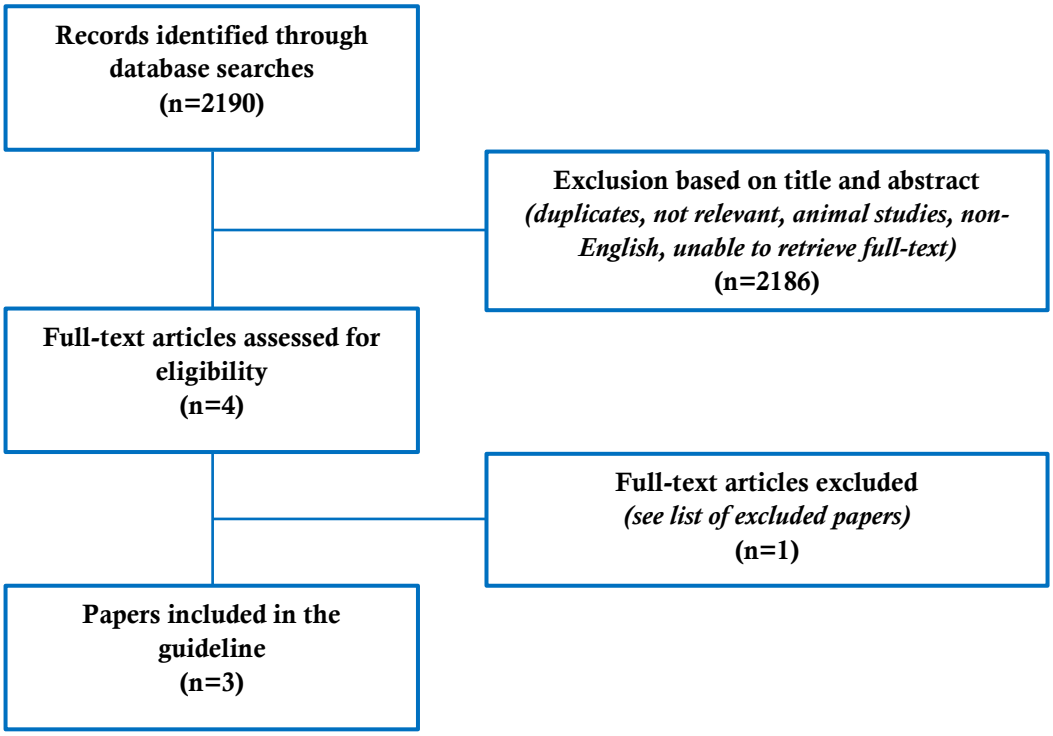
Reference	Exclusion criterion
Badawy, A., Baker El Nashar, A. and El Totongy, M. Clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for augmenting ovulation in the management of unexplained infertility: a randomized double-blind controlled trial. Fertil Steril. 2006; 86 (3): 647-50.	Included in systematic review Showell et al., 2020 but not considered due to being **retracted.**
Cicek, N., Eryilmaz, O. G., Sarikaya, E., Gulerman, C. and Genc, Y. Vitamin E effect on controlled ovarian stimulation of unexplained infertile women. J Assist Reprod Genet. 2012; 29 (4): 325-8.	Included in systematic review Showell et al., 2020 but not considered following integrity assessment
Çoksüer, H., Barut, M. U., Bozkurt, M., Agacayak, E., Sak, S., Demir, M. and Calıskan, E. Acupuncture Enhances Chances of Pregnancy in Unexplained Infertile Patients Who Undergo A Blastocyst Transfer in A Fresh-Cycle. Chin J Integr Med. 2019; 25 (4): 298-302.	Very low quality study
Filipcikova, R., Oborna, I., Brezinova, J., Novotny, J., Wojewodka, G., De Sanctis, J. B., Radova, L., Hajduch, M. and Radzioch, D. Lycopene improves the distorted ratio between AA/DHA in the seminal plasma of infertile males and increases the likelihood of successful pregnancy. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015; 159 (1): 77-82.	Mixture of male infertility and UI but UI not defined to confirm actual UI

Guven, P. G., Cayir, Y. and Borekci, B. Effectiveness of acupuncture on pregnancy success rates for women undergoing in vitro fertilization: A randomized controlled trial. Taiwan J Obstet Gynecol. 2020; 59 (2): 282-286.	Not included due to integrity risk rating
Legro, R. S., Hansen, K. R., Diamond, M. P., Steiner, A. Z., Coutifaris, C., Cedars, M. I., Hoeger, K. M., Usadi, R., Johnstone, E. B., Haisenleder, D. J., Wild, R. A., Barnhart, K. T., Mersereau, J., Trussell, J. C., Krawetz, S. A., Kris-Etherton, P. M., Sarwer, D. B., Santoro, N., Eisenberg, E., Huang, H. and Zhang, H. Effects of preconception lifestyle intervention in infertile women with obesity: The FIT-PLESE randomized controlled trial. PLoS Med. 2022; 19 (1): e1003883.	Not unexplained infertility (UI) as could have had unilat tubal blockage and only considered sperm total motile sperm in the ejaculate in evaluation of male semen anaysis
Murto, T., Skoog Svanberg, A., Yngve, A., Nilsson, T. K., Altmäe, S., Wånggren, K., Salumets, A. and Stavreus-Evers, A. Folic acid supplementation and IVF pregnancy outcome in women with unexplained infertility. Reprod Biomed Online. 2014; 28 (6): 766-72.	Not an intervention study
Neamtiu, I. A., Surcel, M., Begum, T. F., A36Gurzau, E. S., Berindan-Neagoe, I., Braicu, C., Rotar, I., Muresan, D., Bloom, M. S. Specific lifestyle factors and in vitro fertilization outcomes in Romanian women: a pilot study. OeerJ 2022; 10: e14189	No stratification of results according to infertility diagnosis
Park, J. J., Kang, M., Shin, S., Choi, E., Kwon, S., Wee, H., Nam, B. and Kaptchuk, T. J. Unexplained infertility treated with acupuncture and herbal medicine in Korea. J Altern Complement Med. 2010; 16 (2): 193-8.	Combination of 2 interventions.
Salas-Huetos, A., Arvizu, M., Mínguez-Alarcón, L., Mitsunami, M., Ribas-Maynou, J., Yeste, M., Ford, J. B., Souter, I., Chavarro, J. E. Women's and men's intake of omega-3 fatty acids and their food sources and assisted reproductive technology outcomes. Am J Obstet Gynecol 2022; 227(2): 246.e1-246.e11	No stratification of results according to infertility diagnosis
Wang, B., Li, Z., Gao, W., Han, S., Li, Y. and Bai, C. Analysis of the application value of Dakundan combined with acupuncture in patients with infertility. Minerva Surg. 2021;	The interventions had additional treatments.
Wild, R. A., Edwards, R. K., Zhao, D., Kim, A. S., Hansen, K. R. Immediate weight loss before ovarian stimulation with intrauterine insemination is associated with a lower risk of preeclampsia in women with obesity and unexplained infertility. F S Rep 2022; 3(3): 264-268	Not unexplained infertility (UI) as could have had unilat tubal blockage and only considered sperm total motile sperm in the ejaculate in evaluation of male semen anaysis
Youssef, M. A., Abdelmoty, H. I., Elashmwi, H. A., Abduljawad, E. M., Elghamary, N., Magdy, A., Mohesen, M. N., Abdella, R. M., Bar, M. A., Gouda, H. M., Ali, A. M., Raslan, A. N., Youssef, D., Sherif, N. A. and Ismail, A. I. Oral antioxidants supplementation for women with unexplained infertility undergoing ICSI/IVF: randomized controlled trial. Hum Fertil (Camb). 2015; 18 (1): 38-42.	Compared 2 anti-oxidants against each other

4. Quality of life

PICO Question: Is there a difference in QoL for patients with unexplained versus explained infertility?

Flowchart



List of excluded papers

	Exclusion criterion
Krol, M., Nap, A., Michels, R., Veraart, C. and Goossens, L. Health state utilities for infertility and subfertility. Reprod Health. 2019; 16 (1): 47.	No distinction is made for QoL between explained and unexplained infertility.

4. EVIDENCE TABLES

2. Diagnosis

2.1 Confirmation of ovulation

PICO QUESTION: SHOULD COUPLES WITH MILD INFERTILITY FACTORS BE INCLUDED IN THE DEFINITION OF UI?

MENSTRUAL HISTORY + ONE PROGESTERONE/ USS/ LH URINARY MEASUREMENT IN LUTEAL PHASE (NICE)

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Guermandi, E., Vegetti, W., Bianchi, M. M., Uglietti, A., Ragni, G. and Crosignani, P. Reliability of ovulation tests in infertile women. Obstet Gynecol. 2001; 97 (1): 92-6.	CS	101 infertile couples - regular 26-34 days and previous mid-luteal P test normal. Women were excluded if their serum FSH and LH concentrations in early follicular phase were higher than 10 mUI/mL and 12 mUI/mL, respectively, or if their prolactin exceeded 20 ng/mL in the midluteal phase. Exclusion criteria also included clinical signs of PCOS (acne, hirsutism, oligomenorrhea, obesity) or ultrasound evidence of polycystic ovaries according to the criteria of Adams et al,20 any ovarian or	Transvaginal ultrasound monitoring= gold standard; Urinary LH, BBT, Serum P	sensitivity, specificity, and accuracy in predicting or confirming ovulation	evidence of ovulation on USS: 96% (97/101 cycles). Urinary LH surge detected in 99% (100/101 cycles); agreement with USS: 97%; Sensitivity, specificity, and accuracy for LH readings were 1.00, 0.25, and 0.97, respectively BBT: 67 cycles in agreement with USS, 0.77 sensitivity, 0.33 specificity, and 0.74 accuracy for ovulation detection compared with USS. Serum P4 79%	Urinary LH best marker, P4 based on menstrual history performed worse	

		abdominal abnormalities that would interfere with adequate ultrasound investigation, and evidence or history of endocrine or other diseases that might influence the menstrual cycle.					

LUTEINIZING HORMONE (LH) URINARY MEASUREMENT

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Martinez, A. R., Bernardus, R. E., Kucharska, D. and Schoemaker, J. Urinary luteinizing hormone testing and prediction of ovulation in spontaneous, clomiphene citrate and human menopausal gonadotropin-stimulated cycles. A clinical evaluation. Acta Endocrinol (Copenh). 1991; 124 (4): 357-63.	CS	303 (but only 99 in spontaneous cycles that can be used)	Urinary LH (colour test), ultrasound	Agreement Urinary LH vs ultrasound	Positive test results, presumably reflecting the occurrence of a urinary LH surge above 50 IU/1, were observed in 97 (98%) spontaneous cycles The basal body temperature nadir correlated with the day of the positive test in 30% of spontaneous cycles.	Urinary LH testing with the LH Colour proved to be a simple and accurate method to detect the midcycle LH surge and predict ovulation.	
Bischof, P., Bianchi, P. G. and Campana, A. Comparison of a rapid, quantitative and automated assay for urinary luteinizing	CS	32 spontaneously ovulating women.	Serum E2, ultrasound and urinary LH (by automated microparticle enzyme immunoassay for	Agreement quantitative and qualitative LH tests	follicular rupture was seen on day 1 or 2 after the LH peak. The time between the urinary LH peak and follicular rupture (as documented by daily ultrasound scans) varied between 9-51 h	Urinary LH testing was a simpler alternative to repetitive venopuncture	Comparison between qualitative and quantitative scores.

hormone (LH), with an LH detection test, for the prediction of ovulation. Hum Reprod. 1991; 6 (4): 515-8.			serum LH and by color assay)				
Gregoriou, O., Kassanos, D., Vitoratos, N., Papadias, C. and Zourlas, P. A. Clinical efficacy of LH-color: a new home ovulation test. Int J Gynaecol Obstet. 1990; 32 (2): 141-3.	CS	55 women. All patients had been previously investigated and were assumed to have normal ovulatory menstrual cycles. All had prior biphasic BBT charts with cycle lengths of 26 -32 days. All had been previously noted to have single midluteal serum progesterone determination of > 10 ng/ml and in-phase luteal phase endometrial biopsy. All had adequate midcycle cervical mucus and serum testosterone, DHEA sulfate, TSH, and prolactin within normal range.	USS vs LG urinary measurement at 0700 h and 1900 h by LH-Colour. Daily measurements of BBT were recorded and the predictor point of ovulation was the thermal nadir.	Agreement	100% agreement to detect ovulation. In 20 (36.36%) of the cases, the thermal nadir was noted on the day of decolouration, whereas in 22 (40%) and 13 (23.6%) patients the thermal nadir occurred on days - 1 and + 1 and on days -2anddays +2of the LH surge, respectively. The predictive value of LH-Colour was assessed in relation to the day of ovulation by echography. In 39 of the 55 cases (70.91%), ovulation occurred in the 24 h after the decolouration of the LH-Colour. Ultrasound showed the disappearance all of the dominant follicles	The good correlation found between the urinary LH surge and ultrasound, allows us to suggest the LH-Colour test as a reliable method in the study of infertile population and also as an adjunct to natural family planning. It is not to say that a urine test can replace the other methods that have been employed up to now, but the LH-Colour diminishes elaborate cycle monitoring and thus the inconvenience and cost for the patients as well as the workload of the physician.	
Guermandi, E., Vegetti, W., Bianchi, M. M., Uglietti, A., Ragni, G. and Crosignani, P. Reliability of ovulation tests in infertile women. Obstet Gynecol. 2001; 97 (1): 92-6.	CS	101 infertile couples - regular 26-34 days and previous mid-luteal P test normal. Women were excluded if their serum FSH and LH concentrations in early follicular phase were higher	Transvaginal ultrasound monitoring= gold standard; Urinary LH, BBT, Serum P	sensitivity, specificity, and accuracy in predicting or confirming ovulation	evidence of ovulation on USS: 96% (97/101 cycles). Urinary LH surge detected in 99% (100/101 cycles); agreement with USS: 97%; Sensitivity, specificity, and accuracy for LH readings were 1.00, 0.25, and 0.97, respectively	Urinary LH best marker, P4 based on menstrual history performed worse	

		than 10 mUI/mL and 12 mUI/mL, respectively, or if their prolactin exceeded 20 ng/mL in the midluteal phase. Exclusion criteria also included clinical signs of PCOS (acne, hirsutism, oligomenorrhea, obesity) or ultrasound evidence of polycystic ovaries according to the criteria of Adams et al,20 any ovarian or abdominal abnormalities that would interfere with adequate ultrasound investigation, and evidence or history of endocrine or other diseases that might influence the menstrual cycle.			BBT: 67 cycles in agreement with USS, 0.77 sensitivity, 0.33 specificity, and 0.74 accuracy for ovulation detection compared with USS. Serum P4 79%		

SERIAL BASAL BODY TEMPERATURE (BBT)

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Gregoriou, O., Kassanos, D., Vitoratos, N., Papadias, C. and Zourlas, P. A. Clinical efficacy of LH-color: a new home ovulation test. Int J Gynaecol Obstet. 1990; 32 (2): 141-3.	CS	55 women. All patients had been previously investigated and were assumed to have normal ovulatory menstrual cycles. All had prior biphasic BBT charts with cycle lengths of 26 -32 days. All had been previously noted to have single midluteal serum progesterone determination of > 10 ng/ml and in-phase luteal phase endometrial biopsy. All had adequate midcycle cervical mucus and serum testosterone, DHEA sulfate, TSH, and prolactin within normal range.	USS vs LG urinary measurement at 0700 h and 1900 h by LH-Colour. Daily measurements of BBT were recorded and the predictor point of ovulation was the thermal nadir.	Agreement	100% agreement to detect ovulation. In 20 (36.36%) of the cases, the thermal nadir was noted on the day of decolouration, whereas in 22 (40%) and 13 (23.6%) patients the thermal nadir occurred on days - 1 and + 1 and on days -2anddays +2of the LH surge, respectively. The predictive value of LH-Colour was assessed in relation to the day of ovulation by echography. In 39 of the 55 cases (70.91%), ovulation occurred in the 24 h after the decolouration of the LH-Colour. Ultrasound showed the disappearance all of the dominant follicles	The good correlation found between the urinary LH surge and ultrasound, allows us to suggest the LH-Colour test as a reliable method in the study of infertile population and also as an adjunct to natural family planning. It is not to say that a urine test can replace the other methods that have been employed up to now, but the LH-Colour diminishes elaborate cycle monitoring and thus the inconvenience and cost for the patients as well as the workload of the physician.	
Guermandi, E., Vegetti, W., Bianchi, M. M., Uglietti, A., Ragni, G. and Crosignani, P. Reliability of ovulation tests in infertile women. Obstet	CS	101 infertile couples - regular 26-34 days and previous mid-luteal P test normal. Women were excluded if their serum FSH and LH concentrations in early	Transvaginal ultrasound monitoring= gold standard; Urinary LH, BBT, Serum P	sensitivity, specificity, and accuracy in predicting or confirming ovulation	evidence of ovulation on USS: 96% (97/101 cycles). Urinary LH surge detected in 99% (100/101 cycles); agreement with USS: 97%; Sensitivity, specificity, and accuracy for LH readings were 1.00, 0.25, and 0.97,	Urinary LH best marker, P4 based on menstrual history performed worse	

Gynecol. 2001; 97 (1): 92-6.		follicular phase were higher than 10 mUI/mL and 12 mUI/mL, respectively, or if their prolactin exceeded 20 ng/mL in the midluteal phase. Exclusion criteria also included clinical signs of PCOS (acne, hirsutism, oligomenorrhea, obesity) or ultrasound evidence of polycystic ovaries according to the criteria of Adams et al,20 any ovarian or abdominal abnormalities that would interfere with adequate ultrasound investigation, and evidence or history of endocrine or other diseases that might influence the menstrual cycle.			respectively BBT: 67 cycles in agreement with USS, 0.77 sensitivity, 0.33 specificity, and 0.74 accuracy for ovulation detection compared with USS. Serum P4 79%		
Martinez, A. R., Bernardus, R. E., Kucharska, D. and Schoemaker, J. Urinary luteinizing hormone testing and prediction of ovulation in spontaneous, clomiphene citrate and human menopausal gonadotropin-stimulated cycles. A clinical evaluation. Acta Endocrinol (Copenh). 1991; 124 (4): 357-63.	CS	303 (but only 99 in spontaneous cycles that can be used)	Urinary LH (colour test), ultrasound	Agreement Urinary LH vs ultrasound	Positive test results, presumably reflecting the occurrence of a urinary LH surge above 50 IU/1, were observed in 97 (98%) spontaneous cycles The basal body temperature nadir correlated with the day of the positive test in 30% of spontaneous cycles.	Urinary LH testing with the LH Colour proved to be a simple and accurate method to detect the midcycle LH surge and predict ovulation.	

2.2 Oocyte/corpus luteum quality

PICO Question: What is the reliability of parameters detecting good oocyte/ corpus luteum quality?

Mid-luteal phase progesterone levels

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Hull, M. G., Savage, P. E., Bromham, D. R., Ismail, A. A. and Morris, A. F. The value of a single serum progesterone measurement in the midluteal phase as a criterion of a potentially fertile cycle ("ovulation") derived form treated and untreated conception cycles. Fertil Steril. 1982; 37 (3): 355-60.	CS	138 cycles of 72 women with no physical cause for infertility were included as a subgroup.	midluteal serum progesterone level	conception spontaneous or with treatment	Lowest threshold was 8.5 ng/ml for conception cycles.	A midluteal serum P level above 9.4 ng/ml suggests better results.	The study design does not allow definitive conclusions.

ENDOMETRIAL BIOPSY

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Edi-Osagie, E. C., Seif, M. W., Aplin, J. D., Jones, C. J., Wilson, G. and Lieberman, B. A. Characterizing the endometrium in unexplained and tubal factor infertility: a multiparametric investigation. Fertil Steril. 2004; 82 (5): 1379-89.	CS	20 women with UI, 22 tubal factor, 21 fertile controls. Average age of 34, similar characteristics. Basal FSH <10 IU/L	Endometrial histology by Noyes criteria during the midluteal phase.	Endometrial maturation	UI group had similar maturation as fertile controls.		
Coutifaris, C., Myers, E. R., Guzick, D. S., Diamond, M. P., Carson, S. A., Legro, R. S., McGovern, P. G., Schlaff, W. D., Carr, B. R., Steinkampf, M. P. and et al. Reprint of: histological dating of timed endometrial biopsy tissue is not related to fertility status. Fertility and sterility. 2019; 112 (4): e116-e124.	RCT	287 ovulatory female partners of infertile couples, not necessarily UI. And 332 fertile women	Midluteal or late luteal endometrial biopsy, Noyes criteria.	Prevalence of out of phase endometrial biopsies	Prevalence of out of phase endometrial biopsy results were similar between fertile and infertile women in adjusted analyses. ROC curves showed less than 0.5 AUC values for endometrial biopsy to differentiate fertile and infertile women.		Male factor not assessed, not specific to UI, but in general suggests that endometrial dating does not help identifying infertile women.

2.3 Ovarian reserve

PICO Question: Should one or more tests of ovarian reserve be included in the diagnostic work-up?

AMH

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Casadei, L., Manicuti, C., Puca, F., Madrigale, A., Emidi, E. and Piccione, E. Can anti-Müllerian hormone be predictive of spontaneous onset of pregnancy in women with unexplained infertility? J Obstet Gynaecol. 2013; 33 (8): 857-61.	CS	83 women with unexplained infertility aged 35.9 ± 5.4 years (21 - 48 years), AMH 1.76 ± 1.47 ng/ml, 2.8 ± 2.4 years of infertility.	AMH-EIA Beckman Coulter A11893. underwent 6 months expectant management before ART.	Spontaneous pregnancy without live birth rate	14 women (17%) achieved spontaneous pregnancy. AMH had an AUC of 0.385 ± 0.07 (95% CI 0.25 - 0.52) spontaneous pregnancy	Serum AMH was not predictive of spontaneous pregnancy, women with AMH< 0.75 ng/ml had similar pregnancy rates with women who had higher AMH despite the former being older.	

Depmann M., Broer S. L., Eijkemans M. J. C., van Rooij I. A. J., Scheffer G. J., Heimensem J., Mol B. W., Broekmans F. J. M. Anti-Müllerian hormone does not predict time to pregnancy: results of a prospective cohort study. Gynecol Endocrinol. 2017 Aug;33(8):644-648.	CS	Prospective CS. Inclusion criteria were female age ranging between 18 and 46 years, the presence of two ovaries, no adnexal surgery in the past and the presence of a regular menstrual cycle (21–35 days).	A transvaginal ultrasound was performed for the assessment of the number of follicles measuring 2–10 mm. Blood samples were obtained for assessment of AMH and FSH.	Viable pregnancy of at least 11 weeks of gestational age	In the univariate analysis (Table 2), both the AFC and female age were significantly capable of predicting TTOP (p=0.02 and p=0.01 respectively). However, the C-statistic for both variables was poor (0.54 and 0.56, respectively). AMH was not significantly capable of predicting TTOP (HR 1.66, 95% CI 0.97–2.85, p values 0.18, C-statistic 0.55). In the multivariate Cox regression analysis (Table 2), where a correction for female age was performed, none of the variables analysed was significantly correlated with TTOP, nor did they reach a predictive accuracy level of any importance.		
Greenwood, E. A., Cedars, M. I., Santoro, N., Eisenberg, E., Kao, C. N., Haisenleder, D. J., Diamond, M. P. and Huddleston, H. G. Antimüllerian hormone levels and antral follicle counts are not reduced compared with community controls in patients with rigorously defined unexplained infertility. Fertil Steril. 2017; 108 (6): 1070-1077.	CS	277 women with unexplained infertility 32.3 ± 0.2 (25 - 40) years of age, randomly selected from the AMIGOS trial participants (Diamond et al. 2015, FS 2015;103:962) had to have cycle day 1 - 5 FSH <12 IU/L during the previous year, and >9 cycles/year. Male with >5 million/ml sperm. Compared with 226 ovulatory women from the OVA study (Rosen et al. FS 2012;97:238, community based ovarian ageing study), not seeking fertility treatment, aged 33.1 ± 0.3	CD 2 - 4, for infertile women and controls (Shimadzu 4 - 8 MHz transvaginal)	AFC .	Analyses adjusted for age, race, BMI, smoking and study site revealed that infertility was not a predictor of AFC.		Large study with proper definitions of participants and analyses, suggest that women with UI do not have lower AMH levels than healthy women from the community, yet 54% of controls were nulligravid, risking

		years (25 - 40). Women with FSH >12 IU/L were excluded from the control group.					underestimation of a difference.
Hagen C. P., Vestergaard S., Juul A., Skakkebæk N. E., Andersson A., Main K. M., Hjøllund N. H., Ernst E., Bonde J.P., Anderson R.A., Jensen T. K. Low concentration of circulating antimüllerian hormone is not predictive of reduced fecundability in young healthy women: a prospective cohort study. Fertil Steril 2012;98(6):1602-8	CS	Prospective CS. 430 couples with no previous reproductive experience who intended to discontinue contraception to become pregnant were eligible for enrolment.	AMH concentrations were determined in a subgroup of 186 women	Fecundability ratio (monthly probability of conceiving)	Compared with the reference group of women with medium AMH levels, the unadjusted odds ratios of not becoming pregnant within the first six cycles for those with low AMH and high AMH were 1.35 (95 % CI 0.63–2.89) and 1.60 (0.76–3.39), respectively (Fig. 1 and Table 2). Compared with women with medium AMH, the monthly probabilities of conceiving (FR) for those with low and high AMH were 0.87 (95% CI 0.51–1.46) and 0.67 (95% CI 0.42–1.08), respectively (Table 2, unadjusted data in model 1). In the low AMH group, the adjusted FR was not different to the reference group, 0.81 (95% CI 0.44–1.40).		

Hvidman H. W., Bentzen J. G., Thuesen L. L., Lauritsen M. P., Forman J. L., Loft A., Pinborg A., Nyboe Andersen A.. Infertile women below the age of 40 have similar anti-Müllerian hormone levels and antral follicle count compared with women of the same age with no history of infertility. Hum Reprod. 2016;31(5):1034-45	CS	Prospective CS with a historical control group. 382 infertile patients. Excluded: (i) patients referred for PGD, (ii) patients referred due to HIV or contagious hepatitis B or C infection and (iii) single and homosexual women, as they were per se not considered infertile. Furthermore, patients referred directly for oocyte donation (OD) or patients with PCOS were not included.	Study group: infertile women Control group: 350 non-users of hormonal contraception and no history of infertility A transvaginal ultrasonography was performed on CD 2–5. Blood samples were taken on CD 2-5.	Ovarian reserve parameters and age in infertile patients versus controls	The age-related depletion of the ovarian reserve was the same in the two cohorts; AMH levels decreased by 5.5% (95% CI: 4;7%) and AFC decreased by 5% (95% CI: 4;6%) per year age increase. Patients with unexplained infertility had similar AMH levels (age-adjusted: 28%, 95% CI: 223;10%) and AFC (age-adjusted: 25%, 95% CI: 216;7%) compared with other patients. In an age adjusted subgroup analysis comparing patients with unexplained infertility with controls, no differences in neither AMH levels (5%, 95% CI: 222;25%) nor AFC (22%, 95% CI: 214;11%) were observed.		
Nguyen, D. K., O'Leary, S., Gadalla, M. A., Roberts, B., Alvino, H., Tremellen, K. P. and Mol, B. W. The predictive value of anti-Müllerian hormone for natural conception leading to live birth in subfertile couples. Reprod Biomed Online. 2022; 44 (3): 557-564.	CS	Retrospective CS. exclusion criteria were couples who had anovulation, two-sided tubal blockage or total motile sperm count less than 1×10^6 (severe male factor) and couples with female age above 42 years.	AMH (ELISA)	natural conception leading to live birth within 12 months since consultation was recorded.	325 couples were eligible for inclusion in the final analysis. Thirty (9.2%) couples achieved natural conception, whereas 223 (68.6%) started ART treatment within 12 months. Forty-seven (14.5%) couples completed 12 months of follow-up without achieving natural conception and 25 couples (7.7%) were lost to follow-up. The estimated cumulative probability of achieving a natural conception leading to live birth for the cohort within 12 months since consultation was 20.9% (95% CI 12.9% to 28.2%). The unadjusted hazard ratio of serum AMH was 0.94 (95% CI 0.82 to 1.08, P = 0.369), the adjusted HR was 0.85 (95% CI 0.71 to 1.00, P = 0.066).		

Steiner, A. Z., Pritchard, D., Stanczyk, F. Z., Kesner, J. S., Meadows, J. W., Herring, A. H. and Baird, D. D. Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age. Jama. 2017; 318 (14): 1367-1376.	CS	750 women recruited from community, 30 to 44 years of age, women with a risk factor or history of infertility were excluded such as breastfeeding women or those with a partner with known fertility problem, who had been trying ot conceive for 3 months or less.	serum on day 2 - 4, stored at -30 C, Ultrasensitive Ansh AMH kit, trying to conceive spontaneously	spontaneous conception attempt for 6 - 12 months	65% conceived in 6, 77% in 12 months, Cumulative probability of conception was not different for women with AMH <0.7 ng/ml, 0.7 - 8.4 ng/ml, or >8.4 ng(ml after adjusting for age, race, BMI, current smoking, recent contraceptive use.	AMH is not associated with spontaneous pregnancy	Not a population with UI but answers the Question, whether ORTs can predict fertility, despite the limitations.
Yücel, B., Kelekci, S. and Demirel, E. Decline in ovarian reserve may be an undiagnosed reason for unexplained infertility: a cohort study. Arch Med Sci. 2018; 14 (3): 527-531.	CS	148 women with UI (FSH >10 were excluded) and 112 women with male factor infertility, groups were similar for age, BMI, duration of infertility, and type of infertility (primary vs secondary)	serum collected on cycle day 2 - 4, stored at -20C, AMH-EIA Beckman Coulter A11893	women with UI had lower AMH levels then male factor group, 1.42 (0.4 - 6.2) vs 2.04 (0.64 - 8.2) ng(/ml, resp. Log regression with infertility as the dependent showed that AMH was significantly associated with UI, after adjusting for age.	women with UI had lower AMH levels than male factor group, 1.42 (0.4 - 6.2) vs 2.04 (0.64 - 8.2) ng(/ml, resp. Log regression with infertility as the dependent showed that AMH was significantly associated with UI, after adjusting for age.		poor quality study with regard to statistics.
Murto, T., Bjuresten, K., Landgren, B. M. and Stavreus-Evers, A. Predictive value of hormonal parameters for live birth in women with unexplained infertility and male infertility. Reprod Biol Endocrinol. 2013; 11 61.	CS	42 women with UI and 29 women with male infertility (abnormal semen analysis as per WHO criteria at the time), similar age and BMI	cycle day 2 - 5 AMH level Beckman Coulter, probability of live birth in 5 years, spontaneous or by fertility treatment	probability of live birth in 5 years, spontaneous or by treatment	Serum AMH levels were similar between UI and male factor groups, 2.7 (0.18 - 8.5) vs 2.95 (0.74 - 8.5) ng/ml, respectively, p = 0.98. AMH alone was a poor predictor.		small sample, very old study, yet results consistent with others.

AFC

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Casadei, L., Manicuti, C., Puca, F., Madrigale, A., Emidi, E. and Piccione, E. Can anti-Müllerian hormone be predictive of spontaneous onset of pregnancy in women with unexplained infertility? J Obstet Gynaecol. 2013; 33 (8): 857-61.	CS	83 women with unexplained infertility aged 35.9 ± 5.4 years (21 - 48 years), AMH 1.76 ± 1.47 ng/ml, 2.8 ± 2.4 years of infertility.	Day 2 - 5 of cycle, sum of all follicles 2 - 9 mm in both ovaries, Hitachi 6.5 MHz vaginal probe	Spontaneous pregnancy without live birth rate	14 women (17%) achieved spontaneous pregnancy. AFC had an AUC of 0.418 ± 0.08 (95% CI 0.26 - 0.57) spontaneous pregnancy	AFC was not predictive of spontaneous pregnancy, AFC was highly correlated with AMH	
Depmann M., Broer S. L., Eijkemans M. J. C., van Rooij I. A. J., Scheffer G. J., Heimensem J., Mol B. W., Broekmans F. J. M. Anti-Müllerian hormone does not predict time to pregnancy: results of a prospective cohort study. Gynecol Endocrinol. 2017 Aug;33(8):644-648.	CS	prospective CS. Inclusion criteria were female age ranging between 18 and 46 years, the presence of two ovaries, no adnexal surgery in the past and the presence of a regular menstrual cycle (21–35 days).	A transvaginal ultrasound was performed for the assessment of the number of follicles measuring 2–10 mm. Blood samples were obtained for assessment of AMH and FSH.	viable pregnancy of at least 11 weeks of gestational age	In the univariate analysis (Table 2), both the AFC and female age were significantly capable of predicting TTOP (p¼0.02 and p¼0.01 respectively). However, the C-statistic for both variables was poor (0.54 and 0.56, respectively). AMH was not significantly capable of predicting TTOP (HR 1.66, 95% CI 0.97–2.85, p values 0.18, C-statistic 0.55). In the multivariate Cox regression analysis (Table 2), where a correction for female age was performed, none of the variables analysed was significantly correlated with TTOP, nor did they		

					reach a predictive accuracy level of any importance.		
Greenwood, E. A., Cedars, M. I., Santoro, N., Eisenberg, E., Kao, C. N., Haisenleder, D. J., Diamond, M. P. and Huddleston, H. G. Antimüllerian hormone levels and antral follicle counts are not reduced compared with community controls in patients with rigorously defined unexplained infertility. Fertil Steril. 2017; 108 (6): 1070-1077.	CS	277 women with unexplained infertility 32.3 ± 0.2 (25 - 40) years of age, randomly selected from the AMIGOS trial participants (Diamond et al. 2015, FS 2015;103:962) had to have cycle day 1 - 5 FSH <12 IU/L during the previous year, and >9 cycles/year. Male with >5 million/ml sperm. Compared with 226 ovulatory women from the OVA study (Rosen et al. FS 2012;97:238, community based ovarian ageing study), not seeking fertility treatment, aged 33.1 ± 0.3 years (25 - 40). Women with FSH >12 IU/L were excluded from the control group.	CD 2 - 4, for infertile women and controls (Shimadzu 4 - 8 MHz transvaginal)	AFC	Analyses adjusted for age, race, BMI, smoking and study site revealed that infertility was not a predictor of AFC .	Large study with proper definitions of participants and analyses, suggest that women with UI do not have lower AMH levels than healthy women from the community, yet 54% of controls were nulligravid, so this is low quality evidence and can be been excluded.	unfortunately 46% of controls were nulligravid.

Hvidman H. W., Bentzen J. G., Thuesen L. L., Lauritsen M. P., Forman J. L., Loft A., Pinborg A., Nyboe Andersen A.. Infertile women below the age of 40 have similar anti-Müllerian hormone levels and antral follicle count compared with women of the same age with no history of infertility. Hum Reprod. 2016;31(5):1034-45	CS	prospective CS with a historical control group. 382 infertile patients. Excluded: (i) patients referred for PGD, (ii) patients referred due to HIV or contagious hepatitis B or C infection and (iii) single and homosexual women, as they were per se not considered infertile. Furthermore, patients referred directly for oocyte donation (OD) or patients with PCOS were not included.	study group: infertile women control group: 350 non-users of hormonal contraception and no history of infertility A transvaginal ultrasonography was performed on CD 2–5. Blood samples were taken on CD 2-5.	Ovarian reserve parameters and age in infertile patients versus controls	The age-related depletion of the ovarian reserve was the same in the two cohorts; AMH levels decreased by 5.5% (95% CI: 4;7%) and AFC decreased by 5% (95% CI: 4;6%) per year age increase. Patients with unexplained infertility had similar AMH levels (age-adjusted: 28%, 95% CI: 223;10%) and AFC (age-adjusted: 25%, 95% CI: 216;7%) compared with other patients. In an age-adjusted subgroup analysis comparing patients with unexplained infertility with controls, no differences in neither AMH levels (5%, 95% CI: 222;25%) nor AFC (22%, 95% CI: 214;11%) were observed.		

Rosen M. P., Johnstone E., Addauan-Andersen C., Cedars M. I.. lower antral follicle count is associated with infertility. Fertil Steril. 2011;95(6):1950-4	CS	case-control study. inclusion criteria for the infertile group included: 1) age 25–45 years; 2).regular ovulatory menstrual cycles between 22 and 35 days; 3) no endocrinopathies; and 4) with a diagnosis of unexplained infertility. Women with surgically diagnosed endometriosis, ovarian failure, tubal factor, isolated male factor, anovulation, or use of an oocyte donor or gestational surrogate were excluded. The control group for the primary analysis (community group) was composed of ovulatory women with regular menstrual cycles between 22 and 35 days in length, aged 25–45 years, and enrolled in the OVA (Ovarian Aging) study.	women presenting to the infertility clinic with unexplained infertility were compared with a sampling frame of women from the general community. AFC by TVS	relationship between AFC and infertility	The median AFC was lower and FSH significantly higher in the infertile women. The proportion of women with history of a live birth was significantly higher in the community compared with the infertile women (53% versus 8.2%; P<.0001). The infertile women have significantly lower AFCs for each age group except those women between 41–45 years of age. The difference in median AFC between groups was four for women 25–30 and 31–35 years of age and three for women 36–40 years of age.		
Yücel, B., Kelekci, S. and Demirel, E. Decline in ovarian reserve may be an undiagnosed reason for unexplained infertility: a cohort study. Arch Med Sci. 2018; 14 (3): 527-531.	CS	148 women with UI (FSH >10 were excluded) and 112 women with male factor infertility, groups were similar for age, BMI, duration of infertility, and type of infertility (primary vs secondary)	examination on cycle day 2 - 4, medison 7.5 MHz transvaginal probe, total follicle count between 2 - 10 mm	women with UI had lower AFC than male factor group, 9 (3 - 16) vs 10 (3 - 23) , resp., p =0.02. Log regression with infertility as the dependent showed that AFC was NOT	women with UI had lower AFC than male factor group, 9 (3 - 16) vs 10 (3 - 23) , resp., p =0.02. Log regression with infertility as the dependent showed that AFC was NOT significantly associated with UI, after adjusting for age.	poor quality study with regard to statistics.	poor quality study with regard to statistics.

				significantly associated with UI, after adjusting for age.			

DAY 3 FSH AND ESTRADIOL

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Steiner, A. Z., Pritchard, D., Stanczyk, F. Z., Kesner, J. S., Meadows, J. W., Herring, A. H. and Baird, D. D. Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age. Jama. 2017; 318 (14): 1367-1376.	CS	750 women recruited from community, 30 to 44 years of age, women with a risk factor or history of infertility were excluded such as breastfeeding women or those with a partner with known fertility problem, who had been trying ot conceive for 3 months or less.	serum on day 2 - 4, Immulyte Siemens FSH kit	spontaneous conception attempt for 6 - 12 months	65% conceived in 6, 77% in 12 months, Cumulative probability of conception was not different for women with FSH>10 IU/L, after adjusting for age, race, BMI, current smoking, recent contraceptive use (HR 1.22, 0.92 to 1.62.	FSH is not associated with spontaneous pregnancy	Not a population with UI but answers the Question, whether ORTs can predict fertility, despite the limitations.
Yücel, B., Kelekci, S. and Demirel, E. Decline in ovarian reserve may be an undiagnosed reason for unexplained infertility: a cohort study. Arch Med Sci. 2018; 14 (3): 527-531.	CS	148 women with UI (FSH >10 were excluded) and 112 women with male factor infertility, groups were similar for age, BMI, duration of infertility, and type of infertility (primary vs secondary)	examination on cycle day 2 - 4,	Hormone levels	women with UI had similar FSH with male factor group, 7.52 (4.21 - 9.88) vs 6.96 (5.1 - 9.37) , resp., p =0.07. Likewise estradiol levels were similar, 51.5 (27 - 86) pg/ml vs 43.5 (25 - 71) in UI and Male factor, respectively, p = 0.108.	poor quality study with regard to statistics. Method of inhibin measurement not reported.	

CLOMIPHENE CITRATE CHALLENGE TEST (CCCT)

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Scott, R. T., Leonardi, M. R., Hofmann, G. E., Illions, E. H., Neal, G. S. and Navot, D. A prospective evaluation of clomiphene citrate challenge test screening of the general infertility population. Obstet Gynecol. 1993; 82 (4 Pt 1): 539-44.	CS	general infertility population without oligo/anovulation or tubal reversal request. Eventually 236 consecutive women meeting criteria (no prior infertility assessment in addition to aforementioned). Mean 34 years of age 20 - 43 years.	dau 5 - 9 100 mg/Day CC, if FSH was > 10 IU/L on any occasion test was regarded abnormal. Becton dickinson WHO 2nd international reference.	women with abnormal CCCT conceived less often than those with normal results. Moreover women eventually diagnosed with UI had higher rate of abnormal CCCT.	52% of Women with UI (12/32) had abnormal CCCT as compared with 4.3% for tubal factor, 17.4% for oligo/anovulation, 8.7% for male factor, 4.3% for endometriosis, and 0% for pelvic adhesions.		Small number of women with UI, complicated design.

OVARIAN VOLUME, OVARIAN BLOOD FLOW, INHIBIN B

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Steiner, A. Z., Pritchard, D., Stanczyk, F. Z., Kesner, J. S., Meadows, J. W., Herring, A. H. and	CS	750 women recruited from community, 30 to 44 years of age, women with a risk factor or history of infertility	serum on day 2 - 4, stored at -30C, Ansh İnhibin B assay	spontaneous conception attempt for 6 - 12 months	65% conceived in 6, 77% in 12 months, Cumulative probability of conception was not associated with inhibin B levels, after	Inhibin B levels are not associated with probability of	Not a population with UI but answers the Question,

Baird, D. D. Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age. Jama. 2017; 318 (14): 1367-1376.		were excluded such as breastfeeding women or those with a partner with known fertility problem, who had been trying ot conceive for 3 months or less.			adjusting for age, race, BMI, current smoking, recent contraceptive use (HR 0.999, 0.997 to 1.001, per 1 pg/ml increase in inhibin B level).	spontaneous conception	whether ORTs can predict fertility, despite the limitations.
Yücel, B., Kelekci, S. and Demirel, E. Decline in ovarian reserve may be an undiagnosed reason for unexplained infertility: a cohort study. Arch Med Sci. 2018; 14 (3): 527-531.	CS	148 women with UI (FSH >10 were excluded) and 112 women with male factor infertility, groups were similar for age, BMI, duration of infertility, and type of infertility (primary vs secondary)	examination on cycle day 2 - 4, medison 7.5 MHz transvaginal probe, total follicle count between 2 - 10 mm	women with UI had similar ovarian volume with male factor group, 6.2 (3.2 - 10.96) vs 6.06 (3.3 - 12.2) , resp., p =0.64. Likewise inhibin B levels were similar, 119 (40 - 145) pg/ml vs 120 (52 - 150) in UI and Male factor, respectively, p = 0.298.	women with UI had similar ovarian volume with male factor group, 6.2 (3.2 - 10.96) vs 6.06 (3.3 - 12.2) , resp., p =0.64. Likewise inhibin B levels were similar, 119 (40 - 145) pg/ml vs 120 (52 - 150) in UI and Male factor, respectively, p = 0.298.	poor quality study with regard to statistics. Method of inhibin measurement not reported.	
Murto, T., Bjuresten, K., Landgren, B. M. and Stavreus-Evers, A. Predictive value of hormonal parameters for live birth in women with unexplained infertility and male infertility. Reprod Biol Endocrinol. 2013; 11 61.	CS	42 women with UI and 29 women with male infertility (abnormal semen analysis as per WHO criteria at the time), similar age and BMI	cycle day 2 - 5 DSL Gen II ELISA for inhibin B, probability of live birth in 5 years, spontaneous or by fertility treatment	probability of live birth in 5 years, spontaneous or by treatment	Serum inhibin B levels were similar between UI and male factor groups, 37.1 (7.0 - 95.4) vs 47.5 (13 - 138.4) pg/ml, respectively, p = 0.208. Inhibin B alone was a poor predictor of live birth.	small sample, very old study, yet results consistent with others	

2.4 Tubal factor

PICO Question: What is the accuracy of commonly used tests of tubal patency?

Hystero-contrast-sonography (HyCoSy) vs. laparoscopy and dye

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Alcázar, J. L., Martinez, A., Duarte, M., Welly, A., Marín, A., Calle, A., Garrido, R., Pascual, M. A. and Guerriero, S. Two-dimensional hysterosalpingo-contrast-sonography compared to three/four-dimensional hysterosalpingo-contrast-sonography for the assessment of tubal occlusion in women with infertility/subfertility: a systematic review with meta-analysis. Hum Fertil (Camb). 2020; 1-13.	SR	30 studies, 1977 patients and 3885 tubes.	21 studies used 2D-HyCoSy to assess tubal occlusion, 6 of them used 3D/4D-HyCoSy 1 study used both techniques but in different set of patients and 2 of them used both techniques in the same patients. Contrast solution: 4 studies used saline solution, 11 used a galactose solution, 6 used sterile airsaline solution, 5 used sulphurhexafluoride, 2 studies used ExEm FoamTM, 1 study used perflutren lipid microsphere and 1 used air-saline and Exem FoamTM	sensitivity, specificity, LR+, LR-	2D HyCoSy: Pooled sensitivity, specificity, LR+, LR- were 86% (95% CI 80%–91%), and 94% (95% CI 90%–96%), 13.5 (95% CI 8.2–22.5), 0.14 (95% CI¼0.1–0.2), respectively. High heterogeneity was found for sensitivity (I^2=79.23%; Cochran Q=110.7; p<0.001) and for specificity (I^2=90.08%; Cochran Q=231.77; p<0.001). 3D/4D HyCoSy: pooled sensitivity, specificity, LR+ and LR- for detecting tubal occlusion were 95% (95% CI=89%–98%), 89% (95% CI=82%–94%), 8.9 (95% CI=5.0–16.1), and 0.06 (95% CI=0.03–0.13), respectively. High heterogeneity was found for both sensitivity (I^2=76.98%; Cochran Q=34.96; p<0.01) and specificity (I^2=85.76%; Cochran Q=56.17; p<0.001). Both methods had almost identical areas under the curve (0.96 for 2DHyCoSy and 0.97 for 3D/4D-HyCoSy)		

Wang, Y. and Qian, L. Three- or four-dimensional hysterosalpingo contrast sonography for diagnosing tubal patency in infertile females: a systematic review with meta-analysis. Br J Radiol. 2016; 89 (1063): 20151013.	SR	23 studies, 1153 females and 2259 tubes	16 and 7 studies reported the diagnostic accuracy of 3D and 4D HyCoSy for detecting tubal patency in infertile females. The contrast agent was Echovist in 3 studies, saline solution in 1 study and SonoVue in 19 studies.	sensitivity, specificity, LR+, LR-	pooled estimates of sensitivity and specificity were 0.92 (95% CI 0.90–0.94, with I^2=36.68) and 0.92 (95% CI 0.89–0.93 with I^2=38.99), respectively. The area under the ROC curve was 0.97 (95% CI 0.95–0.98)		
Chen, S., Du, X., Chen, Q. and Chen, S. Combined Real-Time Three-Dimensional Hysterosalpingo-Contrast Sonography with B Mode Hysterosalpingo-Contrast Sonography in the Evaluation of Fallopian Tube Patency in Patients Undergoing Infertility Investigations. Biomed Res Int. 2019; 2019 9408141.	CS	prospective CS. 739 female patients, of which 34 (62 tubes) had both hycosy and laparoscopy. The patients included in this study had no history of serious diseases and contraindications	4D-hycosy, B-mode hycosy, laparoscopy and dye	the predictive value of HyCoSy in assessing tubal patency, the sensitivity, specificity, positive and negative predictive values	Compared with the laparoscopy and dye test, tubal occlusion diagnostic accordance rates for 4D-HyCoSy were 88.7%(23+32)/62, with a kappa coefficient of 0.769 and a 76.9% agreement rate (Table 1). Distal occlusion diagnostic accordance rates for 4D-HyCoSy were 100% (8/8), with a k coefficient of 1.000 and a 100% agreement rate (Table 2). The sensitivity, specificity, PPV, and NPV of 4D-HyCoSy compared to laparoscopy were 88.4%, 88.8% 85.1%, and 91.4%, respectively. Twenty tubes were diagnosed as “patent” by 4D-HyCoSy although the B mode-HyCoSy procedure showed these tubes as passable but not smooth (Figure 2). Four tubes were misdiagnosed as proximal partial obstruction by 4D-HyCoSy, while subsequent B mode-HyCoSy indicated that these tubes were “patent”.		
Cimen, G., Trak, B., Elpek, G., Simsek, T. and Erman, O. The efficiency of hysterosalpingo-contrastsonography (HyCoSy) in the evaluation of tubal patency. J Obstet		Forty-seven patients, aged 19 to 41 years, affected with infertility. Patients, with a suspicion of acute or chronic pelvic inflammatory disease, those with galactosemia,	HyCoSy was performed in the late proliferative phase (9± 11 days) of the cycle. In 18 patients laparoscopy was also performed and the results were compared with HyCoSy and R-HSG.	the predictive value of HyCoSy in assessing tubal patency, the sensitivity, specificity, positive and	sensitivity: 81.8%, specificity: 75%, PPV: 75%, NPV: 91.6%, concordance: 86%		

Gynaecol. 1999; 19 (5): 516-8.		age below 18 years and pregnant or who had any suspicion of pregnancy were excluded		negative predictive values			
Liang, N., Wu, Q. Q., Li, J. H., Gao, F. Y., Sun, F. L. and Guo, C. X. Causes of misdiagnosis in assessing tubal patency by transvaginal real-time three-dimensional hysterosalpingo-contrast sonography. Rev Assoc Med Bras (1992). 2019; 65 (8): 1055-1060.		83 infertility patients (162 oviducts),	3D hyscosy and laparoscopy	The consistency of the test results was analysed using the Kappa value	With the results of the laparoscopic dye studies as the gold standard, the accuracy rate of TVS RT-3D-HyCoSy in diagnosing tubal patency was 88.9% (144/162), and the misdiagnosis rate was 11.1% (18/162). Furthermore, the sensitivity of diagnosing oviduct obstruction was 89.6% (86/96), the PPV was 91.5% (86/94), the specificity of diagnosing tubal patency was 87.9% (58/66), and the NPV was 85.3% (58/68). The accuracy of TVS RT-3D-HyCoSy was similar to that of these laparoscopic dye studies, the difference was not statistically significant, and the consistency between these two was good		
Malek-Mellouli, M., Gharbi, H. and Reziga, H. The value of sonohysterography in the diagnosis of tubal patency among infertile patients. Tunis Med. 2013; 91 (6): 387-90.	CS	Prospective CS. 40 consecutive women	hysterosalpingography, sonohysteroography and laparoscopy with dye test, within a period of 6 months.	agreement between laparoscopy and hycosy	Sonosalpingography showed patency in 51(63.7%) tubes, hysterosalpingography in 47 (58.7%) tubes, and laparoscopy in 52 (65%) tubes. The tubal patency found in 51 tubes by SHG was confirmed by laparoscopy in 44 tubes (positive predictive value, 87.9%). A uni- or bilateral tubal occlusion was observed in 28 patients by laparoscopy. In 8 tubes, occlusion suggested by sonosalpingography was not confirmed by laparoscopy and 7 tubes patent by sonosalpingography were found to be occluded by laparoscopy. There were 7 false positive and 8 false negative findings. The sensitivity of sonosalpingography in		

					diagnosing tubal patency was 90% and the specificity 80%.		
Radić, V., Canić, T., Valetić, J. and Duić, Z. Advantages and disadvantages of hysterosonosalpingography in the assessment of the reproductive status of uterine cavity and fallopian tubes. Eur J Radiol. 2005; 53 (2): 268-73.	CS	prospective CS. 37 infertile women.	Hycosy with saline and contrast medium compared to laparoscopy and dye test. The surgeons at laparoscopy and hysteroscopy procedures were blinded to the results of the previous hysterosonosalpingography.	the predictive value of HyCoSy in assessing tubal patency, the sensitivity, specificity, positive and negative predictive values	The ultrasound saline contrast method for the assessment of the tubal status in comparison to laparoscopic findings of chromoperturbations showed 100% sensibility and negative predictive value, but also a low specificity of 66% and a positive predictive value of 57% (Table 2). The method found no false patent tube, 58 true patent and 77 nonpatent tubes. Of these 77 pathologic findings of nonpatent tubes by the ultrasound method, 30 tubes were proved patent by chromolaparoscopy. examination of tubal patency by the Echovist® yielded a better specificity (77%), and positive predictive value (70%) (Table 3) than examination with negative contrast. In addition to no false patent findings, it depicted 68 truly patent tubes, 20 false nonpatent and 47 true nonpatent tubes.		
Shahid, N., Ahluwalia, A., Briggs, S. and Gupta, S. An audit of patients investigated by Hysterosalpingo-Contrast-Sonography (HyCoSy) for infertility. J Obstet Gynaecol. 2005; 25 (3): 275-8.	CS	retrospective CS. 171/186 case notes of patients, referred for HyCoSy as a part of investigation for sub-fertility were reviewed. 34 patients had both hycosy and laparoscopy and dye test	hycosy and laparoscopy and dye test	concordance of results between tests	15 patients had laparoscopy after hycosy. Of these 15 patients HyCoSy showed bilateral patent tubes in 8 patients. Laparoscopy and dye test confirmed these findings in 87.5% (n= 7) patients whereas one patient showed unilateral patent tube. The findings of bilaterally blocked tubes in one patient and unilateral patent tube in 6 patients on HyCoSy were confirmed on laparoscopy and dye test. 19 patients had laparoscopy before hycosy and conclusive results were shown by HyCoSy in 5 cases of inconclusive findings and in 4 cases where tubes filled with dye but there were no spill noted at laparoscopy		

					and dye test in spite of normal appearance of the tubes at laparoscopy.		
Zhou, L., Zhang, X., Chen, X., Liao, L., Pan, R., Zhou, N. and Di, N. Value of three-dimensional hysterosalpingo-contrast sonography with SonoVue in the assessment of tubal patency. Ultrasound Obstet Gynecol. 2012; 40 (1): 93-8.	CS	75 patients. Inclusion criteria included: 1) no vaginal bleeding and 2) no acute or subacute inflammation of the reproductive system. Women with unicornuate uterus or unilateral salpingectomy were not excluded;	3D-SonoVue-HyCoSy and lap and dye	concordance of results between tests	Thirty-four patients were diagnosed as having bilateral tubal occlusion by 3D SonoVue-HyCoSy, compared with 29 diagnosed by lap and dye. Fourteen patients were diagnosed as having unilateral tubal patency by 3D SonoVue-HyCoSy, compared with 19 diagnosed by lap and dye. Twenty-seven patients were diagnosed as having bilateral tubal patency by both 3D SonoVue-HyCoSy and lap and dye.		

HYSTEROSALPINGOGRAPHY (HSG) VS. LAPAROSCOPY AND DYE

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Broeze, K. A., Opmeer, B. C., Van Geloven, N., Coppus, S. F., Collins, J. A., Den Hartog, J. E., Van der Linden, P. J., Marianowski, P., Ng, E. H., Van der Steeg, J. W., Steures, P., Strandell, A., Van der Veen, F. and Mol, B. W. Are patient characteristics associated with the accuracy of hysterosalpingography in diagnosing tubal pathology? An individual patient data meta-analysis. Hum Reprod Update. 2011; 17 (3): 293-300.	SR	10 studies, 4521 women	HSG and laparoscopy	accuracy of HSG for tubal patency	Across the individual studies, sensitivity ranged between 46% and 100% and specificity ranged between 73% and 100% when diagnosing any tubal pathology. The unadjusted pooled accuracy of HSG showed a sensitivity of 70% (95% CI 0.66–0.74) and a specificity of 78% (95% CI 0.75–0.80). After imputation of missing laparoscopy results, these rates were 53% (95% CI 0.50–0.57) and 87% (95% CI 0.86–0.88) for sensitivity and specificity, respectively. In women with a low-risk clinical history, the sensitivity of HSG for detecting unilateral tubal pathology was 38% versus 61% in women with a high-risk history. For bilateral tubal pathology, sensitivity		

					ranged between 0% and 100% and specificity ranged between 87% and 97% across the individual studies. The pooled estimates for sensitivity and specificity were 66% (95% CI 0.55–0.75) and 91% (95% CI 0.89–0.93), respectively. After imputation of laparoscopy results, these rates were 46% (95% CI 0.41–0.51) and 95% (95% CI 0.94–0.95).		
Adelusi, B., al-Nuaim, L., Makanjuola, D., Khashoggi, T., Chowdhury, N. and Kangave, D. Accuracy of hysterosalpingography and laparoscopic hydrotubation in diagnosis of tubal patency. Fertil Steril. 1995; 63 (5): 1016-20.		All patients with factors, such as ovulatory failure or poor semen analysis, that may be contributory to their infertility were excluded from the study.	diagnostic HSG, followed by laparoscopy within a period of 6 months,	HSG and laparoscopy agreement	Whereas laparoscopy showed that both tubes were patent in 51.9% of cases, HSG identified both tubes as patent in 39.4% of cases. There was agreement between laparoscopy and HSG in only 31.7%. Similarly, agreement between the two methods in terms of bilateral tubal blockage was 16.3% of cases and, in terms of unilateral blockage, there was agreement in only 14.5% of cases. There was an overall agreement between the		

					two techniques in 62.5% of cases.		
Agrawal, N. and Fayyaz, S. Can hysterolaparoscopic mediated chromopertubation obviate the need for hysterosalpingography for proximal tubal blockage?: An experience at a single tertiary care center. J Gynecol Obstet Hum Reprod. 2019; 48 (4): 241-245.	CS	prospective CS. 103 infertile patients. Infertile female patients, age between 19 and 33 years were registered to participate in the study after taking the informed written consent.	hysteroscopy and laparoscopy	diagnostic accuracy of HSG	In comparison to HSG with CPT (reference standard) for tubal blockage detection, it was found that HSG was true positive (TP) in 38 patients, true negative in 34 patients, false positive in 31 patients and FN in 0 patients. We found that for detection of tubal blockage, the sensitivity, specificity, PPV, NPV and accuracy of HSG was 100.00%, 52.31%, 36.89%, 57.07% and 67% respectively. Proximal tubal occlusion detected on HSG and CPT showed a moderate agreement (weighted kappa – 0.447; 95% CI -0.312 to 0.583). Also when analysed independently tubal occlusion detection on HSG and CPT, it showed moderate agreement for primary infertile patients (weighted kappa – 0.474; 95% CI -0.294 to 0.654) and secondary infertile patients (weighted kappa –		

					0.411; 95% CI -0.206 to 0.616).		
Berker, B., Şükür, Y. E., Aytaç, R., Atabekoğlu, C. S., Sönmezer, M. and Özmen, B. Infertility work-up: To what degree does laparoscopy change the management strategy based on hysterosalpingography findings? J Obstet Gynaecol Res. 2015; 41 (11): 1785-90.	CS	retrospective CS. All patients who had both HSG and LS testing (n = 264) were included in the study. Patients with missing reports of either HSG or LS were not included. Patients with severe male factor infertility or severe ovarian dysfunction who proceeded to artificial reproductive technologies (ART without LS were excluded.	HSG and laparoscopy	diagnostic accuracy of HSG	diagnostic accuracy of HSG: The sensitivity, specificity, positive predictive and negative predictive values for any tubal pathology were 94%, 81.7%, 54.6%, and 98.3%, respectively. The sensitivity, specificity, positive predictive and negative predictive values for UTO were 72.2%, 84.5%, 26.5%, and 91.5%, respectively. The sensitivity, specificity, positive predictive and negative predictive values for BTO were 78.1%, 94.8%, 67.5%, and 96.9%, respectively. Generally, the validity (true positive +true negative /cohort×100) of the HSG test was 84.1% (47+175/264×100).		
Chang, Y. S., Lee, J. Y., Moon, S. Y. and Kim, J. G. Diagnostic laparoscopy in gynecologic disorders. Asia Oceania J Obstet Gynaecol. 1987; 13 (1): 29-34.		1267 patients	HSG and laparoscopy	concordance of HSG and laparoscopic findings	In 982 (77.5%) of these patients there was complete agreement between HSG and Laparoscopy while 177 patients (17.0%) had a false positive HDG and 108		

					patients (25.9%) a false negative HSG		
Dabekausen, Y. A., Evers, J. L., Land, J. A. and Stals, F. S. Chlamydia trachomatis antibody testing is more accurate than hysterosalpingography in predicting tubal factor infertility. Fertil Steril. 1994; 61 (5): 833-7.	CS	prospective CS. 211 consecutive women, of which 34 had both HSG and laparoscopy	C. trachomatis antibody testing, HSG, laparoscopy.	HSG and laparoscopy agreement	In 24/34 patients the HSG and laparoscopy results corresponded, but in 10 patients a discrepancy was found. The probability of tubal factor infertility with an abnormal HSG was 59%. The LR+ for HSG was 2.6 and LR- 0.5 (OR 4.8, 95% CI 1.0-21.8)		
Foroozanfard, F. and Sadat, Z. Diagnostic value of hysterosalpingography and laparoscopy for tubal patency in infertile women. Nurs Midwifery Stud. 2013; 2 (2): 188-92.	CS	prospective CS. 62 infertile women. Inclusion criteria were no prior pelvic surgery, no history of pelvic infection, normal bimanual pelvic examination, normal semen parameters of partner, no ovulatory dysfunction, and excluding criteria were surgical procedures that had occurred between the performance after HSG, women who did not return for laparoscopy evaluation, technical problems related to HSG and	Laparoscopy was performed three month after HSG (13). The HSG was performed by radiologist. The procedure was performed between days 6 and 12 of the menstrual cycle at least 48 hours after menses had ceased.	sensitivity, specificity of HSG	Forty three cases had normal HSG, among them 81.4% had normal laparoscopy. In the nineteen cases with abnormal HSG (unilateral or bilateral no patency), 47.4 % of patients showed abnormal results on laparoscopy. The sensitivity of HSG on bilateral tubal patency or no bilateral tubal patency was 92.1% and its specificity was 85.7%. The PPV and the NPV were 97.2% and 66.6% respectively. Furthermore, results of HSG were false-negative in 33.3% of patients, false-positive in		

		women who became pregnant after hysterosalpingography.			2.8% and accuracy was 91.1%. The sensitivity and specificity of HSG on bilateral tubal patency and any abnormality of patency (unilateral or bilateral tubal no patency) were 77.8% and 52.9% respectively, the PPV and the NPV were 81.4 % and 47.4% respectively. Furthermore, results of HSG were false-negative in 52.6% of patients, false-positive in 18.6% (Table 3) and accuracy was 71%.		
Gündüz, R., Ağaçayak, E., Okutucu, G., Karuserci Ö, K., Peker, N., Çetinçakmak, M. G. and Gül, T. Hysterosalpingography: a potential alternative to laparoscopy in the evaluation of tubal obstruction in infertile patients? Afr Health Sci. 2021; 21 (1): 373-378.	CS	This retrospective study included 208 infertile patients. Patients with uterine factors, male factors, smokers, premature ovarian failure, patients with chronic diseases, and history of abdominal surgery were excluded in the study. Patients with distal tubal obstructions on HSG and L/S were included in the study, proximal tubal obstruction as it may be secondary to transient	HSG; and also received laparoscopy for showing either pathology or >6 months infertility after HSG	concordance of HSG and laparoscopic findings	HSG and L/S results were compatible in 147 (70.6%) of the 208 patients whose tubes were found to be either patent or obstructed. HSG was found to have a specificity of 64.6%, a sensitivity of 81.3%, a positive predictive value of 56.4%, and a negative predictive value of 86% in the detection of tubal obstruction.		

		tubal spasms (20% of cases) or amorphous debris or minimal adhesions (40% of cases)6 were excluded in the study.					
Hamed, H. O., Shahin, A. Y. and Elsamman, A. M. Hysterosalpingo-contrast sonography versus radiographic hysterosalpingography in the evaluation of tubal patency. Int J Gynaecol Obstet. 2009; 105 (3): 215-7.	CS	Prospective CS. 88 infertile women, of which 57 women had all 3 procedures. The women and their husbands were younger than 40 years, the women had regular cycles with normal ovulation, and the men had normal semen. Exclusion criteria were pelvic infections and organic lesions	Hycosy, HSG and laparoscopy. The HyCoSy and HSG procedures were performed in this order and in the same week at the Department of Radiology. The operator who did the HSG procedure was unaware of the HyCoSy results.	performance of HSG and hycosy, compared to laparoscopy	HyCoSy: sensitivity of 76.1% and a specificity of 79.4%, with a PPV of 71.4% and NPV of 83.1%. The finding of HyCoSy and laparoscopy and the dye test was the same for 89 tubes, for a compatibility rate of 78.1%. HSG: sensitivity of 81.8% and a specificity of 77.1%, with a PPV of 69.2% and a NPV of 87.1%. The compatibility rate between the diagnosis of HSG and laparoscopy was 79.9% (Table 3).		
Hiroi, H., Fujiwara, T., Nakazawa, M., Osuga, Y., Momoeda, M., Kugu, K., Yano, T., Tsutsumi, O. and Taketani, Y. High incidence of tubal dysfunction is determined by laparoscopy in cases with positive Chlamydia trachomatis	CS	retrospective CS. 314 patients	HSG with water-soluble iodinated contrast material and laparoscopy	sensitivity, specificity of HSG	sensitivity and specificity for tubal patency were 0.63 and 0.79, respectively, calculated with laparoscopic findings as the gold standard. For peritubal adhesion, sensitivity and specificity		

antibody despite negative finding in prior hysterosalpingography. Reprod Med Biol. 2007; 6 (1): 39-43.					were 0.65 and 0.61, respectively. NPV for occlusion was 82% in patients with at least one background factor, and 93% in patients without any background factors. 35 patients were diagnosed with fallopian tubes which were observed to be patent by HSG, but not observed to be patent by chromopertubation under laparoscopy		
Ismajovich, B., Wexler, S., Golan, A., Langer, L. and David, M. P. The accuracy of hysterosalpingography versus laparoscopy in evaluation of infertile women. Int J Gynaecol Obstet. 1986; 24 (1): 9-12.	CS	215 women.	HSG and laparoscopy. HSG was performed during the proliferative phase using a water soluble contrast medium. Laparoscopy was performed in the secretory phase, either 6 months after a normal HSG or 1 to 2 months after the abnormal HSG.	concordance of HSG and laparoscopic findings	Thirty-two women (25%) had normal HSG and peritubal adhesions on laparoscopy. Thirty-four (28%) women who had normal pelvic organs on laparoscopy had tubal disease diagnosed on HSG. Forty-seven (22%) women had pelvic pathology undiagnosed by HSG (Table II).		
Keltz, M. D., Gera, P. S. and Moustakis, M. Chlamydia serology screening in infertility patients. Fertil Steril. 2006; 85 (3): 752-4.	CS	prospective CS. 210 infertile patients.	Chlamydia antibody IgG by microimmunofluorescence, A titre of >1:32 was considered a positive result. HSG in all patients for tubal patency,	correlation between chlamydial serology, HSG, and	84/210 (40%) were CAT positive. CAT positivity, both low and high, was 74.0% sensitive and 93.0% specific at detecting tubal disease. PPV		

			laparoscopy when clinically needed.	laparoscopic findings	94.8% and NPV 69.8%. HSG was 78% sensitive and 82% specific for finding tubal disease at laparoscopy. CAT+HSG: 97.3% sensitivity.		
Loy, R. A., Weinstein, F. G. and Seibel, M. M. Hysterosalpingography in perspective: the predictive value of oil-soluble versus water-soluble contrast media. Fertil Steril. 1989; 51 (1): 170-2.	CS	77 consecutive patients with primary and secondary infertility. Both groups were comparable in age.	HSG; OSCM was used in 33 patients and WSCM was used in 44 patients compared to laparoscopy. The mean interval between HSG and laparoscopy was 4.5 months for the OSCM group and 3.5 months for the WSCM group.	concordance of HSG and laparoscopic findings	HSG. Eleven of 12 patients with tubal occlusion were identified by HSG using OSCM (sensitivity = 92%) as compared with 5 of 8 patients (sensitivity= 63%) using WSCM ($P < 0.01$). The specificities were 67% and 75% for OSCM and WSCM, respectively (not significant		
Ngowa, J. D., Kasia, J. M., Georges, N. T., Nkongo, V., Sone, C. and Fongang, E. Comparison of hysterosalpingograms with laparoscopy in the diagnostic of tubal factor of female infertility at the Yaoundé General Hospital, Cameroon. Pan Afr Med J. 2015; 22 264.	CS	cross-sectional study. 208 women.	HSG and laparoscopy	sensitivity, specificity, PPV, NPV	There was a moderate sensitivity (51.0%; 95% IC. 37.5-64.4) and a high specificity (90.0%; 95% IC.74.4-96.5) of HSG in the diagnosis of bilateral proximal tubal occlusion. However, there was a high PPV (89.3 %; 95% IC. 72.8-96.3) and a moderate NPV (52.9%; 95%IC. 39.5-65.9) of HSG in the diagnosis of bilateral proximal tubal occlusion. Concerning		

					distal tubal patency, HSG had a high sensitivity (86.8%; 95%IC. 76.7-92.9) and a low specificity (42.2%; 95% CI. 29.0-56.7) in the diagnosis of bilateral or unilateral tubal occlusion. However, HSG had a moderate PPV (69.4%; 95% IC. 58.9-78.2) and a moderate NPV (67.9%; 95%IC. 49.3-82.0).		
Rice, J. P., London, S. N. and Olive, D. L. Reevaluation of hysterosalpingography in infertility investigation. Obstet Gynecol. 1986; 67 (5): 718-21.	CS	143 women. Patients who had undergone elective tubal ligation were not included.	HSG and laparoscopy with chromopertubation	concordance of HSG and laparoscopic findings	The diagnosis of tubal patency was confirmed by laparoscopy in 63 (85.1%) of the 74 patients. The remaining 11 (14.9%) patients had tubal occlusion by laparoscopy.		
Tan, J., Deng, M., Xia, M., Lai, M., Pan, W. and Li, Y. Comparison of Hysterosalpingography With Laparoscopy in the Diagnosis of Tubal Factor of Female Infertility. Front Med (Lausanne). 2021; 8 720401.		retrospective cohort study with 1276 patients. All the enrolled patients had a regular menstrual cycle, and routine semen examination of the husband was normal. We excluded patients who had an ovarian cyst, uterine malformation, endometriosis,	HSG was performed. If the results of HSG were normal or not patent, but the patients did not become pregnant in the 12 months after examination, we performed a laparoscopic procedure. If the results of HSG were occlusion or hydrosalpinx, but the patients desired to conceive, naturally, they	concordance of HSG and laparoscopic findings	performance of HSG in the diagnosis of right tube patency or occlusion compared to laparoscopy as the gold standard. There was a high sensitivity (73.65%), specificity (83.21%), positive predictive value (50.93%), and negative predictive value (92.08%). The Kappa value was as high as 0.47, 95% CI (0.399, 0.541), p <		

		or any other type of organic lesion that could be found by routine ultrasonography. 20.97% (n = 181) of patients had a history of previous pelvic surgery.	chose to perform the laparoscopic examination.		0.001. The corresponding sensitivity, specificity, positive predictive value, and negative predictive value of HSG in diagnosing left tube patency or occlusion were 78.98, 87.72, 56.19, and 95.44%, respectively. The Kappa value was 0.574, 95% CI (0.505, 0.0.643), $p < 0.001$.		
Tshabu-Aguemon, C., Ogoudjobi, M., Obossou, A., King, V., Takpara, I. and Alihonou, E. HYSTEROSALPINGOGRAPHY AND LAPAROSCOPY IN EVALUATING FALLOPIAN TUBES IN THE MANAGEMENT OF INFERTILITY IN COTONOU, BENIN REPUBLIC. J West Afr Coll Surg. 2014; 4 (2): 66-75.	CS	retrospective CS. 96 patients explored for tubal infertility. Exclusion criteria were infertility of less than two years.	HSG followed by laparoscopy and methylene blue test	concordance of HSG and laparoscopic findings	The concordance of HSG–laparoscopy in tubal obstruction was 46.84%. The concordance HSG -laparoscopy showed 12.5% of proximal tubal obstruction. HSG showed 11.46% of distal tubal obstruction and 6.25% of tubes showing patency at HSG were found to be occluded at laparoscopy. Laparoscopy revealed adhesive bands undetected with HSG in 33.33% of cases, pelvic endometriosis undetected with HSG in 6.25% of cases, and patent tubes but with inflammatory features in 11.46% of cases.		

Tvarijonaviciene, E. and Nadisauskiene, R. J. The value of hysterosalpingography in the diagnosis of tubal pathology among infertile patients. Medicina (Kaunas). 2008; 44 (6): 439-48.		prospective cross-sectional study. 149 infertile women. Inclusion criteria: 1) Infertility diagnosis according WHO definition. 2) Woman's age 19–42 years. 3) Confirmed ovulatory cycles and/or normal ovarian reserve. 4) Absence of severe sperm pathology. 5) Patient's consent to the study. Exclusion criteria: 1) Women younger 19 and older 42 years. 2) Diminished ovarian reserve. 3) Severe sperm pathology. 4) Previous HSG related to infertility. 5) Previous diagnostic laparoscopy related to infertility. 6) Previous laparoscopic or abdominal tubal surgery related to infertility. 7) Contraindications for HSG or laparoscopy. 8) Absence of the patient's consent.	The HSGs were performed by staff gynaecologist and staff radiologist. The results of HSGs were evaluated by one of the three staff radiologists. Laparoscopy and dye test (LS) was performed within one–three months after HSG by staff gynaecologists	Sensitivity, specificity, LH+, LH–, pretest and posttest probabilities of HSG in diagnosis of general tubal pathology, tubal occlusion, and peritubal adhesions were calculated, regarding LS as the reference standard.	For 2 (1.3%) patients, febrile morbidity after the procedure was registered. Following HSG, 63.8% (95/149) of patients were diagnosed with general tubal pathology. Following LS, 39.5% (59/149) of women were found with general tubal pathology. Accuracy of HSG versus laparoscopy for tubal patency: 84.1% (73.3-94.9) sensitivity, 59.1% (49.6-68.5) specificity, 2.1 (1.6-2.7) LR+, 0.3 (0.1-0.5) LR-, post-test probability for positive result: 47.4% (39.0-55.0) and post-test probability for negative result: 11.4% (6.0-16.0)		

CHLAMYDIA ANTIBODY TESTING VS. LAPAROSCOPY AND DYE

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Mol, B. W., Dijkman, B., Wertheim, P., Lijmer, J., van der Veen, F. and Bossuyt, P. M. The accuracy of serum chlamydial antibodies in the diagnosis of tubal pathology: a meta-analysis. Fertil Steril. 1997; 67 (6): 1031-7.	SR	2,729 patients with subfertility in 23 studies	Chlamydia antibody titer and laparoscopy as part of subfertility work-up. CAT: 5 studies used immunoperoxidase (IP) assay (16-18,21,29), 15 studies used immunofluorescense (IF) or microimmunofluorescence (MIF) (7-12, 19, 20, 22-28), 2 studies used ELISA (14 15), and 1 study used both MIF and ELISA (13). The cutoff values for test positivity of most studies varied between 1:8 and 1:64 except 1 study that used a cut-off value of 1:640 (28).	Sensitivity and specificity of Chlamydia antibody titers in the diagnosis of tubal pathology using laparoscopy with chromopertubation as the reference standard.	The sensitivity of Chlamydia antibody testing for tubal pathology-varied between 0.21 and 0.90, with the specificity varying between 0.29 and 1, substantial heterogeneity between studies. The discriminative capacity of Chlamydia antibody testing however, was significantly different between studies using MIF or IF, studies using ELISA, and studies using IP as assay for Chlamydia antibody testing. Performance of CAT varied significantly with the way of tubal pathology verification.		
Akande, V. A., Hunt, L. P., Cahill, D. J., Caul, E. O., Ford, W. C. and Jenkins, J. M. Tubal damage in infertile women: prediction using chlamydia serology. Hum Reprod. 2003; 18 (9): 1841-7.		cross-sectional study. 1006 infertile women	laparoscopy for tubal patency and CAT, IgG was measured using the whole-cell inclusion immunofluorescence test.	CAT and laparoscopy findings	The antibody titres in women with tubal damage were significantly higher than in women without tubal damage. Women with tubal damage but no tubal occlusion had significantly lower median antibody levels than those with at least one tube occluded (1:512 vs. 1:1024; P < 0.001). A linear relationship		

					between serum CAT and the likelihood of tubal damage was observed		
Babay, Z. A. and Al-Meshari, A. The role of Chlamydia trachomatis infection in female infertility. Ann Saudi Med. 1993; 13 (5): 423-8.		158 consecutive females undergoing evaluation for infertility were screened, 75 were enrolled for tubal patency testing. Controls: 50 women attending the postnatal clinic	laparoscopy, endocervix and peritoneal samples for C. trachomatis culture		Infertile group: 37/86 pregnancies (43%) in Chlamydia positive mothers ended in miscarriage, while in the Chlamydia negative mothers, 3 pregnancies (10%) ended in miscarriage. Control group: 90/116 (77.6%) of pregnancies in Chlamydia positive controls while 12/116 (10.3%) Chlamydia negative controls ended in miscarriage. Cervical chlamydia culture was positive in 49/75 (65.3%) infertile patients and in 22/50 (44%) postnatal controls. 33/49 (67.3%) of culture positive infertile patients had tubal blockage and of these, 12 (67.3%) patients had severe pelvic adhesions. Of the culture negative infertile patients 5/26 (19.1%) had blocked tubes and two of these had severe adhesions.		
Coppus, S. F., Opmeer, B. C., Logan, S., van der Veen, F., Bhattacharya, S. and Mol, B. W. The predictive value of medical history taking and Chlamydia IgG ELISA antibody	CS	retrospective CS. 207 consecutive women referred for evaluation of subfertility by laparoscopy	laparoscopy and CAT by ELISA	prognostic value of CAT	prevalence of tubal pathology was 30.4% (63/207). Prediction model: CAT alone: sensitivity 37% (95% CI 26–49), specificity 88% (95% CI 82–93). Clinical history+CAT: AUC to 0.70 (95% CI 0.62–0.78)	The number of laparoscopies that has to be performed to detect one woman with tubal pathology is comparable	

testing (CAT) in the selection of subfertile women for diagnostic laparoscopy: a clinical prediction model approach. Hum Reprod. 2007; 22 (5): 1353-8.						when using history, CAT or history and CAT and much lower than without any workup.	
den Hartog, J. E., Land, J. A., Stassen, F. R., Slobbe-van Drunen, M. E., Kessels, A. G. and Bruggeman, C. A. The role of chlamydia genus-specific and species-specific IgG antibody testing in predicting tubal disease in subfertile women. Hum Reprod. 2004; 19 (6): 1380-4.	CS	Prospective CS. 313 subfertile women. Patients who had undergone previous pelvic surgery (except for an uneventful appendectomy or Caesarean section) were excluded. Of these 313 women, subfertile women without distal tubal pathology served as controls.	Serology for antibodies to C. trachomatis , C. pneumoniae and C. psittaci (by MIF) and antibodies to chlamydia lipopolysaccharide (LPS, by ELISA). Laparoscopy for tubal patency testing	predictive value of CAT for distal tubal pathology	59/254 (18.8%) had distal tubal pathology. The prevalence of species-specific IgG antibodies to C. trachomatis was significantly higher in women with distal tubal pathology (54.2%), as compared to women without distal tubal pathology (7.9%). C. trachomatis: sensitivity 54.2%, specificity 92.1%, OR 13.9 (95% CI 6.6-29.2)		
den Hartog, J. E., Land, J. A., Stassen, F. R., Kessels, A. G. and Bruggeman, C. A. Serological markers of persistent C. trachomatis infections in women	CS	retrospective CS. 313 subfertile women, only patients having a laparoscopy were included in this study.	CAT: IgG by MIF; titre of ≥32 was considered positive; IgA by EIA, threshold index of ≥1.4 was considered positive. Patients with a negative CAT and an otherwise normal fertility work-up underwent a HSG to evaluate the tubal	prognostic value of CAT	59 (18.8%) met the definition of distal tubal pathology (extensive peri-adnexal adhesions and/or distal occlusion of at least one tube), whereas 254 women (81.2%) did not have distal tubal pathology and served as controls. IgG and IgA antibodies to C. trachomatis, IgG		

with tubal factor subfertility. Hum Reprod. 2005; 20 (4): 986-90.			status. If the HSG showed abnormalities, or if they did not conceive within 6 months after the HSG, a laparoscopy with tubal testing was performed. Patients with a positive CAT underwent a laparoscopy with tubal testing immediately after the fertility work-up.		antibodies to cHSP60 and a positive hs-CRP test were found significantly more often in women with distal tubal pathology as compared to women without distal tubal pathology. C. trachomatis IgG test was the best predictor of tubal pathology (OR 13.9, 95% CI 7.0-27.5).		
Logan, S., Gazvani, R., McKenzie, H., Templeton, A. and Bhattacharya, S. Can history, ultrasound, or ELISA chlamydial antibodies, alone or in combination, predict tubal factor infertility in subfertile women? Hum Reprod. 2003; 18 (11): 2350-6.	CS	prospective CS. 207 consecutive women referred for tubal evaluation	Medical history, transvaginal ultrasound or C. trachomatis antibody testing (acute lower tract infection by EIA and confirmed by direct immunofluorescence; serum by ELISA) and laparoscopy and dye to determine tubal factor infertility	CAT and laparoscopy findings	CAT was negative in 167 (81%) women, equivocal in seven (3%) women, and positive in 33 (16%) women. 63 (30%) of the study population were diagnosed with tubal factor infertility by laparoscopy. Performance of CAT in predicting TFI: accuracy 73%, sensitivity 37%, specificity 88%, LR+ 3.1, LR- 0.7		
Ng, E. H., Tang, O. S. and Ho, P. C. Measurement of serum CA-125 concentrations does not improve the value of Chlamydia trachomatis antibody in predicting tubal	CS	prospective CS. 110 consecutive women attending infertility clinic.	CAT (by micro-immunofluorescence) and CA-125 (EIA) serology, laparoscopy and dye test, endocervical swab for C. trachomatis. CA-125 concentration of > 35 IU/ml were considered positive and	CAT, CA-125 positivity and laparoscopic findings	2/110 (1.8%) endocervical swab was positive for C. trachomatis. 28/110 women tested CAT positive (25.5%). 11/110 had positive CA-125 and only one woman tested positive for both CAT and CA-125. 31/110 women had tubal pathology (28.2%), of which 17 with positive CAT and 14 with negative CAT		

pathology at laparoscopy. Hum Reprod. 2001; 16 (4): 775-9.			CAT values of >1:32 were considered positive		p<0.05, CAT in predicting tubal pathology: sensitivity 54.8%, specificity 86.1%, LR+: 3.94, LR-0.53, OR 7.51 (OR 2.90-19.45		
Rantsi, T., Land, J. A., Joki-Korpela, P., Ouburg, S., Hokynar, K., Paavonen, J., Tiitinen, A. and Puolakkainen, M. Predictive Values of Serum Chlamydia trachomatis TroA and HtrA IgG Antibodies as Markers of Persistent Infection in the Detection of Pelvic Adhesions and Tubal Occlusion. Microorganisms. 2019; 7 (10):	CS	retrospective CS. 116 subfertile women. Laparoscopy was performed in women with positive CAT of tubo-ovarian abnormalities by USS, in severe dysmenorrhea, endometriosis or cysts	all women underwent laparoscopy with methylene blue dye test, C. trachomatis TroA, HtrA and MOMP antibodies by EIA. Optical density of >0.4 was considered positive	seroprevalence of TroA, HtrA and MOMP IgG, sensitivity, specificity, accuracy, PPV and NPV	28/79 women had tubal factor infertility. Serology: 28/79 (35.4%) positive for TroA IgG, 27/79 (34.2%) HtrA IgG and 32/79 (40.5%) MOMP IgG. Women with TFI had more often TroA IgG (60.7% vs. 21.6%, p < 0.001) and HtrA IgG antibodies (57.1% vs. 21.6%, p = 0.001) than women without TFI. Accuracy: TroA 72.2%, sensitivity of 60.7% and specificity of 78.4%, PPV 60.7%, NVP 78.4%. HtrA specificity 78.4%, sensitivity 57.1%. MOMP: specificity 66.7% and sensitivity 53.6%. All 3: specificity 88.2%, sensitivity 35.7%.		
Singh, S., Bhandari, S., Agarwal, P., Chittawar, P. and Thakur, R. Chlamydia antibody testing helps in identifying females with possible tubal factor infertility. Int J Reprod Biomed. 2016; 14 (3): 187-92.	CS	prospective CS. 200 consecutive women. There was no statistical difference in mean age of patients with positive and negative titres for chlamydial antibody.	all women underwent diagnostic laparoscopy and Chlamydia serum IgG antibodies were determined by ELISA	laparoscopy findings and Chlamydia trachomatis antibody titers were compared	only 5% (10/200) of women were seropositive for anti-chlamydial IgG antibody. only 30% of patients with positive antibody titre had primary infertility in contrast to 64.73% with negative titres. Association of seropositivity with type of infertility appears to be statistically significant. The positive predictive value of CAT test is 100%, while negative predictive value is 78.95%		

					for diagnosing tubal disease. CAT test was positive in 10/50 patients of tubal disease so sensitivity was 20%, while the test had 100% specificity as it was negative in all 150 patients with normal tubes		
Sönmez, S., Sönmez, E., Yasar, L., Aydin, F., Coskun, A. and Süt, N. Can screening Chlamydia trachomatis by serological tests predict tubal damage in infertile patients? New Microbiol. 2008; 31 (1): 75-9.	CS	prospective CS. 152 women presenting in the fertility clinic; control group: women right after delivery. No statistical difference between CAT positive and CAT negative cases.	all patients underwent laparoscopy and CT titers were measured in serum by IFA (positive if titer >1/10)	laparoscopy findings and Chlamydia trachomatis antibody titers were compared	36 antibody positive cases and 68 antibody negative cases in the study group. CT positivity was similar in the study (34.6%) and control groups (22.5%). Sensitivity for CT positivity for tubal damage was 40%, specificity was 69.49%, PPV was 50%, and NPV was 60.29%.	We found a linear correlation between high titers and severe tuboperitoneal adhesions.	
Tanikawa, M., Harada, T., Katagiri, C., Onohara, Y., Yoshida, S. and Terakawa, N. Chlamydia trachomatis antibody titres by enzyme-linked immunosorbent assay are useful in predicting severity of adnexal adhesion.	CS	prospective CS. 131 women attending fertility clinic. Age and duration of infertility were similar between CAT positive and CAT negative patients	C. trachomatis IgG and A was detected in serum by ELISA. A diagnostic laparoscopy was performed in all patients	sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and likelihood ratio for adnexal adhesions were calculated	51/131 (39%) of patients tested positive for CAT. Tubal occlusion on at least one side in 24/51 (47%) patients with positive CAT and in 20/80 (25%) patients with negative CAT. Abnormal tubal appearance on at least one side: in 25/51 (49%) patients with positive CAT and 19/80 (24%) patients with negative CAT. Adnexal adhesions: predictive value of IgG: sensitivity 68.2%, specificity 78.8%, PPV 57.7% and NPV 87.9%. predictive value of IgA: sensitivity 68.2%, specificity 82.7%,		

Hum Reprod. 1996; 11 (11): 2418-21.					PPV 62.5%, NPV 86.9%. The LR+ for the IgG and IgA antibody titres by ELISA 5=1.11 were 3.2 for IgG and 3.9 for IgA. The LR+ of IgG and IgA 5=2.0 was 7.7 and 5.1 respectively, indicating a patient with adnexal adhesion to be 7.7 and 5.1 times more likely to have a positive test result (antibody titre 5=2.0) than a patient without adnexal adhesion.		
van Dooremalen, W. T. M., Verweij, S. P., den Hartog, J. E., Kebbi-Beghdadi, C., Ouburg, S., Greub, G., Morré, S. A. and Ammerdorffer, A. Screening of Chlamydia trachomatis and Waddlia chondrophila Antibodies in Women with Tubal Factor Infertility. Microorganisms. 2020; 8 (6):	CS	retrospective CS. 891 women attending fertility clinic	CAT was detected in blood by pELISA Medac, women tested positive were offered laparoscopy with methylene blue dye testing. CAT-negative patients underwent HSG and in case of abnormal findings, laparoscopy was offered.	CAT status, HSG and laparoscopy results	119/890 women tested positive for CAT (13.4%). C. trachomatis antibodies were present significantly more often in the TFI+ compared to the TFI- group, respectively, 41.9% vs. 9.6% ($p < 0.0001$; OR: 6.8; 95% CI 4.28–10.76). In the severe TFI group, the prevalence of C. trachomatis (43.9%) was similar to that of the total TFI+ group (41.9%). Tthe prevalence of W. chondrophila antibodies was similar in both the TFI+ and TFI- group (p: 0.457; OR: 0.8; 95% CI: 0.55–1.30), with 39.2% testing positive in the TFI- group and 35.2% and 31.8% in the TFI+ and sTFI group, respectively.		
Veenemans, L. M. and van der Linden, P. J. The value of Chlamydia trachomatis antibody	CS	prospective 295 female infertility patients, unselected. 18 excluded	Chlamydia antibody titre with the C. trachomatis-spot IF test. In patients with a positive CAT test, a laparoscopy with chromotubation was	The diagnostic value of CAT was compared with HSG in tubal pathology,	84/277 patients tested positive for CAT, of which 78 had laparoscopy. 28/78 had tuboperitoneal abnormalities (35.9%) and 50/78 had none (64.1%). 67 patients with a	Laparoscopy with tubal patency testing remains the	

testing in predicting tubal factor infertility. Hum Reprod. 2002; 17 (3): 695-8.			performed. In patients with a negative CAT test, a HSG was performed. If the HSG was abnormal, laparoscopy was performed. patients with a normal HSG who didn't conceive after 6 months also underwent laparoscopy	using likelihood ratios (LR)	negative CAT had laparoscopy, of which 7 (10.4%) had tuboperitoneal abnormalities. the LR+ of CAT was 1.8 (a patient with TFI is 1.8 times more likely to have a positive result than a patient without TFI), and the LR- was 0.4 (a patient with TFI is 0.4 times as likely to have a negative test as a patient without the disease). ROC was 1:32	most accurate method of diagnosing tuboperitoneal pathology.	

2.5 Uterine factor

PICO Question: Which diagnostic procedures should be performed to confirm a normal uterine structure/anatomy, uterine wall/myometrium?

3D Ultrasound vs. 2D ultrasound

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Caliskan, E., Ozkan, S., Cakiroglu, Y., Sarisoy, H. T., Corakci, A. and Ozeren, S. Diagnostic accuracy of real-time 3D sonography in the diagnosis of congenital Mullerian anomalies in high-risk patients with respect to the phase of the menstrual cycle. J Clin Ultrasound. 2010; 38 (3): 123-7.	CS	Prospective cohort study. total number of patients 108 with suspected congenital mullerian defects at HSG, or suspected to have, one group, one centre	1 gynaecologist performed the 2DUS, the 2nd gynaecologist performed the real-time 3DUS results were compared and correlated with the definitive diagnosis obtained by MRI, laparoscopy, or hysteroscopy		sensitivity, specificity, positive-predictive values, negative-predictive values, false-positive and false-negative rates of 2DUS and real-time 3DUS for detecting CMDs, in the follicular and luteal phases	3DUS is an accurate method that can be used for the diagnosis of CMDs	
Jurkovic, D., Geipel, A., Gruboeck, K., Jauniaux, E., Natucci, M. and Campbell, S. Three-dimensional ultrasound for the assessment of uterine anatomy and detection of	CS	total number of patients 61 with a history of recurrent miscarriage or infertility and who had previously been	2DUS images were obtained in 60 (98.3%) and 3DUS images in 58 (95.1%;)cases.		Comparison between hysterosalpingography and US showed that five false-positive diagnoses of arcuate uterus and three of major uterine anomalies were made on 2DUS,	The ability to visualize both the uterine cavity and the myometrium on 3DUS facilitated the diagnosis of uterine anomalies and	

congenital anomalies: a comparison with hysterosalpingography and two-dimensional sonography. Ultrasound Obstet Gynecol. 1995; 5 (4): 233-7.		investigated by hysterosalpingography, one group, one centre			3US agreed with HSG in all cases of arcuate uterus and major congenital anomalies.	enabled easy differentiation between subseptate and bicornuate uteri.	
Ludwin, A., Pityński, K., Ludwin, I., Banas, T. and Knafel, A. Two- and three-dimensional ultrasonography and sonohysterography versus hysteroscopy with laparoscopy in the differential diagnosis of septate, bicornuate, and arcuate uteri. J Minim Invasive Gynecol. 2013; 20 (1): 90-9.	CS	total number of patients 117 with a history of recurrent abortions or infertility and a 2DVUS initial diagnosis of a septate, bicornuate, or arcuate uterus prospective clinical study, university hospital and private hospital and clinic.	2D-TVS, 3D-TVS, 2D-SIS, and 3D-SIS performed by experienced examiners and hysteroscopy with laparoscopy to establish the final diagnosis		Specificity, Sensitivity 3D-SIS showed perfect diagnostic accuracy (100.0%) in general detection of uterine abnormalities, compared with initial 2D-TVS (77.8%), expert 2D-TVS (90.6%), 2D-SIS (94.0%), and 3D-TVS (97.4%).	Although 3D-SIS was identical to HSC/LPSC, with the highest accuracy, there was no significant difference in diagnostic value between 3D-TVS with 2D-SIS and 3D-SIS or between expert 2D-TVS and 3D-TVS with 2D-SIS. The high diagnostic value of US tools questions the need for endoscopy in the differential diagnosis of the most common congenital uterine anomalies	

PICO Question: Which additional diagnostic procedures should be performed to confirm an anatomically normal uterine cavity?

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Fatemi, H. M., Kasius, J. C., Timmermans, A., van Disseldorp, J., Fauser, B. C., Devroey, P. and Broekmans, F. J. Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. Hum Reprod. 2010; 25 (8): 1959-65.	RCT	Sub-analysis of an RCT. 678 asymptomatic subfertile women with normal 2D US women under the age of 43 years with no prior hysteroscopy examination nor prior IVF/ICSI attempt to conceive (Belgian statute book, 2003).Women with any of the predefined abnormalities at TVS followed the regular routine and underwent a therapeutic hysteroscopy to resolve the uterine cavity pathology prior to starting the infertility treatment.	In case no menorrhagia or metrorrhagia was present and TVS did not show abnormalities, women were indicated for a screening hysteroscopy on an outpatient basis	intrauterine abnormalities, defined as endometrial polyps, submucous myomas, intrauterine adhesions or uterine septa.	The frequency of one or more abnormalities per patient was 11% (Fig. 2). Endometrial polyps were identified in 41 cases (6%). Most detected polyps (63%) were smaller than 0.6 cm, in only three cases it concerned a polyp .1.0 cm. Submucous myomas were found in six cases (1%), all with an estimated diameter between 0.5 and 2.0 cm. Also 15 cases with intrauterine adhesions (2%) and 14 cases with a septum (2%) were diagnosed. In two cases more than one abnormality was identified.		

Almog, B., Shalom-Paz, E., Shehata, F., Ata, B., Levin, D., Holzer, H. and Tan, S. L. Saline instillation sonohysterography test after normal baseline transvaginal sonography results in infertility patients. Is it justified? Gynecol Endocrinol. 2011; 27 (4): 286-9.	CS	retrospective CS. 294 women with a baseline TVS as part of the infertility work-up	All TVS results (positive and negative) were further investigated by SIS. Positive SIS results were further investigated by hysteroscopy. The study group (n=124): patients with a completely negative findings on baseline TVS (endometrial line≤5 mm). The control group (n=170): patients with any abnormality on baseline TVS scan.	Abnormalities included highly suggestive findings for ILs (such as polyps, echogenic and thick endometrium, submucous fibroid distorting the cavity, septum) and out of cavity lesions (such as intramural and sub serosal fibroids, adenomyosis).	Table I. Results of SIS, hysteroscopy and pathology in the study group and control. Study group ($n=124$) / Control group ($n=170$) / p Age: 35.6.2 ± 4.9 / 36.6 ± 4.8 / NS Positive SIS results (%): 13 (10.4) / 62 (36.4) / <0.05 Positive hysteroscopic results (%): 3 (23.0) / 42 (67.7) / <0.05 Positive pathology results: 0 (0) / 35 (83.3) / <0.05 PPV* (%): 0 / 56.4 NS, not significant. *positive predictive value of SIS considering pathology reports as gold standard.		
Bakas, P., Hassiakos, D., Grigoriadis, C., Vlahos, N., Liapis, A. and Gregoriou, O. Role of hysteroscopy prior to assisted reproduction techniques. J Minim	CS	prospective CS. 217 women. Inclusion criteria were primary or secondary infertility, age ,40 years, body mass index ,30, follicle-stimulating hormone level ,10 IU/L, and	diagnostic hysteroscopy after normal TVS and HSG	incidence of intrauterine anomalies that were undetected during HSG or TVS	**Table 2** Hysteroscopic findings in women with and without previous ART attempts Variable / Previous ART trial (n = 95) / No previous ART trial (n = 122) / p value Hysteroscopic finding, No. (%) Endometrial polyp: 14 (14.7) / 12 (9.8) / >.05 Uterine septum: 13 (13.6) / 15 (12.3) / >.05 Submucosal myoma: 10 (10.5) / 2 (1.6) / >.05 Synechiae: 3 (3.2) / 0 / >.05 Total: 40 (42) / 29 (23.7) / .006 ART = assisted reproduction technique.		

Invasive Gynecol. 2014; 21 (2): 233-7.		regular menstrual cycle every 26 to 35 days. Exclusion criteria were known presence of endometriosis or adenomyosis and history of recurrent miscarriage. The diagnostic workup included medical history, gynaecologic examination, TVS, HSG, semen analysis, and hormone profile (FSH, luteinizing hormone, estradiol, prolactin, thyroid-stimulating hormone, and anti-mullerian hormone at days 2 to 4 of menses).					
Makled, A. K., Farghali, M. M. and Shenouda, D. S. Role of hysteroscopy and endometrial biopsy in women with unexplained infertility. Arch Gynecol Obstet.	CS	prospective CS. 100 women with unexplained infertility	diagnostic hysteroscopy after normal TVS and HSG	incidence of intrauterine anomalies that were undetected during HSG or TVS	Diagnostic hysteroscopy showed endometrial polyps in 31 of the infertile patients (31 %). Of these patients, only 18 (18 %) were correctly diagnosed by TVS. Seven of the missed patients were diagnosed with hyperplasia, while six patients had no abnormality.		

2014; 289 (1): 187-92.							
Yang, J. H., Chen, M. J. and Yang, P. K. Factors increasing the detection rate of intrauterine lesions on hysteroscopy in infertile women with sonographically normal uterine cavities. J Formos Med Assoc. 2019; 118 (1 Pt 3): 488-493.	CS	retrospective CS. 1726 infertile women.	normal uterine cavities on 2D-TVS, who subsequently underwent office hysteroscopic examinations.	diagnosis of intrauterine lesions were visible, including endometrial polyp, IUA, Caesarean scar defect, tortuous cervical canal, unicornuate uterus, endometritis, myoma compression, and uterine septum, endometritis	intrauterine lesions in 260 women (15.1%) and normal uterine cavities in 1466 women (84.9%). The types of abnormal hysteroscopic findings were endometrial polyps (n=105, 6.1%), IUAs (n=99, 5.7%), Caesarean scar defects (n=25, 1.5%), tortuous cervical canals (n=9, 0.5%), unicornuate uteri (n=8, 0.5%), endometritis (n=8, 0.5%), myoma compressions (n=4, 0.2%), and uterine septa (n=2, 0.1%)		

2.6 Laparoscopy

PICO Question: Should women undergo a laparoscopy before being diagnosed with UI?

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Tanahatoe, S. J., Lambalk, C. B. and Hompes, P. G. The role of laparoscopy in intrauterine insemination: a prospective randomized reallocation study. Hum Reprod. 2005; 20 (11): 3225-30.	RCT	154 women with unexplained infertility > 1 y (mean 2.9 y) , age 31-34 year. Academic Hospital	Intervention Diagnostic laparoscopy before start IUI (DLSF) or DLS after IUI, (IUIF) ic 6 cycles. Surgical treatment of mild/moderate adhesions and/or endometriosis was performed, in case of severe pelvic pathology the treatment consisted of secondary surgery or direct IVF. Surgeons were not blinded.	Analysis according intention to treat. Primary outcome measure was the number of abnormal laparoscopies leading to a change of treatment versus total number of performed laparoscopies. The study was powered on an assumed difference of 25% more abnormal laparoscopies in the IUIF group. Pregnancy was	Laparoscopies performed in group 1 DLSF N=64/77 and group 2 N= 23/77 IUIF. No abnormalities at laparoscopy in 52% DLSF and 44% IUIF (P=0.63 and OR 1.4 (95% CI 0.5-3.6). Abnormalities 45% vs 56 % and intervention (ie surgical treatment in 48% and 56% respectively: adhesiolysis in 4% group 1 vs 0%, evaporation endometriosis in 44% vs 52%, and fimbriolysis in 0 vs 4%). Pregnancies 44% vs 49%: Natural 12 vs 16 and IUI pregnancy 22 vs 22 (P 0.63 OR 1.2 (95% CI: 0.7-2.3). Dropouts before DLS in fig 1 (discontinuation treatment and/or pregnancy before IUI). There was no significant difference in the waiting period	Laparoscopy performed after 6 cycles of IUI for unexplained infertility, did not detect more abnormalities with clinical consequences compared with those performed prior to IUI treatment. The impact of the laparoscopic detection and treatment of pelvic pathology prior to IUI seems negligible in terms of pregnancy outcome.	Not specified if IUI or OS+IUI. The outcome of the study suggests that a diagnostic laparoscopy should not be done routinely after a basic fertility work up which includes patent tubes at HSG. Abnormal findings such as adhesions and endometriosis otherwise missed will be detected , but it is questionable if treatment of

				not an outcome measure. Follow-up stopped after 6 IUI cycles in DLSF or after ongoing pregnancy and in IUIF group after clinical pregnancy or if pregnancy did not occur after 6 completed IUI cycles.	between DLS in DLSF group and start IUI in the IUIF group.		then detected pelvic disease will improve pregnancy rates after IUI. Adequately powered, large RCT's are required to answer this question (a power calculation by the author's suggests that at least 1000 patients are required).
Lavy, Y., Lev-Sagie, A., Holtzer, H., Revel, A. and Hurwitz, A. Should laparoscopy be a mandatory component of the infertility evaluation in infertile women with normal hysterosalpingogram or suspected unilateral distal tubal pathology? Eur J Obstet Gynecol	CS	retrospective CS. 86 patients in whom both HSG and laparoscopy were completed were included in the present study. Patients who underwent laparoscopy 12 months or more after HSG was performed were	Laparoscopy following either normal or abnormal HSG	changes of treatment plan	Of the 63 patients with ‘‘combined normal’’ HSG, three patients were found to have bilateral tubal occlusion on laparoscopy that caused a change in the original treatment regimen and referral to IVF. This represents a false negative rate of 4.8% with regard to the original treatment plan.		

Reprod Biol. 2004; 114 (1): 64-8.		excluded from the study.					
Tanahatoe, S., Hompes, P. G. and Lambalk, C. B. Accuracy of diagnostic laparoscopy in the infertility work-up before intrauterine insemination. Fertil Steril. 2003; 79 (2): 361-6.	CS	retrospective chart review. 495 patients	laparoscopy following normal HSG	The end point of this study is the number of diagnostic laparoscopies leading to a change in treatment decision where IUI was initially indicated.	Laparoscopy did not change the initial treatment decision in 371 (75%) patients, but did in 124 (25%) patients. The latter treatment decisions included direct laparoscopic surgery of the abnormal findings in 103 (20.8%) cases, fertility-increasing operation by laparotomy in 13 (2.6%) cases, and treatment with IVF in 8 (1.6%) cases.		

2.7 Cervical/ vaginal factor

PICO Question: What is the need for female lower genital tract investigations?

Post-coital test

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Oei, S. G., Helmerhorst, F. M. and Keirse, M. J. When is the post-coital test normal? A critical appraisal. Hum Reprod. 1995; 10 (7): 1711-4.	SR	53 study reports 11 studies fulfilled inclusion criteria 4007 women Criteria: (i) the studies should relate to infertile couples; (ii) the reports should provide sufficient data on the materials and methods used; (iii) the test results categorized as normal or abnormal (or positive or negative) should be expressed in numbers of motile spermatozoa per HPF; and	For each study, they calculated the sensitivity, specificity, predictive values of normal and abnormal test results and likelihood ratios for normal and abnormal results	Table II, page 1712 Table III, page 1712 Table IV. Test properties of the post-coital, page 1713 Prevalence Sensitivity Specificity Predictive value of normal result Predictive value of abnormal result Likelihood ratio for normal result Likelihood ratio	The predictive values of normal and abnormal PCT were 0.37-0.92 and 0.58-0.85 respectively. Sensitivity was 0.10- 0.90 and specificity 0.30-0.97. Likelihood ratios for normal and abnormal PCT were 0.77 and 1.85 respectively.	The discriminating ability of the PCT is poor, and altering definitions of normality hardly enhances its predictive power. As long as the value of the PCT for the assessment and treatment of so-called 'cervical factor infertility' remains unclear, a cut-off point with high specificity and a high likelihood ratio for an abnormal test	

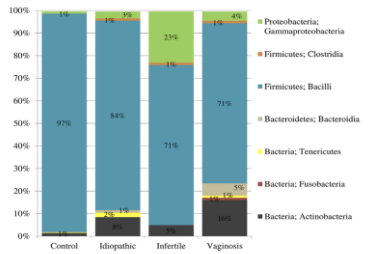
		(iv) the occurrence of pregnancy must be reported for the total group of women with both normal and abnormal PCT.		for abnormal result		result is recommended.	
Oei, S. G., Helmerhorst, F. M., Bloemenkamp, K. W., Hollants, F. A., Meerpoel, D. E. and Keirse, M. J. Effectiveness of the postcoital test: randomised controlled trial. Bmj. 1998; 317 (7157): 502-5.	RCT	total number: 444 couples intervention group 227; control group 217 a university and two non-university teaching hospitals	In the intervention group the postcoital test was planned 14-16 days before menstruation and 6-18 hours after intercourse. Treatment for negative postcoital test results was in accordance with standard clinical practice. Follow-up 24 months	Treatment was given more often in the intervention group than in the control group (54% v 41%). Cumulative pregnancy rates at 24 months in the intervention group (49% (42% to 55%)) and the control group (48% (42% to 55%)) were similar. Reproducibility is questionable	Figure, page 504 Cumulative pregnancy rates for 227 couples in intervention group, which included postcoital test, and 217 couples in control group which excluded the test.	Routine use of the postcoital test in infertility investigations leads to more tests and treatments but has no significant effect on the pregnancy rate.	
Hessel, M., Brandes, M., de Bruin, J. P., Bots, R. S., Kremer, J. A., Nelen, W. L. and Hamilton, C. J.	CS	2476 couples with unexplained infertility PCT was performed in 1624 couples three fertility clinics retrospective study	the protocol for ultrasound timing of PCT is included, Table 1, page 915 Main outcome measures:	pregnancy rates	**Table 1.** Fecundity Rates for the Postcoital Test by Peak Periovulatory Serum Estradiol Levels PCT (sperm/HPF) / Estradiol (pg/mL) 81–200 / 201–500 / 501–1500 / 1501–3433 0: 0/5 / 2/18 (11%) / 13/73 (18%) / 5/24 (21%) 1–10: 0/2 / 5/27 (19%) / 13/77 (17%) / 10/45 (22%) >10: 0/8 / 3/12 (25%) / 6/43 (14%) / 4/21 (19%) P: .61 / .86 / .96 χ^2: 0.994 / 0.30 / 0.088 PCT = postcoital test; HPF = high-power field.	The post-coital test plays a significant role in prognostic models for prediction of spontaneous	

Long-term ongoing pregnancy rate and mode of conception after a positive and negative post-coital test. Acta Obstet Gynecol Scand. 2014; 93 (9): 913-20.			pregnancy rate after three years		Spontaneous and ongoing pregnancy rates after a positive post-coital test were 37.7 and 77.5%compared with 26.9 and 68.8% after a negative test (p < 0.001).	pregnancy in couples with, until then, unexplained infertility. In addition, the post-coital test is particularly useful in male factor infertility, where a positive test was associated with a higher spontaneous pregnancy rate.	
Oei, S. G., Bloemenkamp, K. W., Helmerhorst, F. M., Naaktgeboren, N. and Keirse, M. J. Evaluation of the postcoital test for assessment of 'cervical factor' infertility. Eur J Obstet Gynecol Reprod Biol. 1996; 64 (2): 217-20.	CS	224 couples, who underwent a PCT as part of routine fertility work-up 24 were excluded one fertility clinic retrospective study	The PCT was performed according to the method described by Hull et al.	Cumulative pregnancy rates in relation to results of the PCT follow-up 18 months	The predictive values of normal and abnormal PCTs were 0.54 and 0.58 overall and 0.74 and 0.47 if only untreated women were considered. Sensitivity and specificity were, respectively, 0.47 and 0.65 for all women and 0.54 and 0.68 for untreated women only. Likelihood ratios for normal and abnormal PCTs were 0.83 and 1.32 overall and 0.67 and 1.72 in untreated women.	The PCT has poor predictive power. This and the psychological impact on subfertile couples attest to the need for more rigorous study designs in evaluating this test.	
Glazener, C. M., Ford, W. C. and Hull, M. G. The prognostic power of the post-coital test for natural	Rest	reanalysis of data 207 couples originally studied between 1982 and 1983	PCT	relationship between the result of the PCT and the chance of conception	In couples with less than 3 years and positive PCT, 68% conceived within 2 years compared with 17% of those with negative result.	use of the PCT will enable clinicians to allocate scarce, expensive and invasive resources effectively	

conception depends on duration of infertility. Hum Reprod. 2000; 15 (9): 1953-7.					After 3 years, corresponding rates were 14% and 11%.		

VAGINAL MICROBIOTA TESTING

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Amato, V., Papaleo, E., Pasciuta, R., Viganò, P., Ferrarese, R., Clementi, N., Sanchez, A. M., Quaranta, L., Burioni, R., Ambrosi, A., Salonia, A., Clementi, M., Candiani, M. and Mancini, N. Differential Composition of Vaginal Microbiome, but Not of Seminal Microbiome, Is Associated With Successful	CS	prospective cohort study. 25 couples with UI undergoing IUI	microbiota composition was analysed by 16S rRNA gene amplification and compared to sequences from healthy subject using a reference database	hierarchical clustering for the relative abundance of lactobacillus species, comparison of taxonomic data with pregnancy outcome	women with UI: increase in the diversity of taxa. Pregnancy rate: 5/23 and a reduction in Lactobacillaceae together with an increase in Bifidobacteriaceae, NS compared to healthy controls. a significant lower Shannon index was found in pregnant women compared to non-pregnant women (0.8 ± 0.9 vs. 1.5 ± 1.1)		

Intrauterine Insemination in Couples With Idiopathic Infertility: A Prospective Observational Study. Open Forum Infect Dis. 2020; 7 (1): ofz525.							
Campisciano, G., Florian, F., D'Eustacchio, A., Stanković, D., Ricci, G., De Seta, F. and Comar, M. Subclinical alteration of the cervical-vaginal microbiome in women with idiopathic infertility. J Cell Physiol. 2017; 232 (7): 1681-1688.	CS	96 women: 27 infertile women attending the ART clinic and 69 fertile ones; Four groups: 1- women with idiopathic infertility (14), 2- with a diagnosed infertility (n 13), fertile women with BV (39) and fertile healthy women (30); To identify bacterial species suitable as biomarkers	Biological samples were collected 5–7 days before the menstrual period and before programmed in vitro fertilization practice. BV was diagnosed using the Nugent score criteria. In parallel, the diagnosis was assessed also by culture isolation. A real time quantitative PCR and sequencing ware performed;	Prevalence of BV	The analysis revealed a significant beta-diversity variation ($p < 0.001$) between the 4 groups. L. iners, L. crispatus, and L. gasseri distinguished idiopathic infertile women from the other groups. In these women, a microbial profile similar to that observed in bacterial vaginosis women has been detected.  **FIGURE 1** Comparison of microbiome taxonomic profiles. Comparison between cervical–vaginal microbiomes from the four groups included in the study. The phylum-level taxonomic classification was based on the relative abundance of normalized samples	The quantitative assessment and identification of specific microorganisms of the cervical–vaginal microflora could increase the accuracy of available tools for the diagnosis of infertility and improve the adoption of therapeutic protocols.	

Campisciano, G., Iebba, V., Zito, G., Luppi, S., Martinelli, M., Fischer, L., De Seta, F., Basile, G., Ricci, G. and Comar, M. Lactobacillus iners and gasseri, Prevotella bivia and HPV Belong to the Microbiological Signature Negatively Affecting Human Reproduction. Microorganisms. 2020; 9 (1):	CS	prospective observational study. 47 Infertile couples undergoing the use of ART (25 IU, 22 explained infertility)	vaginal lavages, follicular fluids, embryo culture mediums, and seminal fluids were tested;	Microbial composition of seminal fluid and vaginal lavage	Concerning the unexplained infertility group, there was a different microbial composition between the seminal fluids and the vaginal lavages. Lactobacilli were dominant in the vaginal lavages, and the most abundant species was L. Iners, which is linked to a decreased fertility rate. Prevotella was increased in the seminal fluids of the explained infertility group, along with HPV-positive seminal fluids. **Table 1.** Alpha diversity. The bacterial diversity values are given as the mean and the 95% confidence interval (CI). All of the pairwise comparisons were performed using a Kruskal–Wallis test ($p < 0.001$). ECM: embryo culture medium. **CHAO1** Explained Infertility / Unexplained Infertility / *p* Value Vaginal lavages: 42 (95% CI = 36–48) / 42 (95% CI = 35–49) / 0.4 Follicular Fluids: 59 (95% CI = 53–65) / 63 (95% CI = 49–77) / 0.3 Seminal Fluids: 94 (95% CI = 79–109) / 130 (95% CI = 101–159) / 0.08 ECM: 24 (95% CI = 19–29) / 38 (95% CI = 27–49) / 0.1 **SHANNON** Explained Infertility / Unexplained Infertility / *p* Value Vaginal lavages: 1 (95% CI = 0.7–1.3) / 1.4 (95% CI = 1.1–1.7) / 0.1 Follicular Fluids: 2.6 (95% CI = 2.2–3) / 2.6 (95% CI = 2.2–3) / 0.7 Seminal Fluids: 3.7 (95% CI = 3.4–4) / 4 (95% CI = 3.7–4.3) / 0.09 ECM: 2.7 (95% CI = 2.4–3) / 3 (95% CI = 2.7–3.3) / 0.4	Their results support the concept that the assessment of the reproductive tract microbiome adds a new microbiological perspective to human reproduction. Male and female genital tracts show peculiar microbiomes that can impair the fertility rate. The seminal microbiome used for IVF needs to be taken into consideration.	
Patel, N., Patel, N., Pal, S., Nathani, N., Pandit, R., Patel, M., Patel, N., Joshi, C. and Parekh, B. Distinct gut and vaginal microbiota profile in women with recurrent implantation failure and unexplained infertility. BMC		UE was diagnosed if a cause remains undefined after our routine fertility tests with the following criteria: infertility of more than 1 year, normospermic male partner, normal menstrual rhythm with regular ovulation, bilateral	Study group: n=10, women with UI. Control group: n=11 fertile women Participants collected the faecal samples in a sterile plastic container with a tight closing lid. To collect the vaginal samples, using a sterile swab stick, clinicians	α-diversity and β-diversity. differences in microbial community	Firmicutes accounted for the vast majority of the vaginal bacteria, with higher relative abundance in UI than controls (69.7 vs 53). Fusobacteria (18% vs.0.14) and Bacteriodetes (4.1% vs. 0.92) were relatively more abundant in the controls than in the UI group. Within the genus of Lactobacillus, L. jensenii and L. vaginalis were only detected in the UI group.	Given the small sample size, we could not detect a significant statistical difference between groups.	

Womens Health. 2022; 22 (1): 113.		tubal patency verified through the hysterosalpingogram or laparoscopy, and normal hormonal tests (i.e., thyroid, prolactin, AMH) [23, 24]. Exclusion criteria included diabetes, polycystic ovary syndrome and endometriosis, diarrhoea, ongoing pregnancy, addiction (e.g., drugs, alcohol, tobacco etc.) and the use of antibiotics within at least two weeks before sample collection.	thoroughly wiped the posterior fornix of the vagina of the participants				

Sezer, O., Soyer Çalışkan, C., Celik, S., Kilic, S. S., Kuruoglu, T., Unluguzel Ustun, G. and Yurtcu, N. Assessment of vaginal and endometrial microbiota by real-time PCR in women with unexplained infertility. J Obstet Gynaecol Res. 2022; 48 (1): 129-139.		cross-sectional study. 52 women. The diagnosis of unexplained infertility was made after excluding common causes of infertility using standard fertility studies, including semen analysis, evaluation of ovulation, and tubal patency testing.	study group: 26 women with UI control group: 26 controls with a history of healthy delivery An expert gynaecologist collected vaginal and endometrial samples of 52 women during the regular vaginal speculum examination following at least 3 days of sexual abstinence, in the middle of the second half of their natural menstrual cycles (between 9 and 12th day), with sterile swabs without further intervention.	detection of Lactobacillus spp., Candida spp., Mycoplasma hominis, Mycoplasma genitalium, Enterobacteriaceae family, Staphylococcus spp., Streptococcus spp., Eubacterium spp., Peptostreptococcus spp., Atopobium vaginae	unexplained vs fertile lactobacilli-impaired microbiota proportion: 76.9% vs 26.9% ($p<0.05$). Mycoplasma hominis flora increment or pathogenic microorganism growth rate 34.6% vs 7.7% (<0.05). lactobacilli/TBM mean proportion in the vaginal samples 38.2% vs 76.3% ($p<0.05$). Average Staphylococcus ssp. ($p = 0.003$), C1 ($p = 0.013$), C2 ($p = 0.008$), C3 ($p < 0.001$), C4 ($p = 0.046$), Peptostreptococcus spp. ($p = 0.004$), Atopobium vaginae ssp. ($p = 0.019$), and Mycoplasma hominis ($p = 0.016$) growth rates were significantly higher in the unexplained infertility patients		

Tomusiak, A., Heczko, P. B., Janeczko, J., Adamski, P., Pilarczyk-Zurek, M. and Strus, M. Bacterial infections of the lower genital tract in fertile and infertile women from the southeastern Poland. Ginekol Pol. 2013; 84 (5): 352-8.	CS	161 women; infertility >1 year, asymptomatic. Women and their partners had been thoroughly investigated to exclude other factors which may have played a role in problems with conception, such as anatomical and hormonal abnormalities, endometriosis and abnormal sperm parameters. Women receiving antibiotic therapy or up to three weeks after the treatment were excluded from the study.	Study group: n=161 women with UI. Control group: n=60 with no history of fertility problems and at least one child, comprised the control group. The material was obtained from the posterior vaginal fornix and the cervical canal (swabs; PCR), as well as urine (first-catch urine specimens containing epithelial cells; strand displacement technology).	detection of C. trachomatis, N. gonorrhoeae, M. genitalium, M. hominis, U. urealyticum, G. vaginalis, E. coli, S. agalactiae, E. faecalis.	Infertile vs fertile women. U. urealyticum found in 9% vs 8% (NS). M. hominis found in 4% vs 0%. (p=0.05). C. trachomatis 0% vs 3% (p<0.05). None of the women tested positive for N. gonorrhoeae or M. genitalium. Normal bacterial vaginal flora was confirmed in 80 women (79%) treated for infertility and 51 women (85%) from the control group. BV was confirmed (based on pH, Nugent score and quantitative culture results) in 7 women (7%) treated for infertility, and none from the control group.		

2.8 Male genito-urinary anatomy

PICO Question: Should men undergo additional diagnostic procedures to confirm normal genito-urinary anatomy before being diagnosed with UI?

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Lotti, F., Frizza, F., Balercia, G., Barbonetti, A., Behre, H. M., Calogero, A. E., Cremers, J. F., Francavilla, F., Isidori, A. M., Kliesch, S., La Vignera, S., Lenzi, A., Marcou, M., Pilatz, A., Poolamets, O., Punab, M., Peraza Godoy, M. F., Rajmil, O., Salvio, G., Shaeer, O., Weidner, W., Maseroli, E., Cipriani, S., Baldi, E., Degl'Innocenti, S., Danza, G., Caldini, A. L.,	CS, multi-centre, international observational study (11 centres)	study population is healthy fertile men n=248 (partner pregnant or with a baby). Aim of the study: To report and discuss the scrotal organs CDUS reference ranges and characteristics in HFM and their associations with clinical, seminal, and biochemical parameters. The inclusion criteria: 1. healthy, fertile men. 2. age ≥ 18 years; 3. capacity to give consent for study participation. "Fertile men" were defined as (a)	Scrotal colour Doppler ultrasound (CDUS). The parameters to be analysed and the methods used to evaluate them were standardized and reported at www.andrologyacademy.net/eaa-studies. Intra- and inter-operator comparability of scrotal CDUS parameters: intra- and inter-operator comparability of the male genital tract-CDUS parameters were assessed on seven males of infertile couples. Intra-operator comparability was assessed for the main quantitative and qualitative scrotal CDUS parameters considering the results of three evaluations for each parameter (Table 1). Inter-operator comparability was derived from the measures and observations obtained by six different	A number of CDUS parameters in each category: 1. testis and scrotal sac, 2. Pampiniform plexus and varicocele, 3. Epididymis and proximal vas deferens. Main CDUS are indicated in table 1, but study results expand on more detailed parameters. Study reports reference ranges for CDUS	I wrote results only for correlation between scrotal CDUS and seminal parameters as this can be considered indirectly linked to male infertility (considering that semen analysis is the gold standard for male fertility evaluation. I. Mean TV was positively associated with 1. sperm concentration (r=0.315, p<0.0001 unadjusted, r=0.274 p<0.0001 after adjustment for confounding factors: age, waistline, lifestyle, cFT levels, and # EAA Centers) and 2. total count (r=0.219, p=0.001 unadjusted, r=0.278 p<0.0001 after	No association between scrotal CDUS parameters and time to pregnancy, number of children or history of miscarriage was observed. The present findings in fertile men will help in better understanding the pathophysiology of sperm abnormalities and male infertility, underlying modifications in their management.	Study attempts to bring reference values for CDUS parameters in a fertile cohort of men, but does not answer directly the PICO question. Instead it correlates CDUS parameters with semen parameters.

Terreni, A., Boni, L., Krausz, C. and Maggi, M. The European Academy of Andrology (EAA) ultrasound study on healthy, fertile men: Scrotal ultrasound reference ranges and associations with clinical, seminal, and biochemical characteristics. Andrology. 2021; 9 (2): 559-576.		partners of a pregnant woman in the second or third trimester of pregnancy or (b) men with a child less than one year old, achieved through natural conception. Healthy men were defined as subjects with no personal history of previous or current systemic diseases or treatments with a recognized negative effect on semen parameters.	sonogiraphists for the main quantitative and qualitative param- eters, respectively (Table 1). The comparability of quantitative and qualitative parameters was expressed using the coefficient of variation (CV) [(standard deviation (σ) / mean (μ)) x 100] and the concordance rate (CR) [(number of concordant observations/number of operators) x 100)], respectively. CV < 10 is considered acceptable.	parameters and makes correlations between scrotal CDUS and: 1. clinical parameters, 2. physical examination (PE) parameters, 3. biochemical parameters, 4. seminal parameters. I report results for correlation between CDUS and seminal parameters as rest of outcomes not relevant to the PICO	adjustment for confounding factors). II Subjects with testicular inhomogeneity showed a lower sperm vitality compared with the rest of the sample (Fig. 4 C), while those with any parenchymal calcification had lower sperm concentration and total count (Fig 4 D, E). Intratesticular artery PSV was positively as- sociated with sperm normal morphology (r=0.226, p=0.017 unadjusted, Adj.r=0.240 p<0.008). III. Epididymal head size was positively associated with sperm normal morphology (r=0.385, p<0.0001, Adj. r=0.233, p=0.002) and vas deferens mean sizes was positively associated with progressive motility (r=0.214, p=0.004 Adj. r=0.235, p=0.001). IV. Subjects with MAR test ≥ 1% showed a highe2prevalence of epididymal tail		

					echotexture inhomogeneity (OR=5.75[1.35-24.1], p=0.017), and a higher mean size of vas deferens and of epididymal body and tail (Figure 5), as compared with the rest of the sample.		

2.9 Male additional tests

PICO Question: Is there added value of additional tests in the male with normal WHO semen analysis?

Anti-sperm antibodies

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Ayvaliotis, B., Bronson, R., Rosenfeld, D. and Cooper, G. Conception rates in couples where autoimmunity to sperm is detected. Fertil Steril. 1985; 43 (5): 739-42.	Rest	n=108, Couples divided in 4 sub-categories: (1) no other cause of infertility was found in either partner, ie UI n=35; (2) the woman was apparently normal, but in the face of a significant male factor (semen volume, < 2 ml; sperm concentration, < 20 million/ml; motility, < 45%; oval heads, < 45%); (3) a female factor leading to infertility was present (inadequate luteal phase, as documented by two endometrial	IBT of sperm washed of seminal fluid(Couples were categorized into those where 50% or more of spermatozoa in the ejaculate were antibody-bound (high level) and those where < 50% were antibody-bound (low level)	natural pregnancy rate (follow up between 6 to 46 months). Comparison of PR is within each of the 4 categories, between couples with high and those with low ASA	Category 1, UI: PR in sub-group '> 50% sperm antibody-bound' is 4/26 (15.3%); PR in sub-group <50% sperm antibody bound is 6/9 (66.7%), significantly different p<0.005	The chance of conception was greatest in those couples where antibody binding was < 50%; i.e., most sperm were free of detectable surface-bound immunoglobulins. Th	Overall number of study group is very small (108) and only a subgroup of patients (35) are with UI, rest are either female, male or mixed aetiology; no report of baseline characteristic; no attempts to adjust for confounding factors; Strong detection bias: no precise

		biopsies; oligoovulation, i.e., cycle length more than 45 days; endometriosis, periadnexal adhesions, and immunities to sperm); and (4) both the man and woman were abnormal. aim: determine pregnancy rates in infertile couples where surface-bound immunoglobulins had been demonstrated on the husband's spermatozoa. Each of those categories further divide in low and high ASA.					definition of outcomes & no clear method to determine outcomes
Barbonetti, A., Castellini, C., D'Andrea, S., Minaldi, E., Totaro, M., Francavilla, S. and Francavilla, F. Relationship between natural and intrauterine insemination-assisted live births	CS	n=84 men of IUI couples recruited by call (inclusion criteria: having undergone post-coital test, PCT, exclusion criterion: having an untreatable cause of female infertility and assessment of ovulatory function and tubal patency of the	IgG MAR in semen (positivity ≥50%)	occurrence of natural pregnancies and the effectiveness of IUI were analysed in connection with the degree of sperm autoimmunisation, also accounting for the PCT	Group A: natural LBR 2/44 (4.5%), LBR after IUI 14/38 (36.8%), LBR after ICSI 7/15 (46.7%). Group B: natural LBR 12/40 (30%), LBR after IUI 7/26 (26.9%), LBR after ICSI 5/6 (83.3%). Predictor of natural live birth: % MAR	A 100%-positive IgG-MAR test can represent the sole cause of a couple's infertility, which could be successfully treated with IUI. On the other hand, a lower degree of	Initial strong bias towards including patients in the study who have post-coital test (PCT) done. Though subgroups were comparable at baseline, the inclusion

and the degree of sperm autoimmunisation. Hum Reprod. 2020; 35 (6): 1288-1295.		female partner. All males have immunological infertility (positive MAR test). Couples divided in 2 groups: Group A (100% MAR, n=44) and B (moderate 50-99% MAR, n=40). Comparison controls within each group (IUI vs natural conception); occurrence of natural pregnancies and the effectiveness of IUI were analysed in connection with the degree of sperm autoimmunisation, also accounting for the post-coital test outcome. In group A: couples receiving IUI 38/44 (83.3%), couples receiving ICSI 15/44 (34%). Group B: 26/40 (65%), couples receiving ICSI 6/40 (15%)		outcome; LBR, Predictive value of MAR% positivity for LBR	test positivity: β (95% CI): −0.06 (−0.10, −0.02) p value= 0.007	positivity (50-99%) may only represent a contributing factor to a couple's infertility, and so the decision to treat or wait also depends on the evaluation of conventional prognostic factors including the PCT outcome.	criteria and patients selected could have biased the overall results. The range of age among female patients was large (23-44) which will confound factors. Sub-categorisation of patients in 2 groups is also biased and inappropriate as thresholds for the 2 groups are too close (50-99% and 100%); no precise definition of outcomes & no clear method to determine outcome
Bozhedomov, V. A., Nikolaeva, M. A., Ushakova, I. V., Lipatova, N. A.,	DS	1060 infertile men with normal sperm and 107 fertile men. Female partners had	Semen analysis according to WHO (2000), MAR test, acrosome reaction	Semen analysis, MAR, acrosome reaction (AR), DNA	ASA -IgG increased; MAR>50% in 15.6%; AR decreased in ASA positive men 2.1x	Normozoospermic men with infertility have ASA 8.4x more	Immune dysfunction with ASA positive men

Bozhedomova, G. E. and Sukhikh, G. T. Functional deficit of sperm and fertility impairment in men with antisperm antibodies. J Reprod Immunol. 2015; 112 95-101.		full investigation with no abnormalities and therefore UI.	(AR) by exposure to ionophore A23187 and flow cytometry, DNA fragmentation by the sperm chromatin dispersion method (Halosperm; reference level <20%), ROS by chemiluminiscence with luminol (tests results of the fertile control group was considered normal).	fragmentation, ROS	lower; DNA fragmentation increased in ASA positive men; ROS levels higher in ASA positive men	commonly than fertile men.	more likely in unexplained infertility
Lähteenmäki, A. In-vitro fertilization in the presence of antisperm antibodies detected by the mixed antiglobulin reaction (MAR) and the tray agglutination test (TAT). Hum Reprod. 1993; 8 (1): 84-8.	CS	IVF couples with male autoimmunity as a cause for infertility n=33; normal semen parameters only in subgroups of studied cohort. Another subgroup analysed to look at how sperm motility affects fertilisation, which is also ASA-ve. Some of the couples also had	IgG MAR in semen (If 10-39% of motile spermatozoa were covered by latex particles, the test was interpreted as weakly positive. A positive reaction occurred when > 39% of the motile spermatozoa were incorporated in mixed agglutinates. If	The MAR values were divided into three categories and fertilisation and pregnancy rate (per embryo transfer) compared in those groups (Weakly positive, >0 and <40%; Positive, >40 and <90% ; Strongly positive, >90%)	fertilisation rate as per MAR category (Weakly positive, >0 and <40% ; Positive, >40 and <90% ; Strongly positive, >90%): 42/35/17 where category 2 and 3 significantly differ (p=0.0005). Pregnancy rate as per MAR category: 43/45/33 not	Only the strongly positive MAR group (values > 90%) revealed a significant reduction in fertilization rate compared to the other MAR groups. The pregnancy rate per embryo transfer was not directly	All couples undergo ART treatment (IVF). Hence, not appropriate cohort to look at predictive value of ASA test, though the 'control group' withing this study is patients in which ASA test was not done.

		identified female infertility.	there were >90% of motile spermatozoa in these agglutinates, the test was considered strongly positive). 16 men were further evaluated by direct (If the total binding was > 17% the test was considered positive) and 22 by indirect immunobead test (IBT).		significantly different	associated with either sperm MAR	selection bias: patient cohort are not comparable at baseline; not adjusted for confounding factors female age (big age range), more than one cycle /couple, duration of infertility; no precise definition of outcomes & no clear method to determine outcome
Lähteenmäki, A., Reima, I. and Hovatta, O. Treatment of severe male immunological infertility by intracytoplasmic sperm injection. Hum Reprod. 1995; 10 (11): 2824-8.	CS	Study Group A, n=29 undergoing ICSI (anti-sperm antibodies in the male, by mixed antiglobulin reaction, MAR assay; many of these men with low motile sperm count); some of the female partners have secondary infertility, anovulation or oligoovulation; Group	Sperm MAR tests for immunoglobulin (Ig) G (group A, n = 29; group C, n = 37) and IgA antibodies (group A, n = 26; group C, n = 22) (FertiPro, Gentbrugge, Belgium) were carried out according to the	miscarriage, clinical pregnancy, live birth rate (LBR)	Clinical pregnancy (%): Group A : total 13/28 (46) AI: 9/22 AII: 4/6, five miscarriages; Group B: 6(30), Group C: 11/37 (30), no miscarriages. The couples in group A had higher antibody levels in the male partner than those in group C, but	Fertilization rate in group C (conventional IVF) was significantly lower than in groups A and B. In addition, group C patients more often had only single-embryo transfers, which had a significant effect on the	all couples are assigned to ART treatments for known infertility, (male & female factor in some of the females in one of control groups, group B and positive group, group A) or female only

		A subdivided in 2 (AI: at least 1 previous IVF attempt n=22, AII: no previous IVF attempts n=7); Control Group B (ICSI couples in general n=20, male infertility, MAR negative); females with normal tubal patency and endocrinology; divided in 2 sub-groups BI: at least 1 previous IVF attempt n=13, BII: no previous IVF attempts n=7); Second Control Group, undergoing conventional IVF C (n=37, males with anti-sperm antibodies detected by MAR, tray agglutination test, TAT, and/or flow cytometry, CM); women with impaired tubal patency or ovulatory problems. Mild endometriosis in all groups ignored; Setting: single centre	instructions of the manufacturer. The test result was considered to be positive when >10% of motile spermatozoa were attached to the latex particles. Serum samples in groups A and C were checked by TAT according to the method described by Friberg (1974). Agglutination of the washed donor spermatozoa at a serum dilution of 3=1:16 was considered positive. Flow cytometry has been described in detail elsewhere (Rasanen et al., 1992). When >5% of the live spermatozoa were covered with antibodies, the		differences were not significant.	outcome. The effects that anti-sperm antibodies have at the level of gamete interaction can be circumvented by direct ICSI. Post-fertilization failures may still have an effect on the outcome of this treatment of severe male immunological infertility. ICSI offers a good chance of fertilization for couples with male immunological infertility.	factor (Control group C), hence huge selection bias that will affect outcomes; lack of appropriate controls; study seems to be not blinded; no precise definition of outcomes & no clear method to determine outcome; no statistical attempts to adjust for confounders (e.g., female age, previous unsuccessful ART attempts, abnormal semen parameters present in some subgroups)

			assay result was considered positive.				
Pagidas, K., Hemmings, R., Falcone, T. and Miron, P. The effect of antisperm autoantibodies in male or female partners undergoing in vitro fertilization-embryo transfer. Fertil Steril. 1994; 62 (2): 363-9.	CS	n=31, Control: IVF tubal infertility (n=312), Group A: IVF +ve ASA in female sera (n=15); Group B: IVF +ve ASA on sperm (n=16); all with normal semen characteristics. Group A and B subdivided in 2 categories, pregnancy with high % ASA (≥ 50%) and pregnancy in sub-category with low % ASA (<50%). sub-group A high % ASA (≥ 50%) n=8, sub-group A low % ASA (<50%) n=8	IBT (IgA, M, G), A specimen was classified as positive when >10% of the motile sperm showed positive binding	pregnancy rate	overall pregnancy in group A: 9/15 and in group B: 7/16. Pregnancy per subcategory. Pregnancy rate in sub-group B with high % ASA (≥ 50%) was 38% and in low % ASA (<50%) was 50%	In conclusion, fertilization rates or failure to con-ceive in our study could not be related to the pro- portion of antibody-coated spermatozoa or by the antibody class (isotype) detected by the immuno-bead test because the IVF-ET parameters were similar among the study groups and the controls. In addition, neither the regional specificity (or localization of the antibody) as defined by localization of the immunobead on the sperm surface, nor the antibody titer	Control group defined by the study is not appropriate as it would introduce bias (female factor). Real comparison is between Group A and B, but these groups have small size; In reality, group A would serve as 'control ' group because it is ASA+ve only in female sera; no precise definition of outcomes & no clear method to determine outcome

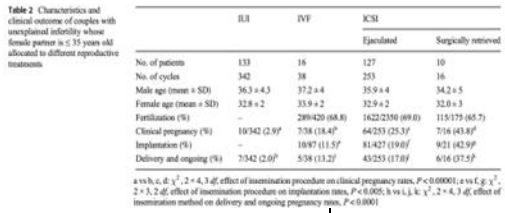
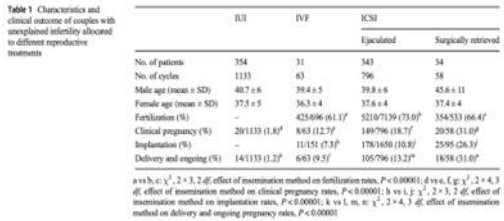
						could be correlated with success or failure of IVF-ET procedure.	
Rajah, S. V., Parslow, J. M., Howell, R. J. and Hendry, W. F. The effects on in-vitro fertilization of autoantibodies to spermatozoa in subfertile men. Hum Reprod. 1993; 8 (7): 1079-82.	CS	n=36 IVF couples; Group 1, n=16: couples with ASA positive male partners (either in sera or on sperm) with normal semen parameters characteristics Control group 2, n=20: IVF female factor, with no ASA in either semen or sera	MAR (the test was scored + , + + or+++when up to 20%,80% or >80% of spermatozoa were adhering to the erythrocytes); direct IBT (The test was regarded as positive if 20% or more of motile spermatozoa were attached to one or more beads)	fertilisation and pregnancy rate	fertilisation rate (per eggs collected): Group 1 (53/105, 50.5%) Group 2: 93/128, 72.2%) difference significant p=0.001;. Pregnancy rate (per embryo transfer): Group 1: 46.1% Group 2: 33.3% difference not significant	Antisperm antibodies in the male interfere with sperm—egg fusion and subsequent fertilization but once fertilization has occurred, the pregnancy rate remains the same.	potential selection bias: no clear inclusion criteria applied; groups are expected to not be comparable at clinical baseline level because of aetiology of infertility (Control Group 2 is female factor; no adjustment for confounders (big age range for males and females in both groups; duration of infertility); small sample size in both groups (Group 1: 16 couples,

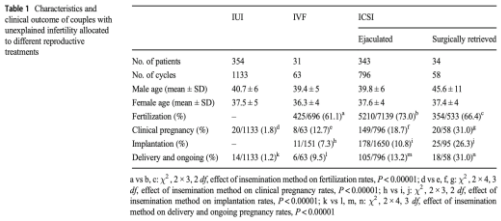
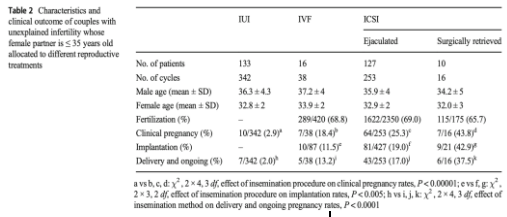
							Group 2: 20 couples)
Vazquez-Levin, M. H., Notrica, J. A. and Polak de Fried, E. Male immunologic infertility: sperm performance on in vitro fertilization. Fertil Steril. 1997; 68 (4): 675-81.	CS	IVF couples, Control, n=9: tubal infertility; study group n=7: females with tubal infertility and men with significant levels of sperm bound ASA (at least 20% of the sperm were swimming with adhered particles between the clumps of erythrocytes)	IgG MAR (The reaction observed under the microscope was considered to be positive if at least 20% of the sperm were swimming with adhered particles between the clumps of erythrocytes.)	pregnancy rate	study group: 1/9 (11%); control group: 4/9 (44%), differences not statistically significant	The fertilization rate and early embryonic cleavage of human embryos was found to be reduced significantly in patients with high levels of surface-bound antisperm antibodies. Moreover, embryonic quality and the PR may be compromised by the presence of significant levels of surface-bound antisperm antibodies.	potential selection bias at level of inclusion criteria: no clear inclusion criteria applied and no rationale provided as to choice for analysing these groups; groups are expected to not be comparable at clinical baseline level because of aetiology of infertility (Control group is female factor); no provision of baseline characteristics, hence no adjustment for potential confounding factors; mall

							sample size in both groups (control group: 9 couples, study group: 7 couples). The study had no appropriate length of follow-up (up to pregnancy rate but no LBR reported)

DNA FRAGMENTATION TEST

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Borges, E., Jr., Zanetti, B. F., Setti, A. S., Braga, Dpaf, Provenza, R. R. and Iaconelli, A., Jr. Sperm DNA fragmentation is correlated with poor embryo development,	prospective CS	First ICSI couples with female factor; inclusion criteria: couples with primary infertility undergoing their first ICSI cycle as a result of non–male factor infertility indications, which exclusively had fresh ET at day 5. The exclusion criteria were	sperm chromatin dispersion (SCD) test; Threshold values : low fragmentation (%30% SDF, n=433) and high fragmentation (>30% SDF, n=42)	1. comparison in fertilisation rate, embryo quality, implantation rate and pregnancy rate between couples with high and low DNA fragmentation index, DFI (as categorical	Higher miscarriage rate was observed in cycles with SDF above the cut-off (P=.018) ;No influence of continuous SDF was observed on laboratory and clinical parameters (Supplemental Table 3)		comparison groups discrepant in terms of numbers (low DFI n=433 vs high DFI n=42); Couples not UI (female factor) though authors provide analysis showing that female factor infertility did not influence laboratory

lower implantation rate, and higher miscarriage rate in reproductive cycles of non-male factor infertility. Fertil Steril. 2019; 112 (3): 483-490.		as follows: presence of any altered seminal parameter according to the cut-off values established, history of male factor infertility, any alteration detected during male partner workup, paternal smoking habit, previous conventional IVF cycle, ICSI cycle with vitrified/ thawed or donated oocytes, surgical sperm retrieval, cryopreserved sperm, vitrified/thawed ET, or preimplantation genetic tests. Couples with a history of pregnancy loss were also excluded from the analysis. Cycles were divided according to SDF rate into two groups: low fragmentation (%30% SDF, n=433) and high fragmentation (>30% SDF, n=42)		variable) 2. As continuous variable, influence of DNA fragmentation on ICSI outcomes. Definitions of outcomes: Clinical pregnancy was diagnosed when fetal heartbeat was detected. Implantation rate was calculated as the number of gestational sacs divided by the number of embryos transferred. Pregnancy rates were calculated per ET. Miscarriage was defined as a pregnancy loss before 20 weeks.	 		and clinical outcomes. Selection bias present. male patient subgroup with high DFI has statistically significant longer abstinence period
O'Neill, C. L., Parrella, A., Keating, D., Cheung, S.,	CS, retrospective	couples with unexplained infertility (male normal semen parameters and female with regular	SCSA and TUNEL. Threshold: for SCSA < 25% and for	comparison of fertilisation rate (for IVF and ICSI groups) clinical			selection bias: female age is confounding factor.

Rosenwaks, Z. and Palermo, G. D. A treatment algorithm for couples with unexplained infertility based on sperm chromatin assessment. J Assist Reprod Genet. 2018; 35 (10): 1911-1917.		ovulation, tubal patency, and a normal uterine cavity unable to conceive after 1 year) and poor IUI outcome (n=354) included in a treatment algorithm depending on the outcomes of their DNA fragmentation test (SCSA or TUNEL). The algorithm is as follows: if sperm DNA frag results normal couples were allocated to IVF, if abnormal, they were allocated to ICSI with ejaculated sperm. Of the ICSI couples if no pregnancy was achieved, ICSI with surgically retrieved sperm was offered ; Outcomes: Fertilization rate, implantation rate, pregnancy characteristics, and delivery rates	TUNEL ≤ 15% was considered normal	pregnancy and delivery between IUI initial results and following IVF and ICSI (with ejaculated and surgically retrieved sperm)	 **Table 1** Characteristics and clinical outcome of couples with unexplained infertility allocated to different reproductive treatments IUI / IVF / ICSI (Ejaculated / Surgically retrieved) No. of patients: 354 / 31 / 343 / 34 No. of cycles: 1133 / 63 / 796 / 58 Male age (mean ± SD): 40.7 ± 6 / 39.4 ± 5 / 39.8 ± 6 / 45.6 ± 11 Female age (mean ± SD): 37.5 ± 5 / 36.3 ± 4 / 37.6 ± 4 / 37.4 ± 4 Fertilization (%): – / 425/696 (61.1)[a] / 5210/7139 (73.0)[b] / 354/533 (66.4)[c] Clinical pregnancy (%): 20/1133 (1.8)[d] / 8/63 (12.7)[e] / 149/796 (18.7)[f] / 20/58 (31.0)[g] Implantation (%): – / 11/151 (7.3)[h] / 178/1650 (10.8)[i] / 25/95 (26.3)[j] Delivery and ongoing (%): 14/1133 (1.2)[k] / 6/63 (9.5)[l] / 105/796 (13.2)[m] / 18/58 (31.0)[n] a vs b, c: χ^2, 2 × 3, 2 *df*, effect of insemination method on fertilization rates, $P < 0.00001$; d vs e, f, g: χ^2, 2 × 4, 3 *df*, effect of insemination method on clinical pregnancy rates, $P < 0.00001$; h vs i, j: χ^2, 2 × 3, 2 *df*, effect of insemination method on implantation rates, $P < 0.00001$; k vs l, m, n: χ^2, 2 × 4, 3 *df*, effect of insemination method on delivery and ongoing pregnancy rates, $P < 0.00001$  **Table 2** Characteristics and clinical outcome of couples with unexplained infertility whose female partner is ≤ 35 years old allocated to different reproductive treatments IUI / IVF / ICSI (Ejaculated / Surgically retrieved) No. of patients: 133 / 16 / 127 / 10 No. of cycles: 342 / 38 / 253 / 16 Male age (mean ± SD): 36.3 ± 4.3 / 37.2 ± 4 / 35.9 ± 4 / 34.2 ± 5 Female age (mean ± SD): 32.8 ± 2 / 33.9 ± 2 / 32.9 ± 2 / 32.0 ± 3 Fertilization (%): – / 289/420 (68.8) / 1622/2350 (69.0) / 115/175 (65.7) Clinical pregnancy (%): 10/342 (2.9)[a] / 7/38 (18.4)[b] / 64/253 (25.3)[c] / 7/16 (43.8)[d] Implantation (%): – / 10/87 (11.5)[e] / 81/427 (19.0)[f] / 9/21 (42.9)[g] Delivery and ongoing (%): 7/342 (2.0)[h] / 5/38 (13.2)[i] / 43/253 (17.0)[j] / 6/16 (37.5)[k] a vs b, c, d: χ^2, 2 × 4, 3 *df*, effect of insemination procedure on clinical pregnancy rates, $P < 0.00001$; e vs f, g: χ^2, 2 × 3, 2 *df*, effect of insemination procedure on implantation rates, $P < 0.005$; h vs i, j, k: χ^2, 2 × 4, 3 *df*, effect of insemination method on delivery and ongoing pregnancy rates, $P < 0.0001$		Possible performance bias (different ovarian stimulation protocols) and detection bias (no precise definition of outcomes). Later authors mention that their inclusion criteria for females was <35yrs, though they also analysed couples above that age. No even number of couples allocated to treatments.
Repalle, D., Saritha, K. V., Bhandari, S. Sperm DNA fragmentation negatively	CS	prospective CS; couples (n=145) with unexplained infertility (normal semen analysis and no obvious female factor); inclusion &	Acridine orange; Threshold values: low fragmentation (SDF ≤%30, n of patients =97) and high	primary outcome: CLBR; other outcomes: implantation rate; cumulative pregnancy rate;	semen parameters do not differ between high and low DNA frag group, only the DNA frag results differed (Table 2). Subgroup analysis (fresh vs frozen embryo transfers)	In conclusion, SDF negatively influenced the CLBR, and a high SDF was associated	Selection bias: confounders: 1. abstinence period (not mentioned), 2. previous failed assisted conception

influences the cumulative live birth rate in the intracytoplasmic sperm injection cycles of couples with unexplained infertility. Clin Exp Reprod Med 2022; 49(3): 185-195		exclusion criteria: Couples undergoing their first ICSI cycle. The diagnosis of unexplained infertility was based on the following criteria: (1) normal ovarian reserve with an antral follicle count ≥ 8 and anti-Müllerian hormone levels ≥ 1.5 ng/mL, (2) normal tubal patency and uterine function evaluated by diagnostic laparoscopy and hysteroscopy, and (3) normal semen parameters for the male partner according to WHO 2010 criteria. None of the female partners were ≥ 41years of age in this study population. Female partners with < 5 mature metaphase II oocytes and male partners with normal semen parameters (WHO 2010 criteria) altered on the day of transvaginal oocyte recovery (TVOR) or egg	fragmentation (SDF >30% , n of patients=48)	miscarriage rate; predictive value of DNA frag for CLBR and miscarriage rate, but in sub-group analysis (positive vs negative live birth group), but not in low vs high DNA frag group	shows higher implantation rate, clinical pregnancy rate and LBR in the low DNA frag group for fresh embryo transfers, but not in frozen transfers (Table 3); Subgroup analysis in negative vs positive live birth groups (Table 4) shows that potential confounders (day of embryo transfer and fresh vs frozen embryo transfer) do not affect live birth rate and as such they don't affect the prognostic value of DNA frag results on CLBR and miscarriage, but that's based on analysis of negative and positive live birth groups, not the initial 2 groups of low and high DNA frag. I still think that there is a bias introduced by the different number of patients in low and high DNA frag group. Subgroup analysis between positive and negative live birth groups shows DNA frag as independent predictor for CLBR and miscarriage rate when adjusted for Female partner's age, embryo utilization rate, high-quality	with a higher miscarriage rate in the ICSI cycles of couples with unexplained infertility. These findings suggest that there is a need to evaluate SDF prior to ART cycles in couples with unexplained infertility to enable better counselling.	(IUI cycles), 3. discrepant number of patients in both groups, study does not account for number of embryos transferred per cycle or number of embryo transfers as potential confounder considering the n difference. 4. Subgroup analysis shows stat difference in CLBR between low and high DNA frag group only in fresh cycles (here the discrepancy in the total number of transfers between the groups is 2-fold, Authors look at day of embryo transfer and type of transfer as confounding factors on the prognostic value of DNA frag but in a subgroup of positive and negative live birth groups. They don't account for the bias on these two confounders coming

		collection were excluded. Participants with life-threatening diseases such as cancer or chronic kidney disease were also excluded from the study. Control for confounders: day of embryo transfer and type of transfer (fresh vs frozen); Embryo utilization (the ratio of the number of embryos transferred and the number of embryos frozen to the total number of embryos formed); patients were later divided in 2 groups on live birth outcomes (positive and negative live birth group)			embryo rate, but not male age (Table 6).		from the number of patients within the two comparison groups (high and low DNA frag group). 5. Male age as potential confounder Performance bias: confounder: number of embryo transfers between groups

2.10 Additional tests for systemic conditions

PICO QUESTION: SHOULD THERE BE ADDITIONAL EVALUATIONS OF POSSIBLE SYSTEMIC CAUSE OF UI IN THE COUPLE?

AUTO-IMMUNITY

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Anti-sperm antibodies in serum							
Mardesic, T., Ulcova-Gallova, Z., Huttelova, R., Muller, P., Voboril, J., Mikova, M. and Hulvert, J. The influence of different types of antibodies on in vitro fertilization results. Am J Reprod Immunol. 2000; 43 (1): 1-5.		44 couples referred for IVF treatment in whom the presence of antibodies was the only detectable cause of infertility	indirect MAR test for IgG, IgA, IgM and IgE. AZA were detected by passive hemagglutination test and ELISA	pregnancy rate	In 44 treated couples, 19 pregnancies occurred after IVF (43.2%). In 22 couples, the fertilization rate was lower than in patients with infertility of other etiology, but was satisfactory without ICSI (118:270, fertilization rate 43.7%) and ten pregnancies were achieved (45.5%). Standard IVF was possible in ten out of 15 cases (66.6%) with ASA (fertilization rate 37.6%) and in ten out of 11 couples (91%) with APA (fertilization rate 46.6%), but only in two women (11.1%) with AZA.		

Menge, A. C., Medley, N. E., Mangione, C. M. and Dietrich, J. W. The incidence and influence of antisperm antibodies in infertile human couples on sperm-cervical mucus interactions and subsequent fertility. Fertil Steril. 1982; 38 (4): 439-46.		698 human couples with primary or secondary unexplained infertility	detecting serum antibodies against sperm-the tray agglutination test (TAT)	pregnancy rate	In the study 14.8% of the men and 19.6% of the women had sperm-agglutinating antibodies. The incidence of pregnancy was influenced significantly by the presence of circulating spermagglutinating and -immobilizing antibodies in both sexes (Table 1). In men the pregnancy rate dropped significantly from 42.7% to 7.1% at agglutinin titers> 1:16. in women at titers ≥ 1:16 the incidence of pregnancy was only 4.0%, compared with 46.2% in the negative group		
Monem, F. M. and Moalla, H. A. Antisperm antibodies and unexplained infertility in Syria. An unsolved problem? Saudi Med J. 2003; 24 (8): 912-3.		group 1: 30 men and 24 women with UI group 2: controls, 45 fertile men and women	antisperm antibodies (ASA) (immunoglobulin (Ig) A, IgM, and IgG antibody classes) in their serum by indirect immunofluorescence and ELISA	presence of antibodies and association with UI	IIF: 22/54 patients positive and 3/45 controls ELISA: 20/54 positive and 4/45 controls There was a strong correlation between UI and antisperm antibodies		
Yasin, A. L., Yasin, A. L. and Basha, W. S. The Epidemiology of Anti-Sperm Antibodies Among Couples with Unexplained Infertility in North West Bank, Palestine. J Clin Diagn		42 couples with UI	ASA by ELISA	presence of antibodies and association with UI	The prevalence of ASA was 14.3% (6/42) among all couples, 9.5% (4/42) among males and 4.8% (2/42) among females. 22 couples managed with IVF-ICSI, and it was found that no relation between ASA status and the successfulness of IVF-ICSI exists		

Res. 2016; 10 (3): Qc01-3.							
Coeliac disease							
Tersigni, C., Castellani, R., de Waure, C., Fattorossi, A., De Spirito, M., Gasbarrini, A., Scambia, G. and Di Simone, N. Celiac disease and reproductive disorders: meta-analysis of epidemiologic associations and potential pathogenic mechanisms. Hum Reprod Update. 2014; 20 (4): 582-93.	SR	Unexplained infertility well defined n=586. Controls included n=6096	Clinical and biochemical diagnosis of CD	Prevalence of CD in unexplained infertility versus controls	Unexplained infertility OR for CD was 5.06 (CI 2.13-11.35)		Recommend screening for CD in unexplained infertility. More pregnancy complications in CD too including miscarriage, IUGR, LBW and preterm delivery
Karaca, N., Yılmaz, R., Aktun, L. H., Batmaz, G. and Karaca, Ç. Is there any relationship between unrecognized Celiac disease and unexplained infertile couples? Turk J Gastroenterol. 2015; 26 (6): 484-6.	CS	68 patients unexplained infertility, included males; after exclusion 65 couples studied	CD by Antigliadin antibodies (IgG and IgA), antiendomysial (IgG and IgA) and tissue transglutamininase antibodies (IgG and IgA) and total IgA followed by gastroscopy+biopsy if positive serological tests.		7.9% positive for autoantibodies; only one female and one male positive for celiac disease		Very small study in Turkish population

			Histopathological examination of biopt				
Thyroid antibodies							
Abalovich, M., Mitelberg, L., Allami, C., Gutierrez, S., Alcaraz, G., Otero, P. and Levalle, O. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol. 2007; 23 (5): 279-83.	CS	retrospective cohort study. 244 women with infertility (14 unexplained) and 155 controls	TSH and T4	TSH and T4	Subclinical hypothyroidism (SH) found in 13.9% infertile and 3.9% fertile. In UI: 0% subclinical hypothyroidism, 3/14 (21.4%) diagnosed with thyroid autoimmunity	Recommend measuring TSH in all infertile women	Marginal value as only 14 unexplained infertility patients
Kilic, S., Tasdemir, N., Yilmaz, N., Yuksel, B., Gul, A. and Batioglu, S. The effect of anti-thyroid antibodies on endometrial volume, embryo grade and IVF outcome. Gynecol Endocrinol. 2008; 24 (11): 649-55.	CS	case control study. 79 patients unexplained infertility n=31 thyroid pathology, n=23 normal thyroid function but positive anti-thyroid peroxides ot positive anti thyroidgloulin antibodies n=15 euthyroid with treatment, positive anti-TPO or anti-Tg antibodies. All going through IVF	thyroid function tests TAA and thyroid ultrasonography)	Embryo quality, clinical and biochemical pregnancy rates	No differences except clinical pregnancy rate less in last group. Clinical pregnancy 41% vs 30% vs 13%	Anti-TPO titre above a cut-off point affects clinical pregnancy rate	Small and unconvincing study
Poppe, K., Glinoer, D., Van Steirteghem, A., Tournaye, H., Devroey, P.,	CS	case control study. 73 unexplained infertility cases	TSH, FT4, TPO-Ab	TSH and FT4 levels, TPO antibodies	TSh 1.3 mIU/L vs 1.1; Ft4 12 vs11; TPO-Ab 14%vs8% RR 1.68 (0.27-2.73)	No increase in thyroid abnormalities	No evidence of increased thyroid autoimmunity

Schiettecatte, J. and Velkeniers, B. Thyroid dysfunction and autoimmunity in infertile women. Thyroid. 2002; 12 (11): 997-1001.						in unexplained infertility	in unexplained infertility
Other auto-immune tests							
Bellver, J., Soares, S. R., Alvarez, C., Muñoz, E., Ramírez, A., Rubio, C., Serra, V., Remohí, J. and Pellicer, A. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Hum Reprod. 2008; 23 (2): 278-84.	CS/D	prospective cohort study. 31 patients with unexplained infertility	Protein C resistance, IgM, IgG anticardiolipin antibodies, homocysteine, Factor V Leiden, prothrombin, MTHFR, TSH, thyroxine, anti-thyroid peroxidase and anti-thyroglobulin measured	Only positives against controls were ATPO 29% vs 12.5%; ATG 25.8% vs 9.4%; both together 32.3% vs 15.6%; all other non significant			Low numbers but well conducted
Hovav, Y., Almagor, M., Benbenishti, D., Margalioth, E. J., Kafka, I. and Yaffe, H. Immunity to zona pellucida in women with low response to ovarian stimulation, in unexplained infertility and after multiple IVF	CS	15 patients unexplained infertility compared with other infertility and 20 fertile women	Zona pellucida antibodies	Zona pellucida antibodies	Zero positive in case or controls	Not relevant for unexplained infertility	Low numbers and no other papers on this

attempts. Hum Reprod. 1994; 9 (4): 643-5.							
Kovács, M., Hartwig, M., Aleksza, M., Tihanyi, M., Nagy, T., Vajda, G., Daru, J. and Gasztonyi, B. Antiphospholipid antibodies in relation to sterility/infertility. Hum Immunol. 2012; 73 (7): 726-31.	CS	100 patients with unexplained infertility	Antiphospholipids, anticardiolipin, ANA, ENA, anti-TPO, aPS, aPT, ab2glycoprotein, aANX, ASA	Presence of Antiphospholipids, anticardiolipin, ANA, ENA, anti-TPO, aPS, aPT, ab2glycoprotein, aANX, ASA	27% positive aCL, 4 of these has previously diagnosed APS and others no clinical features	Recommend testing	High percentage positive but no controls
Aoki, K., Dudkiewicz, A. B., Matsuura, E., Novotny, M., Kaberlein, G. and Gleicher, N. Clinical significance of beta 2-glycoprotein I-dependent anticardiolipin antibodies in the reproductive autoimmune failure syndrome: correlation with conventional antiphospholipid antibody detection systems. Am J Obstet Gynecol. 1995; 172 (3): 926-31.	Rest	65 unexplained infertility patients	IgG autoantibodies to 6 phospholipid antigens by ELISA. B2 -GPI-dependent and independent antibodies studied.	Presence of phospholipid antigens	Anticardiolipin antibody 12.3% vs 3.1% $p<0.05$; 2 or more aPS, aCL, aPI 6.2% vs 0%; no difference for aPS, aPI, B2-GPI dependent or independent anticoardiolipin antibody	Worth measuring anticardiolipin antibody	Small study from 1995

Luborsky, J., Llanes, B., Davies, S., Binor, Z., Radwanska, E. and Pong, R. Ovarian autoimmunity: greater frequency of autoantibodies in premature menopause and unexplained infertility than in the general population. Clin Immunol. 1999; 90 (3): 368-74.	Rest	53 people with unexplained infertility. 12 normally cycling women as controls and 53 blood bank specimens	Ovarian antibodies by ELISA. Other organ autoantibodies tested.	Ovary and thyroid autoantibodies more common.	Ovarian antibodies 33-61%vs 17%; thyroid antibodies 47-66% vs 34%	Ovarian and thyroid antibodies more common in unexplained infertility	Controls not ideal and blood bank specimens had no history
Luborsky, J., Llanes, B., Roussev, R. and Coulam, C. Ovarian antibodies, FSH and inhibin B: independent markers associated with unexplained infertility. Hum Reprod. 2000; 15 (5): 1046-51.	Rest	52 women with unexplained infertility. Controls 12 cycling women	Ovarian antibodies	Presence of ovarian antibodies	Ovarian antibodies positive while FSH levels normal	In unexplained infertility ovarian antibodies are an independent marker of potential ovarian failure and may precede changes in regulatory hormones	No a prevalence study and controls debateable
Palacio, J. R., Iborra, A., Gris, J. M., Andolz, P. and Martínez, P. Anti-endometrial	Rest	5 unexplained infertility 6 controls	Anti-endometrial antibodies	Presence of anti-endometrial antibodies	40-60% were positive depending on cell line	Anti-endometrial antibody may be common	Numbers too small to be convincing

autoantibodies in women with a diagnosis of infertility. Am J Reprod Immunol. 1997; 38 (2): 100-5.							
Radojcić, L., Ma+A21:H21rjanović, S., Vićovac, L. and Kataranovski, M. Anticardiolipin antibodies in women with unexplained infertility. Physiol Res. 2004; 53 (1): 91-6.	Rest	42 unexplained infertility and 27 fertile women	Anticardiolipin antibodies; antithyroglobulin antibodies	Presence of Anticardiolipin antibodies; antithyroglobulin antibodies	aCL positive in 23.8%; anti-TG antibodies in 21.4%		
Witkin, S. S., Bongiovanni, A. M., Berkeley, A., Ledger, W. J. and Toth, A. Detection and characterization of immune complexes in the circulation of infertile women. Fertil Steril. 1984; 42 (3): 384-8.	Rest	39 unexplained and 38 control women	Circulating immune complexes, immunoglobulins, sperm related antigens, sperm agglutination	Presence of Circulating immune complexes, immunoglobulins, sperm related antigens, sperm agglutination	CICs positive in 38% vs 3% with all containing igG, half activating complement.4/39 had antisperm antibodies, half causing sperm agglutination.	Limitation of assays noted. Some may be antisperm antibodies. May indicate underestimate of undetected antisperm antibodies.	I am not sure of the validity of the assays

THROMBOPHILIA

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Bellver, J., Soares, S. R., Alvarez, C., Muñoz, E., Ramírez, A., Rubio, C., Serra, V., Remohí, J. and Pellicer, A. The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Hum Reprod. 2008; 23 (2): 278-84.	CS	31 patients unexplained infertility 32 controls	Protein C, protein S, antithrombin III, lupus anticoagulant, APCR, IgM, IgG, ACA, homocysteine, Factor V, prothrombin G20210a, MTHFR, TSH, FT4, TPO, ATG	Prevalence of analyte	APCR more common (15.4%), lupus (11.5%) and combined thrombophilia (19.2%) higher but not statistically. Anti=TPO, Anti-TG both statistically increased	Anti-thyroid antibodies more common	Small numbers
Casadei, L., Puca, F., Privitera, L., Zamaro, V. and Emidi, E. Inherited thrombophilia in infertile women: implication in unexplained infertility. Fertil Steril. 2010; 94 (2): 755-7.	CCS	case-control study. 100 unexplained, 200 controls	Factor V, prothrombin, MTHFR mutations	Factor V, prothrombin, MTHFR mutations	No differences between groups. MTHFR OR 1.28 (95% CI 0.68-2.4); Factor V (OR 1 (95% CI 0.36-2.75); prothrombin OR 0.85 (95% CI 0.22-3.37)		Good study

Steinvil, A., Raz, R., Berliner, S., Steinberg, D. M., Zeltser, D., Levran, D., Shimron, O., Sella, T., Chodick, G., Shalev, V. and Salomon, O. Association of common thrombophilias and antiphospholipid antibodies with success rate of in vitro fertilisation. Thromb Haemost. 2012; 108 (6): 1192-7.	CS	retrospective cohort study. 594 women with unexplained infertility undergoing IVF, 637 fertile, 17337 no history of thrombosis.	Factor V Leiden, prothrobin G20210A, APC, Ig-anti-cardiolipin, beta2 glycoprotein antibodies, lupus anticoagulant with Russell viper venom time, APT	Prevalence of analyte	APCR and/orFVL7.9% vs. 3.8%, OR 2.18, 95% CI 1.28-3.72; prothrombin 3.1% vs. 4.2%, OR 0.73, 95% CI 0.39-1.37; lupus/anticardiolipin 3.3% vs. 4.7%, OR 0.70, 95% CI 0.38-1.28	None of the three thrombophilia's significantly associated with number of IVF cycles or lower fertility success rates. Rather women with positive APCR and/or Factor V leiden had higher live birth rates.	Big well conducted study
Behjati, R., Modarressi, M. H., Jeddi-Tehrani, M., Dokoohaki, P., Ghasemi, J., Zarnani, A. H., Aarabi, M., Memariani, T., Ghaffari, M. and Akhondi, M. A. Thrombophilic mutations in Iranian patients with infertility and recurrent spontaneous abortion. Ann Hematol. 2006; 85 (4): 268-71.	CCS	case-control study 36 unexplained infertility, 62 healthy fertile women	Factor V Leiden, MTHFR, prothrombin mutations	Factor V Leiden, MTHFR, prothrombin mutations	Factor V (31%) higher in unexplained and no difference others	Mild difference in factor V, nil in others	Poor study

Coulam, C. B. and Jeyendran, R. S. Thrombophilic gene polymorphisms are risk factors for unexplained infertility. Fertil Steril. 2009; 91 (4 Suppl): 1516-7.	CCS	92 unexplained infertility, 60 fertile controls	MTHFR, Factor V, prothrombin, factor XIIIV34L, b fibrinogen, PAI, HPA, MTHFR C677T and MTHFR A1298C	MTHFR different between groups	MTHFR C677T 22% vs 0%, p=0.01	Difference in C677T but not A1298C - needs testing	Minor difference and does not test hetero-vs homozygosity
Fatini, C., Conti, L., Turillazzi, V., Sticchi, E., Romagnuolo, I., Milanini, M. N., Cozzi, C., Abbate, R. and Noci, I. Unexplained infertility: association with inherited thrombophilia. Thromb Res. 2012; 129 (5): e185-8.	CCS	case control study. 230 unexplained infertility, 240 fertile	Prothrombin, Factor V, protein S and C, antithrombin	General thrombophilia and prothrombin increased, factor V not; no live birth or pregnancy data	General thrombophilia 13% vs 7.1%; FVL 4.8% vs 3.8% ; PT (5.7% vs. 2.1%, OR 2.82, 95% CI 1.02-8.03). ; PC+PS+AT 2.6% vs 1.2%		Age difference significant; like all above studies no evidence of effect on pregnancy chance or outcome; recognise expensive and not common
Kydonopoulou, K., Delkos, D., Rousso, D., Ilonidis, G. and Mandala, E. Association of plasminogen activator inhibitor-type 1 (PAI-1) -675 4G/5G polymorphism with unexplained female infertility. Hippokratia. 2017; 21 (4): 180-185.	CCS	retrospective case control study. 115 Greek women unexplained infertility; 107 fertile	PAI-1 4G -675 allele	Prevalence of gene	5G/5G 22.6% vs 39.3%; 4G/5G 48.7% vs 41.1%; 4G/4G 28.7vs 19.6%	4G/5G associated with female infertility when dominant model followed	Difficult to see their conclusion from the data

Milenkovic, J., Milojkovic, M., Mitic, D., Stoimenov, T. J., Smelcerovic, Z., Stojanovic, D., Vujic, S. and Bojanic, N. Interaction of thrombophilic SNPs in patients with unexplained infertility-multifactor dimensionality reduction (MDR) model analysis. J Assist Reprod Genet. 2020; 37 (6): 1449-1458.	CCS	prospective case control study. 105 unexplained and 120 controls	Factor V Leiden, prothrombin, MTHFR, PAI-1 4G/5G	Prevalence data - no pregnancy outcomes.	MTHFR C677T CC 19.1% vs 40.8%, Ct 60%vs45.8%, 20.9% vs 13.3% p<0.002; others not significant. Interaction of MTHFR plus FVL significant p<0.013.	MTHFR C677T polymorphism plus FVL G1691A associated with unexplained infertility	Association rather than causation

OXIDATIVE STRESS

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Aktan, G., Doğru-Abbasoğlu, S., Küçükgergin, C., Kadıoğlu, A., Ozdemirler-Erata, G. and Koçak-Toker, N. Mystery of idiopathic male infertility: is oxidative stress an actual risk? Fertil Steril. 2013; 99 (5): 1211-5.	CS	prospective cohort study. 28 men in unexplained infertility plus 14 fertile donors	DNA fragmentation by TUNEL assay and the intracellular formation of ROS by oxidation of the cell-permeable dye 20,70-dichlorodihydrofluorescein diacetate (DCFH2-DA) to fluorescent 20,70-	Prevalence data - no pregnancy outcomes.	Tunel 72 vs 4.2%; ROS 56 vs 4.7%; MDA 8.6 vs 5.2%; PC 0.78 vs 0.46% NT 234 vs 148% all significant in UI vs fertile while FRAP not significant	Idiopathic infertility males, while having normal semen parameters, have oxidative stress features	Small numbers and no other clinical information

			dichlorofluorescein (DCF)., MDA, PC and NT levels in semen and seminal plasma				
Desai, N., Sharma, R., Makker, K., Sabanegh, E. and Agarwal, A. Physiologic and pathologic levels of reactive oxygen species in neat semen of infertile men. Fertil Steril. 2009; 92 (5): 1626-31.	CCS	Case-control study. 54 men partners of unexplained infertility couples, 51 healthy fertile male volunteers	WBC, ROS by cheminiluminiscence with luminol	Prevalence	Concentration higher in controls, ROS 0.35 vs 0.01 p<0.001. Using cut-off of 0.0185 PPV 82.4$ vs NPV 77.8%	ROS measured by luminol based chemiluminesence highly specific and sensitive test in males	Convincing study but semen anlyses different
Saleh, R. A., Agarwal, A., Nada, E. A., El-Tonsy, M. H., Sharma, R. K., Meyer, A., Nelson, D. R. and Thomas, A. J. Negative effects of increased sperm DNA damage in relation to seminal oxidative stress in men with idiopathic and male factor infertility. Fertil Steril. 2003; 79 Suppl 3 1597-605.	CS	prospective cohort study. 23 men from unexplained couples, 16 controls	ROS using luminol, TAC, SCSA DNA damage	Prevalence, clinical pregnancy	ROS-TAC score 47 (45,51) UI vs 43 (32,49) p<0.009; DFI 23 (15,32) vs 15 (11,21) p=0.02; ROS negatively correlated with fertilisation (r=-0.59) and embryo quality (r=-0.89); DFI negatively correlated with fertilisation (r=-0.70) and embryo quality (r=-0.70)	Males have higher DNA damage than controls as well as oxidative stress. Although not separated in unexplained couples, relate to lower pregnancy outcomes	Good techniques but clinical comparisons less well done
Venkatesh, S., Shamsi, M. B., Dudeja, S., Kumar, R. and Dada, R. Reactive oxygen species measurement in neat and washed semen: comparative analysis and its significance in male infertility assessment. Arch	CCS	Case-control study. 17 men with normal sperm in unexplained and 43 fertile controls	SA, ROS by luminol	Prevalence data - no pregnancy outcomes.	NROS unexplained vs controls (0.79 (IQR 0.41-2.01) vs. 0.03 (IQR 0.014-0.11) 104 RLU/min/20 million sperms; WROS 2.35 (IQR 0.91-23.1) vs. 0.24 (IQR 0.12-0.38) 104 RLU/min/20 million sperms)	ROS measurement useful in unexplained	No pregnancy data, small numbers

Gynecol Obstet. 2011; 283 (1): 121-6.							
Faure, C., Leveille, P., Dupont, C., Julia, C., Chavatte-Palmer, P., Sutton, A. and Levy, R. Are superoxide dismutase 2 and nitric oxide synthase polymorphisms associated with idiopathic infertility? Antioxid Redox Signal. 2014; 21 (4): 565-9.	CCS	case-control study. 35 women and 34 men from unexplained infertility couples and compared to 34 men and 35 women fertile controls	DNA studies MnSOD, MPO, Gpx1, catalase, eNOS	Prevalence data - no pregnancy outcomes.	MnSOS men 2.94 (1.14-7.60) higher; women eNOS 1.91 (1.03-3.54)	Genetic susceptibility to oxidative stress is a risk factor for male infertility	Multiple comparisons - hard to justify data
Mayorga-Torres, B. J. M., Camargo, M., Cadavid Á, P., du Plessis, S. S. and Cardona Maya, W. D. Are oxidative stress markers associated with unexplained male infertility? Andrologia. 2017; 49 (5):	CCS	case-control study. 23 men unexplained infertility, 54 donors, 34 fertile controls	SA, ROS (flow using dichlorofluorescein diacetate), lipid peroxidation, mitochondrial membrane potential, DNA fragmentation	Comparison of prevalence	SA similar, ROS unexplained vs fertile (121.2±29.9 vs. 71.7±8.7) ; all other not significant. DFI only different against general population not fertile men	Oxidative stress important	Good data but unclear interpretation
Oborna, I., Wojewodka, G., De Sanctis, J. B., Fingerova, H., Svobodova, M., Brezinova, J., Hajduch, M., Novotny, J., Radova, L. and Radzioch, D. Increased lipid peroxidation and abnormal fatty acid profiles in seminal and blood plasma of normozoospermic males from infertile couples. Hum	CCS	case-control study. 12 normospermic males with idiopathic infertility compared with 17 fertile controls	Lipid peroxidation (TBARS assay), fatty acid analysis	Comparison of prevalence	TBARS and AA higher. DHA not different	Systemic oxidative stress may result in lipid peroxidation and altered fatty acid profile leading to infertility	Unexplained part of larger group. Results not shown but differences stated

Reprod. 2010; 25 (2): 308-16.							
Pekel, A., Gönenç, A., Turhan, NÖ and Kafalı, H. Changes of sFas and sFasL, oxidative stress markers in serum and follicular fluid of patients undergoing IVF. J Assist Reprod Genet. 2015; 32 (2): 233-41.	Rest	31 unexplained infertility in women with 40 male infertility as control group undergoing IVF.	sFas, sFasL, MDA, SOD, TAC in serum and follicular fluid	Comparison of prevalence	Serum Fas 2.85 lower in unexplained than control 2.90; serum sFasL lower (3.24) but FF higher (3.87) in unexplained compared with endometriosis. MDA FF lower, SOD higher. FF TAC lower than controls but higher in blood.	Serum and FF sFas lower in unexplained infertility implying increased apoptosis. Antioxidant levels lower	Hard to find the data - merely stated rather than present in tables. No fertile control - reject paper
Taken, K., Alp, H. H., Eryilmaz, R., Donmez, M. I., Demir, M., Gunes, M., Aslan, R. and Sekeroglu, M. R. Oxidative DNA Damage to Sperm Cells and Peripheral Blood Leukocytes in Infertile Men. Med Sci Monit. 2016; 22 4289-4296.	CCS	prospective case-control study. 30 unexplained infertility men and 22 healthy volunteers fertile	MDA, NO, DNA isolation and hydrolyzation	Comparison of prevalence	Sperm parameters different but in normal range; seminal MDA higher 9.68 vs 6.63; serum MDA higher 12.55 vs 7.7; seminal NO not different; serum NO higher 19.3 vs 11,2; serum 8-OHdG/106dG higher 1.55 vs 1.03, leukocyte 8-OHdG/106dG higher 1.25 vs 0.77	Oxidative condition have potential pathogenetic role in reduction of sperm motility and count	Include
Veena, B. S., Upadhya, S., Adiga, S. K. and Pratap, K. N. Evaluation of oxidative stress, antioxidants and prolactin in infertile women. Indian J Clin Biochem. 2008; 23 (2): 186-90.	CCS	case-control study. 13 unexplained infertility compared with controls	Serum MDA by thiobarbituric acid reaction, LDH, FRAP by colorimetric method as measures of antioxidant status.	Comparison of prevalence	Serum nitrite lower unexplained vs controls 3.0 vs 5.0; LDH higher 83vs 68; MDA higher 3.92 vs 2.82	Oxidative damage increased in unexplained	Small numbers and no pregnancy information

Verit, F. F., Verit, A., Kocyigit, A., Ciftci, H., Celik, H. and Koksal, M. No increase in sperm DNA damage and seminal oxidative stress in patients with idiopathic infertility. Arch Gynecol Obstet. 2006; 274 (6): 339-44.	CCS	case-control study. 30 men from unexplained partnership and 20 fertile donors	Sperm DNA damage using comet; TAS in semen; TOS semen; oxidative stress index	Comparison of prevalence	TAO, TOS, OSI, sperm DNA damage no different	No differences	reasonable paper
Zhang, J., Mu, X., Xia, Y., Martin, F. L., Hang, W., Liu, L., Tian, M., Huang, Q. and Shen, H. Metabolomic analysis reveals a unique urinary pattern in normozoospermic infertile men. J Proteome Res. 2014; 13 (6): 3088-99.	Rest	71 men from unexplained partnership and 47 fertile controls	Urinary metabolome performed looking at 37 biomarkers re energy production, antioxidation and hormone regulation.		Able to distinguish between groups using multiple analytes	Should use this to distinguish	Complicated paper with many different pathways
Lazzarino, G., Pallisco, R., Bilotta, G., Listorti, I., Mangione, R., Saab, M. W., Caruso, G., Amorini, A. M., Brundo, M. V., Lazzarino, G., Tavazzi, B. and Bilotta, P. Altered Follicular Fluid Metabolic Pattern Correlates with Female Infertility and Outcome Measures of In Vitro Fertilization. Int J Mol Sci. 2021; 22 (16):		135 women with different infertility diagnosis, 35 controls		follicular fluid metabolites	27/55 metabolites were different between infertile women and controls		

Şentürk, R., Tola, E. N., Bozkurt, M. and Doğuç, D. K. The role of oxidant status on the etiopathogenesis of unexplained infertility and intracytoplasmic sperm injection - embryo transfer success: a case-control study. J Obstet Gynaecol. 2021; 1-7.		case-control study. Exclusion criteria were endocrinopathy, chronic disease or medication use, ovarian pathology, hypogonadotropic hypogonadism, and having a history of pelvic surgery on the ovary/uterus. Couples who had received any form of vitamin supplementation within 3 months before the commencement of treatment were also excluded.	study group: 20 primary UI patients control group: 20 women having ICSI for male factor infertility	primary outcome: follicular fluid and serum TAS, TOS levels and OSI. secondary outcome: embryo quality, implantation, clinical pregnancy and living birth rate.	FF-TOS and FF-OSI of the UI patients were statistically higher than the control group (p=0.04, p=0.02, respectively). The systemic TOS and OSI were also significantly increased in the UI group compared to the control group (p=0.019, p=0.01, respectively). No significant difference in implantation, clinical PR or LBR		

GENETIC/GENOMIC TESTS

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Rull, K., Grigorova, M., Ehrenberg, A., Vaas, P., Sekavin, A., Nõmmemees, D., Adler, M., Hanson, E.,	Rest	36 idiopathic infertility couples, 169 controls	FSHB -211, FSHRc2039, FSHR-29 variants and	Hormone levels	Unexplained infertility exhibited double T allele frequency (23.6% vs 12.4%) and greater than 3X excess of TT homozygotes (5.6%	This allele is more common in unexplained infertility	Little relevance to clinical outcome

Juhanson, P. and Laan, M. FSHB -211 G>T is a major genetic modulator of reproductive physiology and health in childbearing age women. Hum Reprod. 2018; 33 (5): 954-966.			association with FSH, LH, AMH		vs 1.8%) for FSHB-211 G>t on increased LH/FSH ratio.		
Sahmani, M., Sakhinia, E., Farzadi, L., Najafipour, R., Darabi, M., Mehdizadeh, A., Shahnazi, V., Shaaker, M. and Noori, M. Two common polymorphisms in the peroxisome proliferator-activated receptor γ gene may improve fertilization in IVF. Reprod Biomed Online. 2011; 23 (3): 355-60.	CS	prospective cohort study. 98 patients with unexplained infertility undergoing IVF. Unable to ascertain controls ? Population based data?	Genotype His447His and Pro12Ala polymorphisms of PPAR gamma gene	Frequency of polymorphisms Fertilization rate	No relationship pregnancy rate and SNPs. T allele of His447His associated with higher fertilisation. Also Pro12 Ala had higher fertilisation		No real clinical outcome
Salas-Huetos, A., Blanco, J., Vidal, F., Grossmann, M., Pons, M. C., Garrido, N. and Anton, E. Spermatozoa from normozoospermic fertile and infertile individuals convey a distinct miRNA cargo. Andrology. 2016; 4 (6): 1028-1036.	CCS	8 males from unexplained couples and 10 fertile men	736 human miRNAs measured using Nano-RNA chip from sperm RNA	Frequency of miRNAs	115 miRNAs ubiquitous in all normospermic infertile individuals while 59 miRNAs were not detected. 57 miRNAs differentially expressed; 20 regulated by host promoter that in 3 cases comprised genes involved in fertility.	Specific sperm miRNA expression in normospermic fertile individuals	Evolving area but may have diagnostic relevance. Small sample.
Suganya, J., Kujur, S. B., Selvaraj, K., Suruli, M. S., Haripriya, G. and Samuel, C. R. Chromosomal Abnormalities in Infertile Men from Southern India. J	CCS	180 men with all wives described as normal; 28 normal sperm count	Karyotype	Karyotype performed	All normal karyotype	No value if sperm count normal but numbers of men low	Small sample

Clin Diagn Res. 2015; 9 (7): Gc05-10.							
Vani, G. T., Mukesh, N., Rama Devi, P., Usha Rani, P. and Reddy, P. P. Methylenetetrahydrofolate reductase C677T polymorphism is not associated with male infertility in a South Indian population. Andrologia. 2012; 44 Suppl 1 252-9.	CCS	case-control study. 206 men with unexplained infertility and 230 healthy individuals	MTHFR polymorphism in blood	C and Y allele frequencies	CT and TT homozygotes against control 1.36 (0.83-2.22). CT genotype 1.19 ().71-1.97)	No value in measuring this	No value in measuring MTHFR in blood of males
Witkin, S. S., Bierhals, K., Linhares, I., Normand, N., Dieterle, S. and Neuer, A. Genetic polymorphism in an inflammasome component, cervical mycoplasma detection and female infertility in women undergoing in vitro fertilization. J Reprod Immunol. 2010; 84 (2): 171-5.	CS	prospective cohort study. 243 females undergoing IVF; 19 unexplained infertility	NALP3 polymorphism in interleukin 1 (CIAS1 7 unit repeat)	Frequency of polymorphisms	Frequency was 18.4% in unexplained vs 28.9% female infertility and 17% male infertility	Absence of CIAS1 12 unit repeat and presence of 7 unit repeat reduces NALP3 gene transcription associated with female infertility and cervical mycoplasma infection.	Not relevant to unexplained with the numbers presented
Papanikolaou, E. G., Vernaeve, V., Kolibianakis, E., Assche, E. V., Bonduelle, M., Liebaers, I., Van Steirteghem, A. and Devroey, P. Is chromosome analysis mandatory in the initial investigation of normovulatory women seeking infertility treatment? Hum Reprod. 2005; 20 (10): 2899-903.		1206 normo-ovulatory subfertile women. Inclusion criteria were: (i) infertility duration of >12 months; (ii) regular menstrual cycles (21–35 days). Besides a full medical history and general clinical examination, the diagnostic work-up of these couples included the following: a complete endocrine investigation of	cytogenetic analysis (FISH)	chromosome abnormalities (CA)	The cause of infertility was not associated with the prevalence of CAs in the patients analysed. However, a significantly higher (P = 0.04) prevalence of CAs was observed in women with secondary infertility (1.25%) compared to those with primary infertility (0.25%)		

		the hypothalamo-hypophyseogonadal axis including ovulation confirmation; thyroid function and prolactin status; evaluation of semen characteristics according to the criteria of Kruger et al. (1986); minor pelvic ultrasound examination; hysterosalpingography; and when indicated, hysteroscopy and/or laparoscopy.					
Trková, M., Kapras, J., Bobková, K., Stanková, J. and Mejsnarová, B. Increased micronuclei frequencies in couples with reproductive failure. Reprod Toxicol. 2000; 14 (4): 331-5.		50 couples with unexplained infertility. Exclusion criteria included work-related exposure to mutagenic agents, anticancer therapy, viral infections, use of a medical treatment for at least 3 months, and previous exposure to diagnostic X ray.	chromosome analysis in 50 couples with UI and 15 fertile couples by karyotyping (G-banding)	chromosome abnormalities (CA)	Micronucleated cells evaluated by couple Parameter / Infertile/abortion / Abortion / Infertile / Controls Number of couples: 50 / 31 / 19 / 10 Micronucleated cells/1000 cells; mean ± SD (range): 29.88 ± 8.35 (18–53) / 30.23 ± 9.34 (18–52) / 29.32 ± 6.63 (23–53) / 21.20 ± 4.26 (12–27) *P* value (compared to controls): <0.0001 / 0.0005 / <0.000		
Ertosun, M. G., Araci, D. G., Peker, A., Uzuner, S. Y., Toylu, A., Ozekinci, M., Usta, M. F., Clark, O. A. Investigation of the relationship between reproductive disorders and chromosomal abnormalities in a large-scale, single-center 10-year retrospective study. J	CS	4345 individuals with reproductive disorders undergoing genetic analysis. Unexplained infertility included but no detail on tests performed to make this diagnosis. UI was 11% of the total patients	Conventional karyotype testing	chromosome abnormalities (CA)	Abnormalities in 3% UI compared with 2.2% ART failure and 1.6% recurrent miscarriage. No statistical analysis. No recommendation re testing in UI specifically.	General recommendation for karyotype testing in infertility but no recommendation for UI specifically	karyotype testing cannot be preferentially recommended other than for general infertility

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VITAMIN D DEFICIENCY

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Butts, S. F., Seifer, D. B., Koelper, N., Senapati, S., Sammel, M. D., Hoofnagle, A. N., Kelly, A., Krawetz, S. A., Santoro, N., Zhang, H., Diamond, M. P. and Legro, R. S. Vitamin D Deficiency Is Associated With Poor Ovarian Stimulation Outcome in PCOS but Not Unexplained Infertility. J Clin Endocrinol Metab. 2019; 104 (2): 369-378.	RCT	900 subjects with unexplained infertility treated with letrozole or clomiphene citrate. 647 had banked serum. 607 patients were PCOS and probably anovular; 647 AMIGOS and unexplained	25 hydroxy vitamin D. 4 cycles of ovarian stimulation	live birth rate, miscarriage rate	34.7% had a pregnancy and rates were comparable with study treatment. (1.07, 0.73-1.58). Vitamin D deficiency had a higher miscarriage rate 1.82, 0.92-3.61 p=0.09. Cumulative live birth same 32% vs 29% (1.1, 0.7-1.7)	Vitamin D deficiency may have a role in PCOS but not shown for unexplained infertility	Good study but no statistical significance
Lopes, V. M., Lopes, J. R., Brasileiro, J. P., Oliveira, I., Lacerda, R. P., Andrade, M. R., Tierno, N. I., Souza, R. C. and Motta, L. A. Highly prevalence of vitamin D deficiency among Brazilian women of reproductive	CCS	retrospective case-control study. 26 women with unexplained infertility, 90 other infertility, reference group	25 hydroxyvitamin D prevalence of deficiency	Unexplained (23.3 ng/ml) identical to other infertility and no difference to reference group (23.8 ng/ml)	women with UI and women with male factor infertility (23.3 ± 8.6 vs. 26.2 ± 9.2 ng/ml)	Vitamin D deficiency high in infertility but same as control	No evidence for deficiency

age. Arch Endocrinol Metab. 2017; 61 (1): 21-27.							
Rudick, B., Ingles, S., Chung, K., Stanczyk, F., Paulson, R. and Bendikson, K. Characterizing the influence of vitamin D levels on IVF outcomes. Hum Reprod. 2012; 27 (11): 3321-7.	CS	retrospective cohort study. 188 infertile women for IVF. 22 had unexplained infertility	Pregnancy rate by vitamin D status	No difference with other infertility classes for vitamin D deficiency or pregnancy outcomes. In all infertility Asian who were depleted had higher pregnancy rates.	No specific effect on unexplained infertility but deficiency associated with lower pregnancy rates in non-Hispanic whites but not in Asians	Contributes little to unexplained infertility data.	
Güngör, K., Güngör, N. D., Başar, M. M., Cengiz, F., Erşahin, S. S. and Çil, K. Relationship between serum vitamin D levels semen parameters and sperm DNA damage in men with unexplained infertility. Eur Rev Med Pharmacol Sci. 2022; 26 (2): 499-505.		58 UI infertile couples. Detection of pathology in any of the semen parameters, presence of known etiological factors such as cryptorchidism or history of reproductive tissue surgery, history of chemotherapy or radiotherapy or severe oligoasthenoteratozoospermia, patients who received hormonal treatment or vitamin D supplementation at last six months were excluded. couples with IVF/ICSI decision were excluded from the study	study group: 58 men with UI control group: 50 age and BMI matched fertile men with at least 2 children	vit D levels sperm DNA damage	Compared with the fertile group, male patients with unexplained infertility had significantly lower vit D levels (27.00 ng/mL (12.63-39.30) vs.23.66 ng/mL (7.50-55.00), p<0.004). sperm DNA damage, it was found in 31.50% (9.0-71.0) of infertile men and 26.00% (11.0-54.0) of fertile men. DNA damage was found to be significantly higher in the unexplained infertile group (p<0.002).		
Ko, J. K. Y., Shi, J., Li, R. H. W., Yeung, W. S. B. and Ng, E. H. Y. 100 YEARS OF VITAMIN D: Effect of serum vitamin D level before	CS	retrospective CS. Women undergoing their 1st IVF cycle. Those undergoing donor oocyte IVF, in vitro maturation, pre-implantation genetic testing and	vitamin D levels between vitamin D deficient,	CLBR/initiated cycle clinical pregnancy rate (per cycle started and per transfer in the fresh	the CLBR in the vitamin D-deficient group was significantly lower compared to the non-deficient group (43.9%, 208/474 vs 50.9%,		

ovarian stimulation on the cumulative live birth rate of women undergoing in vitro fertilization: a retrospective analysis. Endocr Connect. 2022; 11 (2):		women whose archived serum sample could not be retrieved were excluded	insufficient and replete groups	cycle); (v) ongoing pregnancy rate (per transfer in the fresh cycle); (vi) miscarriage rate (in the fresh cycle) and (vii) live birth rate (per transfer in the fresh cycle).	325/639, OR 0.755, 95% CI 0.595–0.959, P = 0.021, unadjusted). The clinical/ongoing pregnancy rate, live birth rate and miscarriage rate in the fresh cycle did not show significant differences between the vitamin D deficient and non-deficient groups		

THYROID HORMONES

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Unuane, D., Velkeniers, B., Anckaert, E., Schiettecatte, J., Tournaye, H., Haentjens, P. and Poppe, K. Thyroglobulin autoantibodies: is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? Thyroid. 2013; 23 (8): 1022-8.	CSS	95 patients unexplained among other cause patients	Thyroid function	TSH, Ft4, TAI	86% TAI negative and 14% positive, same as all cause infertility and slightly higher than fertile controls (87% normal)	Thyroid testing important in infertility but no different in unexplained	No extra benefit of testing in unexplained

Duran, ., Ozlü, T., Koç, O., Eşitken, C. and Topçuoğlu, A. Relationship of thyroid hormone levels and thyroid autoantibodies with early pregnancy loss and infertility. J Obstet Gynaecol. 2013; 33 (8): 862-4.	CCS	25 unexplained, 45 controls	Thyroid function	TSH, fT4, fT3, anti-TPO, anti-TG	UI ft4 1.14 vs 0.88 and fT3 3.48 vs 4.7 ($p<0.001$) but in normal range. No difference in TAI	Changes in thyroid in unexplained but not autoimmunity	Thyroid results were in normal range
Rehman, R., Rajpar, H. I., Ashraf, M., Iqbal, N. T., Lalani, S. and Alam, F. Role of oxidative stress and altered thyroid hormones in unexplained infertility. J Pak Med Assoc. 2020; 70 (8): 1345-1349.	CCS	44 unexplained, 44 controls	Thyroid function	Thyroid tests including T4,T3,TSH,oxidative stress markers	TSH slightly higher than controls (1.49 vs1.12 $p=0.027$) T4 was also higher in unexplained $p<0.001$	Unexplained and thyroid related	While there were statistical difference , well within normal range
Orouji Jokar, T., Fourman, L. T., Lee, H., Mentzinger, K. and Fazeli, P. K. Higher TSH Levels Within the Normal Range Are Associated With Unexplained Infertility. J Clin Endocrinol Metab. 2018; 103 (2): 632-639.	CCS	187 unexplained infertility vs 52 male infertility	TSH and prolactin	Absolute levels and correlations	Unexplained TSH higher 1.95 (1.5-2.6) vs male TSH 1.66 (1.25-2.17) $p=0.003$. More women had level >2.5uU/ml in unexplained 26.9 vs13.5%. TPO higher in male factor and prolactin similar results	TSH higher in unexplained than male infertility couples even after allowing for variables.	Useful but no real controls as partners of male infertility may not be true controls

PROLACTIN

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Subramanian, M. G., Kowalczyk, C. L., Leach, R. E., Lawson, D. M., Blacker, C. M., Ginsburg, K. A., Randolph, J. F., Jr., Diamond, M. P. and Moghissi, K. S. Midcycle increase of prolactin seen in normal women is absent in subjects with unexplained infertility. Fertil Steril. 1997; 67 (4): 644-7.	CS	prospective cohort study. 12 fertile, 12 unexplained women	Prolactin	Midcycle increase in prolactin	Midcycle bioactive prolactin (34.2±8.3 vs. 19.2±3.4 ng/ml) but not immunoactive (26.9±4.3 vs. 22.1±2.6 ng/mL) were reduced in unexplained women compared to controls	May play a subtle role in unexplained	All other times of the cycle were normal so hard to be sure this is important especially since bioactive was normal
Orouji Jokar, T., Fourman, L. T., Lee, H., Mentzinger, K. and Fazeli, P. K. Higher TSH Levels Within the Normal Range Are Associated With Unexplained Infertility. J Clin Endocrinol Metab. 2018; 103 (2): 632-639.	CSS	Cross-sectional study187 unexplained infertility vs 52 male infertility	TSH and prolactin	Absolute levels and correlations	Unexplained TSH higher 1.95 (1.5-2.6) vs male TSH 1.66 (1.25-2.17) p=0.003. More women had level >2.5uU/ml in unexplained 26.9 vs13.5%. TPO higher in male factor and prolactin similar results	TSH higher in unexplained than male infertility couples even after allowing for variables.	Useful but no real controls as partners of male infertility may not be true controls
Qu, T., Yan, M., Shen, W. J., Li, L., Zhu, P., Li, Z., Huang, J., Han, T., Hu, W., Zhou, R., Li, P., Xu, L., Huang, T., Zhong, Y. and Gu, J. Predictive serum markers for unexplained	CS	prospective cohort study. 84 women with unexplained infertility vs44 fertile women	25 hormones and cytokine markers particularly prolactin, MCP-1 and leptin	Absolute levels and predictive model with ROC calculated	Using prolactin, MCP-1 and leptin in a predictive model significant ROC of 0.89. Other contributors included inhibin alpha, G-CSF, IL10, IL4, IL9, follitropin, LIF	Suggest use of predictors may improve detection of unexplained infertility	I was unable to sort out which components were

infertility in child-bearing aged women. Am J Reprod Immunol. 2020; 83 (1): e13194.							increased or decreased
Veena, B. S., Upadhya, S., Adiga, S. K. and Pratap, K. N. Evaluation of oxidative stress, antioxidants and prolactin in infertile women. Indian J Clin Biochem. 2008; 23 (2): 186-90.	CCS	case-control study. 13 unexplained among many other causes of infertility and 25 controls	Prolactin, MDA, LDH, nitrite and FRAP levels as oxidative stress markers and antioxidants	Absolute levels	Prolactin no different but MDA increased (3.92 vs 2.82) while nitrite less (3.0vs 5.0 umol/l). LDH also increased (83.4 vs 67.9 U/L)	Increased ROS elements while antioxidants not increased. Claims hyperprolactinemia can produce this no backed by data)	Prolactin of no value for prediction

BMI

Reference	Study Type	Patients	Diagnostic test evaluated Reference standard test	Outcome measures	Effect size	Authors conclusion	Comments
Noventa, M., Quaranta, M., Vitagliano, A., Cinthya, V., Valentini, R., Campagnaro, T., Marci, R., Paola, R. D., Alviggi, C., Gangemi, M., Saccardi, C., Nardelli, G. B. and Gizzo, S. May Underdiagnosed Nutrition Imbalances	CS	epidemiological survey. 198 unexplained and 59 pregnant controls	Dietary tests including energy intake, exercise	Dietary and exercise measurements	UI 33% daily physical exercise vs 69%. Calories for UI 2688 vs control 2115 significant $p<0.001$. Unexplained had lower intake of carbohydrates, higher lipids. Many vitamins were lower in the intake.	Italian cohort unexplained had inappropriate calorie intake and macronutrient intake. Fatty acid and vitamins also changed.	Useful approach to study

Be Responsible for a Portion of So-Called Unexplained Infertility? From Diagnosis to Potential Treatment Options. Reprod Sci. 2016; 23 (6): 812-22.							
Lintsen, A. M., Pasker-de Jong, P. C., de Boer, E. J., Burger, C. W., Jansen, C. A., Braat, D. D. and van Leeuwen, F. E. Effects of subfertility cause, smoking and body weight on the success rate of IVF. Hum Reprod. 2005; 20 (7): 1867-75.	Rest	1828 first IVF cycles out of 8457 total cycles compared with other causes.	BMI	Live birth rate, miscarriage , implantation rate	There was a significantly higher live birth rate per cycle in women with normal weight (BMI ≥20–25 kg/m2) and slight overweight (BMI 25–27 kg/m2) compared with women with evident overweight with a BMI ≥27 kg/m2. The unfavourable effect of overweight was largest for women with unexplained subfertility. Underweight women had similar LBR compared to women of normal weight.	Smoking and overweight harmful. Patients would benefit from stopping smoking and reducing weight	Observational but difficult to elicit cause
Wang, L. T., Wang, C. X., Sun, H. L., Wang, X., Li, X. F., Wang, Y. L. and Li, Q. C. Effect of BMI on blood value of patients on HCG day with IUI treatment. BMC Womens Health. 2020; 20 (1): 105.	Rest	2319 cycles of IUI in unexplained infertility women.	BMI and hormone levels	Hormone levels	E2 day of hCG lower in overweight/obese on day of HCG (natural and stimulated cycles) where patient <35 years but not in over 35 years. In older women E2, Prog and LH were lower in woman with greater weight.	BMI affects E2, LH, Prog values but not the pregnancy rate.	Observational data

3. Treatment

3.1 Expectant management

PICO Question: What is the value of expectant management compared to active treatment for patients with UI?

Clomiphene citrate with timed intercourse (+/- ovulation trigger)

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Bhattacharya, S., Harrild, K., Mollison, J., Wordsworth, S., Tay, C., Harrold, A., McQueen, D., Lyall, H., Johnston, L., Burrage, J., Grossett, S., Walton, H., Lynch, J., Johnstone, A., Kini, S., Raja, A. and Templeton, A. Clomifene citrate or unstimulated intrauterine insemination compared with expectant	RCT	Inclusion criteria were at least two years of infertility, bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography), ovulation demonstrated by appropriately timed mid-luteal progesterone, and normal semen variables (according to World Health Organization criteria).We also included couples with minimum sperm motility of 20% or minimal endometriosis	Expectant management (n=193): This involved 6 months during which no clinic visits or medical interventions were scheduled. Couples were given general advice regarding the need for regular intercourse, but no specific measures such as basal temperature charts or luteinising	live birth per woman, clinical pregnancy rate per woman, multiple PR, acceptability, adverse events, anxiety, depression	expectant management: LBR: 32/193 (17%) vs. CC: LBR: 26/192 (14%), 3 women conceived spontaneous (2%). Compared with expectant management, the odds ratio of a live birth was 0.79 (95% CI 0.45 to 1.38) with clomiphene citrate. Compared with expectant management, the adjusted HR for the time to a pregnancy leading to a live birth was 0.83 (99% CI 0.42 to 1.63). CPR: expectant management and clomifene citrate (17% v 15%), NS; multiple PR: 1% vs 1%;	CC seems to be no more effective than expectant management in couples with unexplained infertility.	

management for unexplained infertility: pragmatic randomised controlled trial. Bmj. 2008; 337 a716.		(rAFS stage 1). Blinding was not possible because of the nature of the interventions.	hormone kits were recommended. Clomiphene citrate (n=192): oral dose of 50 mg between day 2-6 of each treatment cycle. Couples were advised to have intercourse on days 12-18 of the cycle. If three or more ovarian follicles were detected by scan in the first cycle, the cycle was cancelled and the couple advised to avoid intercourse. Duration of intervention: 6 months		miscarriage rate: 30% vs 26%; ectopic pregnancy: 2% vs 0%. women on active treatments found the process of treatment more acceptable than those randomised to expectant management.		
Fisch, P., Casper, R. F., Brown, S. E., Wrixon, W., Collins, J. A., Reid, R. L. and Simpson, C. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. Fertil	RCT	155 couples with UI in a double-blind, prospective study. Inclusion: primary infertility of 2 or more years' duration; normal history and physical examination; proven ovulation by either regular cycles and biphasic basal body temperature charts,	Group 1: placebo (two tablets) taken by mouth on cycle days 5 to 9 followed by i.m. saline injections on cycle days 19, 22, 25, and 28. Group 2: placebo tablets with i.m. hCG injections	pregnancy rates	Group 1 vs. 2 vs. 3 vs. 4. The pregnancy rates were 0% (0/36), 11% (4/36), 19% (7/37; $p<0.05$ vs. group 1), and 7.6% (3/39), respectively.		

Steril. 1989; 51 (5): 828-33.		serum progesterone (P) > 10 ng/ml in the midluteal phase or an in-phase, secretory endometrial biopsy in the late luteal phase; a normal HSG; a normal laparoscopy done within the last 2 years confirming bilateral tubal patency and no other pelvic pathology; a normal serum prolactin; and at least two normal semen analyses fitting the following criteria: volume > 1 cc, count ~ 20 X 106 sperm/cc, morphology > 60% normal, and motility> 50%.	5,000 IU on cycle days 19, 22, 25, and 28. Group 3: CC tablets 100 mg on cycle days 5 to 9 with saline injections as in group 1. Group 4: CC and hCG injections with dosage and schedule as noted previously. Each patient received the same treatment for all four cycles. Patients were followed for 6 months after the end of the trial.				
Wordsworth, S., Buchanan, J., Mollison, J., Harrild, K., Robertson, L., Tay, C., Harrold, A., McQueen, D., Lyall, H., Johnston, L., Burrage, J., Grossett, S., Walton, H., Lynch, J., Johnstone, A., Kini, S., Raja, A., Templeton, A. and Bhattacharya, S.	RCT	Inclusion criteria were at least two years of infertility, bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography), ovulation demonstrated by appropriately timed mid-luteal progesterone, and normal semen variables (according to World Health	Expectant management (n=): This involved 6 months during which no clinic visits or medical interventions were scheduled. Couples were given general advice regarding the need for regular intercourse,	cost-effectiveness	average cost for CC: £87.65 (mainly ultrasound scans) vs. £0 for expectant; the bootstrapped 95% CI for the cost difference between EM and CC (IUI) is £303–£370 (£286–£353). EM has the lowest cost per live birth at £72 (£0–£206), whereas CC has the highest at £2611 (£1870–£4166).	CC has a very small chance of being cost-effective, regardless of the value of the ceiling ratio.	

Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective? Hum Reprod. 2011; 26 (2): 369-75.		Organization criteria).We also included couples with minimum sperm motility of 20% or minimal endometriosis (rAFS stage 1). Blinding was not possible because of the nature of the interventions.	but no specific measures such as basal temperature charts or luteinising hormone kits were recommended. Clomiphene citrate (n=): oral dose of 50 mg between day 2-6 of each treatment cycle. Couples were advised to have intercourse on days 12-18 of the cycle. If three or more ovarian follicles were detected by scan in the first cycle, the cycle was cancelled and the couple advised to avoid intercourse. Duration of intervention: 6 months				

INTRA-UTERINE INSEMINATION (IUI) IN A NATURAL CYCLE VS EXPECTANT MANAGEMENT

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments

Bhattacharya, S., Harrild, K., Mollison, J., Wordsworth, S., Tay, C., Harrold, A., McQueen, D., Lyall, H., Johnston, L., Burrage, J., Grossett, S., Walton, H., Lynch, J., Johnstone, A., Kini, S., Raja, A. and Templeton, A. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. Bmj. 2008; 337 a716.	RCT	Inclusion criteria were at least two years of infertility, bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography), ovulation demonstrated by appropriately timed mid-luteal progesterone, and normal semen variables (according to World Health Organization criteria).We also included couples with minimum sperm motility of 20% or minimal endometriosis (rAFS stage 1). Blinding was not possible because of the nature of the interventions.	Expectant management (n=193): This involved 6 months during which no clinic visits or medical interventions were scheduled. Couples were given general advice regarding the need for regular intercourse, but no specific measures such as basal temperature charts or luteinising hormone kits were recommended. IUI: A single insemination was performed 20-30 hours after an endogenous surge was detected.	live birth per woman, clinical pregnancy rate per woman, multiple PR, acceptability, adverse events, anxiety, depression	Treatment vs expectant: LBR: 38/165 vs. 26/167;	No indication that treatment with IUI was effective over no treatment after two failed IUI cycles, in couples with unexplained subfertility and a poor prognosis on natural conception. Only when in vitro fertilization (IVF) cycles were performed, treatment	

OVARIAN STIMULATION WITH IUI VS EXPECTANT MANAGEMENT

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments

Ayeleke, R. O., Asseler, J. D., Cohlen, B. J. and Veltman-Verhulst, S. M. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2020; 3 (3): Cd001838.	SR	2 RCTs	OS+IUI vs expectant management in a natural cycle	LBR, multiple pregnancy rate, cumulative pregnancy rate, miscarriage rate,	OS+IUI vs expectant management. cLBR in couples with poor prognosis: OR 4.48, 95% CI 2.00 to 10.01, 1 RCT, 334 women; cLBR in couples with moderate prognosis: OR 0.82, 95% CI 0.45 to 1.49; 1 RCT, 334 women. Multiple PR: OR 3.01, 95% CI 0.47 to 19.28; 2 RCTs, 454 women. cPR in couples with poor prognosis: OR 4.68, 95% CI 2.22 to 9.86; 1 RCT, 201 women; cPR in couples with moderate prognosis: OR 0.80, 95% CI 0.45 to 1.42; 1 RCT, 253 women. Miscarriage rate: OR 2.87, 95% CI 1.18 to 7.01; 2 RCTs, 454 women.		

IVF VS EXPECTANT MANAGEMENT

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Carosso, A. R., van Eekelen, R., Revelli, A., Canosa, S., Mercaldo, N., Stura, I., Cosma, S.,		retrospective CS. N=635 couples with UI and female age 39 or more	n=359 immediate treatment 276 expectant for one year	live birth	LBR: 70 (19.5%) in immediate group (11 natural, 59 IVF) and 57 (20.7%) in those who waited.(37 natural, 20 IVF). NS		

Scarafia, C., Benedetto, C. and Gennarelli, G. Expectant Management Before In vitro Fertilization in Women Aged 39 or Above and Unexplained Infertility Does Not Decrease Live Birth Rates Compared to Immediate Treatment. Reprod Sci. 2022; 29 (4): 1232-1240.					cLBR same for expectant treatment for 1 year and immediate IVF treatment in couples with female age of 39 years and above.		

3.2 Active treatment

PICO Question: If active treatment is pursued, which type of active treatment for UI?

Timed intercourse

No evidence identified following integrity assessment

Timed intercourse vs. IUI in a natural cycle

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Bhattacharya, S., Harrild, K., Mollison, J., Wordsworth, S., Tay, C., Harrold, A., McQueen, D., Lyall, H., Johnston, L., Burrage, J., Grossett, S., Walton, H., Lynch, J., Johnstone, A., Kini, S., Raja, A. and Templeton, A. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised	RCT	Inclusion criteria were at least two years of infertility, bilateral tubal patency (demonstrated by laparoscopy or hysterosalpingography), ovulation demonstrated by appropriately timed mid-luteal progesterone, and normal semen variables (according to World Health Organization criteria).We also included couples with minimum sperm motility of 20% or minimal endometriosis (rAFS stage 1). Blinding was not possible	Clomiphene citrate (n=192): oral dose of 50 mg between day 2-6 of each treatment cycle. Couples were advised to have intercourse on days 12-18 of the cycle. If three or more ovarian follicles were detected by scan in the first cycle, the cycle was cancelled and the couple advised to avoid intercourse. Duration of intervention: 6 months IUI: A single insemination was performed 20-30 hours after an endogenous surge was detected.	live birth per woman, clinical pregnancy rate per woman, multiple PR, acceptability, adverse events, anxiety, depression	Treatment vs expectant: LBR 23/173 (13%) vs. 38/165 (23%)		

controlled trial. Bmj. 2008; 337 a716.		because of the nature of the interventions.					

TIMED INTERCOURSE VS. OVARIAN STIMULATION AND IUI

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Ayeleke, R. O., Asseler, J. D., Cohlen, B. J. and Veltman-Verhulst, S. M. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2020; 3 (3): Cd001838.	SR	N=2068; Couples with unexplained subfertility, defined as follows. 1. Normal ovulatory status 2. Tubal patency 3. Normal semen sample according to World Health Organization criteria current at the time of the trial. II. Couples who had tried to conceive for at least one year.	OS+IUI vs OS+TI	Primary outcomes Live birth rate per couple: all cycles. Multiple pregnancy rate per couple. Secondary outcomes Pregnancy rate per couple: all cycles. Pregnancy includes clinical pregnancy, and/or ongoing pregnancy, Other adverse events: Moderate or severe ovarian hyperstimulation syndrome (OHSS), rate per woman; Miscarriage rate per couple	Live birth rate: OR 1.59, 95% CI 0.88-2.88, 2 RCT, 208 women. Multiple PR: OR 1.46, 95% CI 0.55-3.87, 4 RCT, 316 women. Clinical PR: OR 1.69, 95% 1.14-2.53, 6 RCT, 517 women. Miscarriage rate: OR 1.66, 95% CI 0.56-4.88, 2 RCT, 208 women. OHSS: OR 2.75, 95% CI 0.11-69.83, 1RCT, 68 women.		

IUI IN A NATURAL CYCLE VS. OVARIAN STIMULATION AND IUI

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Ayeleke, R. O., Asseler, J. D., Cohlen, B. J. and Veltman-Verhulst, S. M. Intra-uterine	SR	N=2068; Couples with unexplained subfertility, defined as follows. 1. Normal ovulatory status	natural cycle+IUI vs OS+IUI	Primary outcomes Live birth rate per couple: all cycles. Multiple pregnancy rate per	Live birth rate: OR 2.07, 95% CI 1.22-3.50, 4 RCT, 396 women. Multiple PR:		

insemination for unexplained subfertility. Cochrane Database Syst Rev. 2020; 3 (3): Cd001838.		2. Tubal patency 3. Normal semen sample according to World Health Organization criteria current at the time of the trial. II. Couples who had tried to conceive for at least one year.		couple. Secondary outcomes Pregnancy rate per couple: all cycles. Pregnancy includes clinical pregnancy, and/or ongoing pregnancy, Other adverse events: Miscarriage rate per couple;	OR 3.00 95% CI 0.11-78.27, 1 RCT, 39 women. PR: OR 6.43, 95% CI 0.56-73.35, 1 RCT, 26 women. Miscarriage rate: OR 5.21, 95% CI 0.19-141.08, 1 RCT, 26 women.		

IVF

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments

PICO QUESTION: WHAT IS THE VALUE OF IVF VERSUS ICSI?

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Foong, S. C., Fleetham, J. A., O'Keane, J. A., Scott, S. G., Tough, S. C. and Greene, C. A. A prospective randomized trial of conventional in vitro fertilization versus intracytoplasmic sperm injection in unexplained infertility. J Assist Reprod Genet. 2006; 23 (3): 137-40.		60 with unexplained infertility had IVF or ICSI	Study period 1997 - 2001, participants were followed up end of treatment or to live birth	Fertilisation rate, pregnancy rate, live birth rate	No differences in fertilisation rate (72.2% vs 82.4%), implantation rate (38.2% vs 44.4%), clinical pregnancy rate (50% vs 50%), live birth rate (46.7% vs 50%)	There were no differences in clinical outcomes associated with IVF versus ICSI in the treatment of unexplained infertility.	
Dang, V. Q., Vuong, L. N., Luu, T. M., Pham T. D., Ho, T. M., Ha, A. N., Truong, B. T., Phan, A. K., Nguyen, D. P., Pham, T. N., Pham, Q. T., Wang R., Norman, R. J, Mol, B. W. Intracytoplasmic sperm injection versus conventional in-vitro fertilisation in couples with infertility in whom the male partner has normal total sperm count and motility: an open-label, randomised controlled trial. Lancet 2021; 397: 1554–63.	RCT	Eligible couples were aged at least 18 years and the male partner's sperm count and motility (progressive motility) were normal based on WHO 2010 criteria (total sperm count ≥39 × 10^6 sperm, progressive motility ≥32%).12 Couples had to have undergone two or fewer previous conventional IVF or intracytoplasmic sperm injection attempts, have used an antagonist protocol for ovarian stimulation, and agree to have two or fewer	Random assignment to IVF (n=199) and ICSI (n=183) group, blinded except for the embryologist and the couple	The primary outcome was changed from ongoing pregnancy resulting in livebirth obtained from all embryos of the started treatment cycle to ongoing pregnancy resulting in livebirth after the first embryo transfer of the started treatment cycle, and the former was changed to a	IVF vs ICSI: LBR: 65/183 (35.5%) vs. 73/199 (36.7%), RR 1.03 (95% CI 0.79-1.35), NS		

		embryos transferred, and not simultaneously be participating in other IVF trials.		secondary outcome, with a fixed time point at 12 months after randomisation			
Bhattacharya, S., Hamilton, M. P., Shaaban, M., Khalaf, Y., Seddler, M., Ghobara, T., Braude, P., Kennedy, R., Rutherford, A., Hartshorne, G. and Templeton, A. Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial. Lancet. 2001; 357 (9274): 2075-9.	RCT	N = 100 couples in the UI subgroup analysis of the RCT. 48 had IVF, 52 had ICSI. Female partner <37 years	Participants were followed up to end of scheduled treatment cycle, 10 participants were lost to follow up in the entire study involving 435 cycles, loss to follow up not specified for the UI subgroup	Outcomes provided for UI subgroup = pregnancy rate, fertilisation rate/ oocyte retrieved, fertilisation rate/ oocyte inseminated or injected	Pregnancy rate 1VF 32% vs ICSI 38%, RR 0.83, 95% CI 0.48-1.45; Fertilisation rate/ oocyte retrieved 61% vs 50%, 95% CI for difference 5 to 17, Fertilisation rate per oocyte inseminated or injected 61% vs 70%, 95% CI for difference 2 to 14.	No difference in pregnancy rates between IVF vs ICS, fertilisation rate/ oocyte retrieved significantly higher with IVF than ICSI, fertilisation/ per oocyte inseminated or injected significantly lower with IVF than ICSI	

3.3 Mechanical-surgical procedures

PICO Question: What is the value of mechanical-surgical procedures?

Resection of polyps or fibroids

No evidence identified following integrity assessment

Tubal flushing

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Wang, R., Watson, A., Johnson, N., Cheung, K., Fitzgerald, C., Mol, B. W. J. and Mohiyiddeen, L. Tubal flushing for subfertility. Cochrane Database Syst Rev. 2020; 10 Cd003718.	SR	15 Randomised trials involving 3864 women with infertility.	Intervention: Tubal flushing with different contrast media (oil soluble contrast media(OSCM) or water soluble contrast media (WSCM)), alone or in combination, with each other or no treatment, were compared.	Primary outcome was live birth rate, other outcome measures were clinical pregnancy rate, miscarriage rate, complications such as intravasation and infection.	OSCM vs no treatment: OSCM may increase the odds of live birth (OR 3.27, 95% CI 1.57 to 6.85, 3 RCT's, 204 women). OCSM may increase the odds of clinical pregnancy (OR 3.54, 95% CI 2.08 to 6.02, 4 RCT's, 506 women). WSCM vs no treatment: it is uncertain whether flushing with WSCM increases live birth rate (OR 1.13, 95% CI 0.67 to 1.91, 1 RCT, 334 women). It is uncertain increases clinical pregnancy rate (OR 1.14, 95% CI 0.71 to 1.84, 1 RCT, 334 women). OSCM vs WSCM: live birth rate reported in 3 RCT's. In two a higher live birth rate with OSCM (OR 1.64 95% CI 1.27 to	The evidence suggests that compared to no treatment, tubal flushing with oil-soluble contrast media (OSCM) may increase the chance of live birth and clinical pregnancy, while it is uncertain whether tubal flushing with : water soluble contrast media (WSCM) improves those outcomes. Compared to tubal flushing with WBCM, OSCM may	

					2.11, 1119 women; OR 3.45, 95% CI 1.97 to 6.03, 398 women). In one no evidence of a difference between groups (OR 0.92, 95% CI 0.60 to 1.40, 533 women) I= 86%, therefore no meta-analysis. Tubal flushing with OSCM vs WSCM probably increases the odds of clinical pregnancy (OR 1.42, 95% CI 1.10 to 1.85, 6 RCT's, 2598 women). Flushing with OSCM probably increased the odds in intravasation (OR 5.00, 95% CI 2.25 to 11.12, 4 RCT's, 1912 women). No difference in infection or haemorrhage between OSCM and WSCM and no serious adverse events reported.	improve clinical pregnancy while meta-analysis was not performed due to heterogeneity. Evidence also suggests that OSCM is associated with an increased risk of intravasation. Overall adverse events, especially long-term adverse events, are poorly reported across the studies.	
van Welie, N., Pham, C. T., van Rijswijk, J. Dreyer, K., Verhoeve, H. R., Hoek, A., de Bruin, J. P., Nap, A. W., van Hooff, M. H. A., Goddijn, M., Hooker, A. B., Gijsen, A. P., Traas, M. A. F., Smeenk, J. M. J., Sluijmer, A. V., Lambers, M. J., van Unnik, G. A., de Koning, C. H., Mozes, A., Timmerman, C. C. M., Lambalk, C. B., Karnon, J. D., Mijatovic, V., Mol, B. W. J. The long-term costs and effects of tubal flushing with oil-based versus water-based contrast during hysterosalpingography.	RCT	Couples with male infertility (total motile sperm count after sperm washing of less than 3 million spermatozoa per millilitre), endocrine disorders (e.g. polycystic ovary syndrome, diabetes, hyperthyroidism or hyperprolactinaemia), iodine allergy or a high risk of tubal pathology (a history of pelvic inflammatory disease, previous Chlamydia infection or known endometriosis) were excluded.	1119 women were randomly assigned to HSG with oil-based contrast (n = 557) or water-based contrast (n = 562). The baseline characteristics were similar across the two groups	long-term reproductive outcomes	In the OSCM group, 39.8% of the women needed no other treatment, 34.6 % underwent IUI and 25.6% had IVF/ICSI in the 5 years following HSG. In the WSCM group, 35.0% of the women had no other treatment, 34.2% had IUI and 30.8% had IVF/ICSI in the 5 years following HSG (p=0.113)		

Reprod Biomed Online 2021; 42(1): 150-157							

MINIMAL TO MILD ENDOMETRIOSIS

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Bafort, C., Beebeejaun, Y., Tomassetti, C., Bosteels, J., Duffy, J. M. Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev 2020; 10: Cd011031	SR	women with minimal to mild endometriosis	3 RCTs pooled, 528 women.	pregnancy rate	Laparoscopic ablation or excision probably increases pregnancy rate compared to diagnostic laparoscopy only (OR 1.89, 95% CI 1.25 to 2.86, 3 RCTs, 528 participants; moderate quality evidence). Sensitivity analysis excluding poor quality studies (Gad 2012; Moini 2012) did not affect the results of the main analysis for this outcome. No subgroup analysis was possible.		

ENDOMETRIAL INJURY/SCRATCH

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Ghuman, N. K., Raikar, S., Singh, P., Gothwal, M., Yadav, G. Improving reproductive outcomes of intrauterine insemination: Does endometrial scratch injury help? A	RCT	this study included couples in whom the women were diagnosed with unexplained infertility and had an indication for UI. Inclusion criteria BMI < 30 kg/m2, age 18-35 years, normal US findings and patent tubes. The quality of partners' semen of recruited women was normal. Other exclusion criteria were advanced maternal age and a history of	150 women with UI. Scratch group (n=75) , on day 6-7 of their stimulated cycle. All women received up to 3 cycles IUI with ovarian stimulation.	Clinical PR, ongoing PR, Miscarriage Rate, Pain	scratch vs. Control CPR: 8/75 (10.7%) vs. 9/75 (12.0%); RR 0.89, 95% CI 0.36-2.17, p=0.797 ongoing PR: 6/75 (8.0%) vs. 8/75 (10.7%); RR 0.75, 95% CI 0.27-2.06, p=0.575 Multiple PR: 0/75 vs. 1/75		

randomised controlled trial. Eur J Obstet Gynecol Reprod Biol 2020. 253: 225-31.		fertility treatment or previous intrauterine procedures in the preceding 3 months.					
Wong, T. Y., Lensen, S., Wilkinson, J., Glanville, E. J., Acharya, S., Clarke, F., Das, S., Dawson, J., Hammond, B., Jayaprakasan, K., Kearsley, N., Milner, M., Shankaralingaiah, N., Wood, S., Sadler, L. and Farquhar, C. Effect of endometrial scratching on unassisted conception for unexplained infertility: a randomized controlled trial. Fertil Steril. 2022; 117 (3): 612-619.	RCT	women with unexplained infertility. Inclusion criteria: age ≤42 years, BMI ≤35 kg/m², unsuccessfully trying to conceive for at least 12 months; normal ovulation (21–42 day menstrual cycles with variation <8 days); and the male partner had a normal semen analysis according to the WHO criteria	220 women randomized scratch: n=113, scratch between D1-12 of the menstrual cycle; second attempt if the first was unsuccessful control: n=107 Regular unprotected sexual intercourse for 3 cycles	live birth/woman randomized clinical PR ongoing PR multiple PR miscarriage	scratch vs. Controls LBR: 10/113 (9%) vs. 7/107 (7%), OR 1.39, 95% CI 0.50-4.03, p=0.53 CPR: 12/113 (11%) vs. 8/107 (7%), OR 1.43, 95% CI 0.56-3.84, p=0.46 OPR: 10/113 (9%) vs. 7/107 (7%), OR 1.39, 95% CI 0.50-4.03, p=0.53 multiple PR: none in either group miscarriage rate: 2/113 (2%) vs. 1/107 (1%), OR 20.01, 95% CI 0.19-43.82, p=0.57		
Yildiz, G., Kurt, D., Mat, E. and Yildiz, P. The effect of local endometrial injury on the success of intrauterine insemination. Journal of Experimental and Clinical Medicine (Turkey). 2021; 38 (4): 521-524.	RCT	Inclusion criteria: Age between 20-40, BMI <30 kg/m2, Primary infertility and at least one year history of infertility, patent bilateral tuba in HSG, FSH value of <10 mIU/ml and LH, estradiol, TSH and prolactin values within normal range, no history of known systemic disease or of regular use of drugs, no history of surgical intervention that can play part in the aetiology of infertility (endometrial polypectomy, myomectomy, endometriosis surgery, congenital uterine anomaly surgery, ovary cyst surgery, hydrosalpinx surgery etc.), normal pelvic USG, no endometrial biopsy, endometrial curettage and hysterescopic procedure within the last three months, normal spermiogram results according to WHO criteria. There was no statistically significant	96 women randomized scratch: n=54, scratch between D21-26 (luteal phase) of menstrual cycle control: n=42 all women OS with rFSH, 250µg rhCG followed by IUI 32-36h after trigger	biochemical PR clinical PR ongoing PR	scratch vs controls CPR: 4/54 (10%) vs. 2/42 (4.76%), p=0.18 OPR: 4/54 (10%) vs. 2/42 (4.76%) multiple PR and miscarriage: not observed		

		difference between study and control groups in terms of age of female, age of male, duration of infertility, BMI, serum FSH, LH, levels mean dose of gonadotropin, mean duration of ovulation induction					

3.4 Alternative therapeutic approaches

PICO Question: What is the effectiveness of alternative therapeutic approaches?

Antioxidants

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Showell, M. G., Mackenzie-Proctor, R., Jordan, V. and Hart, R. J. Antioxidants for female subfertility. Cochrane Database Syst Rev. 2020; 8 Cd007807.	SR	The SRV Included 63 RCTs involving 7760 women attending a reproductive clinic comparing oral antioxidants (AO) versus placebo, no treatment/standard treatment or another antioxidant. However, this evidence table captures the subgroup analyses performed in women with unexplained infertility comparing oral AO versus placebo or no treatment/standard treatment.	I grp: Oral antioxidant (melatonin) 3g or 6g plus IVF C grp: No melatonin treatment (IVF) + IVF/ICSI or healthy fertile women	Primary: live birth rate per woman randomised (LBR) Secondary: clinical pregnancy rate per woman randomised (CPR)	One pilot RCT by Espino et al. examined whether exogenous melatonin ameliorated oxidative stress and improved in vitro fertilization (IVF) success rates in UI. Slight improvement in LBR and CPR (30% vs 20% for no melatonin versus 3g or 6 melatonin) but not statistically significant.	Not applicable as the RCT evidence in the subgroup of women with unexplained infertility not mentioned in the conclusion.	

ACUPUNCTURE

No evidence identified following integrity assessment

NUTRACEUTICALS (INOSITOL)

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Montanino Oliva, M., Buonomo, G., Carra, M. C., Lippa, A. and Lisi, F. Myo-inositol impact on sperm motility in vagina and evaluation of its effects on foetal development. Eur Rev Med Pharmacol Sci. 2020; 24 (5): 2704-2709.	RCT	Total no. of Ps: 86 women with unexplained infertility undergoing 1-3 consecutive cycles of timed intercourse No. of Ps in I grp: 43 No. of Ps in C grp: 43 Relevant baseline characteristics in I grp: not reported Relevant baseline characteristics in C grp: not reported Baseline characteristics in total patient population: Mean age (34.63 years), mean BMI (22.71 kg/m2), Grps comparable: Not known	I grp: MI (myo-inositol) PV suppositories x 3 every 2nd day peri-ovulatory C grp: Placebo PV suppositories x 3 every 2nd day peri-ovulatory Peri-ovulatory was expected day of ovulation (EDO) – 3, EDO – 1 & EDO + 1 where EDO – 3 = day when lead follicle on U/S > 16mm.	Primary: not stated Secondary: not stated Outcomes were pregnancy rate (not defined)	No effect sizes reported. PR: 18.6% (8/43) V 6.97% (3/43); no test of statistical significance performed MCR: 0% (0/43) V 0% (0/43); no test of statistical significance performed I performed a Chi-Square test on PR data: P = 0.106.	MI improves sperm motility and cervical mucus quality, increasing the probability of conception. The absence of adverse events both for the mother and the foetus confirmed the safety of this molecule in pregnancy, supporting even more its use for couples seeking pregnancy.	

TRADITIONAL CHINESE MEDICINE (TCM)

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Choi, S. J., Kim, D. I., Yoon, S. H., Lim, C. Y., Lee, J. M. and Choe, C. M. Effectiveness and safety of Korean medicine for treating women with unexplained infertility: A multi-center observational study. Integr Med Res. 2021; 10 (4): 100751. BACKGROUND: This study was	Case series (uncontrolled before / after study)	Total no. of Ps: 100 women aged 20-44 years with unexplained infertility undergoing treatment for 4 menstrual cycles followed by 3 menstrual cycles of observation No. of Ps in I grp: 100 (90 women completed the study) No. of Ps in C grp: not applicable Relevant baseline characteristics in I grp: Mean age (35.91 years), mean BMI (21.5 kg/m2), Relevant baseline characteristics in C grp: not applicable Groups comparable: not applicable	I grp: Onkyeong-tang (120cc) twice daily between menstrual cycle day (MCD) 3 and 12, and herbal medicine for ovulation and implantation (120cc) twice daily between MCD 13 and 28 for 4 menstrual cycles (They also received acupuncture and moxibustion treatment during 4 menstrual cycles) followed by 3 menstrual cycles of observation	Primary: Clinical PR (CPR Secondary: Ongoing pregnancy rates (OPR); Live birth rates (LBR); Adverse events	LBR: 7.8% (7/90) OPR per pregnancy: 53.85% (7/13 pregnant women) CPR: 14.4% (13/90) Adverse events: 37% (33/90) but none were serious	The findings of this study may provide the possibility of effectiveness and safety of Korea medicine treatment for unexplained infertile women. Further study is required due to lack of control and small sample size in this study.	

4. Quality of Life

PICO Question: Is there a difference in QoL for patients with unexplained versus explained infertility?

Reference	Study Type	Patients	Interventions + comparisons	Outcome measures	Effect size	Authors conclusion	Comments
Santoro, N., Eisenberg, E., Trussell, J. C., Craig, L. B., Gracia, C., Huang, H., Alvero, R., Casson, P., Christman, G., Coutifaris, C., Diamond, M., Jin, S., Legro, R. S., Robinson, R. D., Schlaff, W. D. and Zhang, H. Fertility-related quality of life from two RCT cohorts with infertility: unexplained infertility and polycystic ovary syndrome. Hum Reprod. 2016; 31 (10): 2268-79.	Combination of data from two RCT cohorts	Women with PCOS and their partners (n = 733 and n = 641, respectively), and couples with UI (n = 865 women and 849 men) completed the questionnaires. QoL was determined before the start of treatment in about 45% of the couples; 55% of couples had received prior therapy (same percentages for both cohorts).	The participants completed a validated fertility-specific QOL survey (FertiQOL) at the time of the study screening visit.	The primary outcome for the PPCOSII trial was live birth. The primary outcome in the AMIGOS study was the rate of multiple pregnancies. The outcome measure of the combined study was FertiQOL (= Fertility related Quality of Life)	Women with PCOS had lower total FertiQOL scores (72.3 ±14.8) than those with UI (77.1 ±12.8; P < 0.001); this was true for each domain (except Relational). These differences were largely explained by variation in BMI, hirsutism, household income and age. Women had lower overall FertiQOL scores than their male partners. Males with PCOS partners had higher scores than males with UI (84.9 ±10.2 versus 83.3 ±10.8; P = 0.003). Scores were not consistently associated with conception or pregnancy outcome.	In summary, we used a new instrument, devised to assess specifically the fertility-related QOL (FertiQOL), to test the largest US-based cohort to date and found that QOL is reduced for women with PCOS compared with those with UI. Men have overall less compromise of QOL in association with an infertility diagnosis, but men with UI had lower QOL than men whose partners had PCOS. Finally, QOL did not overall predict conception or live birth in this study.	
Kowalcek, I., Wihstutz, N., Buhrow, G. and Diedrich, K. Subjective	Cohort	110 infertile couples: 13 with female infertility (group 1), 55 with male	Intervention: von Zerssen symptom checklist (24 items)	Mean ratings on the von Zerssen test manual (=	Table 3 (the 6 'unknown' couples are excluded): EXPLAINED INFERTILITY	With the exception of sterile women of fertile men (group 1),	

well-being in infertile couples. J Psychosom Obstet Gynaecol. 2001; 22 (3): 143-8.		infertility (group 2), 31 with infertility in both partners (group 3), 5 with idiopathic infertility (group 4) and 6 unknown. Acording to table 3 101 women and 98 men were included (exclusion of 6 'unknwon' couples).	to establish the degree of subjective wellbeing once during the intake at the fertility clinic (Lübeck).	subjective well-being). The average values for healthy test persons fall close to 14.3. The mean of somatically ill is 23.7, the mean of psychiatrically ill is 30.	Group 1. Mean women = 17.58 vs. men = 13.17 Group 2. Mean women = 13.07 vs. men = 10.44 Group 3. Mean women = 15.13 vs. men = 11.52 UNEXPLAINED INFERTILITY Group 4. Mean women = 14.8 vs. men = 9.4	women and men in the overall randomized sample and the diagnostic groups 2, 3, and 4 report fewer general symptoms than the overall population of patients with somatic and psychiatric diseases (abstract).	
Warchol-Biedermann, K. The Etiology of Infertility Affects Fertility Quality of Life of Males Undergoing Fertility Workup and Treatment. Am J Mens Health. 2021; 15 (2): 1557988320982167.	Cohort		Respondents completed Emotional, Mind–Body, Relational, and Social subscales of the Polish version of FertiQoL and a baseline demographic survey. The timing of psychological testing was strictly related to andrological visits and to medical procedures, that is, respondents completed the tests (1) before their first fertility testing (T1) at the baseline, before a diagnostic disclosure; (2) before the second andrological visit, 2–	The Core module of FertiQoL consisting of 4 domains (emotional, mind-body, relational, and social).	The Core FertiQoL score The mean score in the UFI subgroup, which amounted to 83.97 ± 4.95, at T1 has not significantly changed after the diagnostic disclosure and in the follow-up (at T3 and T4) (p values = .19, = .11, and = .73, respectively) (see Figure 2a for details). The emotional subscale The average score in the subgroup with the UFI reached 89.88 ± 8.49 at T1. The analysis could not indicate any significant changes in respondents' scores at T2, T3, and T4 (p values = .27, = .33 and = .61, respectively) (see Figure 2b for details). The Mind-body subscale The baseline score in the UFI subgroup, which averaged at 93.65 ± 7.97, remained stable after the diagnostic disclosure (T2) (p value = .27).	The research demonstrated that the FertiQoL scores across the Emotional, Mind–Body, and Relational subscales markedly decreased after the diagnostic disclosure, particularly in the subgroups with male and concurrent male and female factor. Social subscale scores in all subgroups peaked at T1 and remained stable after the diagnostic disclosure (at T2) but significantly decreased in the follow-up (at T3 and T4). The investigation of the results at the baseline and in the	The results of this paper are partially discordant with the results of the study by Santoro et al. (2016). Santoro and co-workers indicated differences in FertiQoL associated with the perceived diagnosis but male UFI participants of Santoro's study were characterized by lower FertiQoL scores compared with FFI respondents whose partners

			3 months after the diagnostic disclosure when their emotional response to the diagnosis stabilized (T2); and (3) before the third and the fourth treatment-related or check-up testing appointments (T3, T4). T2, T3, and T4 were 2–3 months apart.		The score significantly increased at T3 (p value = .03) and then plateaued at T4 (p value = .66) (see Figure 2c for details). The relational subscale The average score in the UFI respondents, which reached 74.80 ± 6.65 at T1, remained stable after the diagnostic disclosure (T2) (p value = .86). Subsequently, no significant changes could be found at T3 and T4 (p values = .62 and = .92, respectively) (see Figure 2d for details). Social subscale The average Social subscale score in the UFI subgroup reached 77.57 ± 5.66 at the baseline (T1). The score remained stable after the diagnostic disclosure (T2) (p value = .63) and in the follow-up (at T3 and T4) (p values = .57 and = .17, respectively) (see Figure 2e for details).	follow-up also demonstrated respondents with UFI were characterized by significantly higher scores in the Emotional, Mind–Body, and Relational domains than those with other diagnoses. Significant differences in FertiQoL scores associated with respondents' infertility factor could be demonstrated at each time point. The study identifies the FertiQoL in unintentionally childless males is significantly affected by their factor of infertility and evolves across the pathway of treatment-related/follow-up appointments.	had polycystic ovary syndrome.

5. SUMMARY OF EVIDENCE

EXPLANATIONS

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; **RR**: Risk ratio; **OR**: Odds ratio

3. Treatment

3.1 Expectant management

PICO Question: What is the value of expectant management compared to active treatment for patients with UI?

Clomiphene citrate with timed intercourse (+/- ovulation trigger)

CC + timed intercourse compared to expectant management for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: CC + timed intercourse
Comparison: Expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with CC + timed intercourse				
Live birth rate (Bhattacharya et al. 2008)	156 per 1,000	0 per 1,000 (0 to 0)	not estimable	340 (1 RCT)	⨁⨁◯◯ Low[a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of inconsistency because only 1 RCT.
b. Small sample size with a low event rate and effect estimate with a wide confidence interval.

Intra-uterine insemination (IUI) in a natural cycle vs. expectant management

IUI in a natural cycle compared to expectant management for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: IUI in a natural cycle
Comparison: Expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with IUI in a natural cycle				
Live birth rate (Bhattacharya et al. 2008)	156 per 1,000	0 per 1,000 (0 to 0)	not estimable	332 (1 RCT)	⨁⨁◯◯ Low[a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of inconsistency because only 1 RCT.
b. Small sample size with a low event rate and effect estimate with a wide confidence interval.

OVARIAN STIMULATION WITH IUI VS. EXPECTANT MANAGEMENT

OS+IUI compared to expectant management for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: OS+IUI
Comparison: Expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with OS+IUI				
Cumulative live birth rate, poor prognosis patients (Ayeleke et al. 2020)	90 per 1,000	307 per 1,000 (165 to 497)	OR 4.48 (2.00 to 10.01)	201 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Cumulative live birth rate, moderate prognosis patients (Ayeleke et al. 2020)	238 per 1,000	204 per 1,000 (123 to 318)	OR 0.82 (0.45 to 1.49)	253 (1 RCT)	⨁⨁◯◯ Low[a,c]	
Multiple pregnancy rate (Ayeleke et al. 2020)	4 per 1,000	13 per 1,000 (2 to 79)	OR 3.01 (0.47 to 19.28)	454 (2 RCTs)	⨁⨁◯◯ Low[c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of inconsistency because only 1 RCT.
b. Small sample size with a low event rate.
c. Small sample size with a low event rate and effect estimate which includes the point of no effect.

IVF VS. EXPECTANT MANAGEMENT

IVF compared to expectant management for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: IVF
Comparison: Expectant management

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with IVF				
Live birth rate (Pandian, Gibreel, and Bhattacharya 2015)	37 per 1,000	458 per 1,000 (90 to 879)	OR 22.00 (2.56 to 189.37)	51 (1 RCT)	⨁◯◯◯ Very low[a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of inconsistency because only 1 RCT.
b. Small sample size with a low event rate and a wide confidence interval.

3.2 Active treatment

PICO Question: If active treatment is pursued, which type of active treatment for UI?

Timed intercourse

No evidence identified following integrity assessment.

Timed intercourse vs. IUI in a natural cycle

Natural cycle + IUI compared to CC + timed intercourse for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: Natural cycle + IUI
Comparison: CC + timed intercourse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with CC + timed intercourse	Risk with natural cycle + IUI				
Live birth rate (Bhattacharya et al. 2008)	133 per 1,000	**0 per 1,000 (0 to 0)**	not estimable	338 (1 RCT)	⨁⨁◯◯ Low[a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of inconsistency because only 1 RCT.
b. Small sample size with a low event rate

Timed intercourse vs. ovarian stimulation and IUI

OS+IUI compared to Gonadotropins + timed intercourse for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: OS+IUI
Comparison: Gonadotropins + timed intercourse

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Gonadotropins + timed intercourse	Risk with OS+IUI				
Live birth rate (Ayeleke et al. 2020)	255 per 1,000	**352 per 1,000 (231 to 496)**	OR 1.59 (0.88 to 2.88)	208 (2 RCTs)	⨁⨁◯◯ Low[a,b]	
Multiple pregnancy rate (Ayeleke et al. 2020)	38 per 1,000	**59 per 1,000 (17 to 188)**	OR 1.61 (0.44 to 5.89)	208 (2 RCTs)	⨁⨁◯◯ Low[b,c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Statistically significant heterogenity between studies (I^2=72%)
b. Large confidence intervals in the individual studies, and the effect estimate includes the point of no effect.
c. Small sample size with a very low event size.

IUI IN A NATURAL CYCLE VS. OVARIAN STIMULATION AND IUI

OS+IUI compared to natural cycle IUI for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: OS+IUI
Comparison: Natural cycle IUI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with natural cycle IUI	Risk with OS+IUI				
Live birth rate (Ayeleke et al. 2020)	139 per 1,000	251 per 1,000 (165 to 361)	OR 2.07 (1.22 to 3.50)	396 (4 RCTs)	⨁⨁◯◯ Low[a,b]	
Multiple pregnancy rate (Ayeleke et al. 2020)	0 per 1,000	0 per 1,000 (0 to 0)	OR 3.00 (0.11 to 78.27)	39 (1 RCT)	⨁◯◯◯ Very low[c,d,e]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of bias due to incomplete reporting of methodology in included studies.
b. Small sample size with a very low event rate.
c. Unknown risk of performance and attrition bias.
d. Serious risk of inconsistency because only 1 RCT.
e. Serious imprecision because only 1 event, very large confidence intervals.

IVF

IVF compared to natural cycle + IUI for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: IVF
Comparison: Natural cycle + IUI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with natural cycle + IUI	Risk with IVF				
Live birth rate (Pandian, Gibreel, and Bhattacharya 2015)	184 per 1,000	358 per 1,000 (211 to 536)	OR 2.47 (1.19 to 5.12)	156 (2 RCTs)	⨁⨁◯◯ Low[a]	
Multiple pregnancy rate (Pandian, Gibreel, and Bhattacharya 2015)	30 per 1,000	31 per 1,000 (1 to 460)	OR 1.03 (0.04 to 27.29)	43 (1 RCT)	⨁◯◯◯ Very low[b,c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. The quality rating was downgraded by 2 levels due to serious imprecision. There were only 44 events and there was substantial statistical heterogeneity (I^2=60%) though the direction of effect was consistent.
b. Serious risk of inconsistency due to only 1 study.
c. There was only 1 event and the pooled estimate includes the line of no effect.

IVF compared to OS+IUI for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: IVF
Comparison: OS+IUI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with OS+IUI	Risk with IVF				
Live birth rate (Nandi et al. 2022)	318 per 1,000	490 per 1,000 (331 to 726)	RR 1.54 (1.04 to 2.28)	1391 (7 RCTs)	⨁⨁◯◯ Low[a,b]	

IVF compared to OS+IUI for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: IVF
Comparison: OS+IUI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with OS+IUI	Risk with IVF				
Multiple pregnancy rate (Nandi et al. 2022)	126 per 1,000	105 per 1,000 (63 to 174)	RR 0.83 (0.50 to 1.38)	507 (6 RCTs)	⨁⨁◯◯ Low[a,c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Risk of bias because blinding of participants and personnel and of outcome assessment was not specified or not blinded in most studies.
b. Significant heterogeneity among included studies (I^2=83%).
c. Wide confidence intervals in the individual studies and the pooled estimate includes the point of no effect.

PICO QUESTION: WHAT IS THE VALUE OF IVF VERSUS ICSI?

IVF compared to ICSI for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: IVF
Comparison: ICSI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ICSI	Risk with IVF				
Live birth rate (Foong et al. 2006)	500 per 1,000	0 per 1,000 (0 to 0)	not estimable	60 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Live birth rate (Dang et al. 2021)	367 per 1,000	378 per 1,000 (290 to 495)	RR 1.03 (0.79 to 1.35)	382 (1 RCT)	⨁⨁◯◯ Low[b,d]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Risk of selection and performance bias due to poor reporting of methodology.
b. Serious risk of inconsistency because only 1 study.
c. Very small sample size, no calculation of optimal information size reported.
d. The CI crosses the clinical decision threshold between recommending and not recommending treatment

3.3 Mechanical-surgical procedures

PICO Question: What is the value of mechanical-surgical procedures?

Resection of polyps or fibroids

No evidence identified following integrity assessment.

Tubal flushing

Tubal flushing with oil-based contrast media compared to expectant management for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: Tubal flushing with oil-soluble contrast media (OSCM)
Comparison: No tubal flushing

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with tubal flushing with OSCM				
Live birth rate (Wang et al. 2020)	111 per 1,000	**290 per 1,000 (164 to 461)**	OR 3.27 (1.57 to 6.85)	204 (3 RCTs)	⨁⨁◯◯ Low[a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Small sample size with a low event rate
b. Optimal information size not met.

Tubal flushing with water-based contrast media compared to expectant management for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: Tubal flushing with water-soluble contrast media (WSCM)
Comparison: No tubal flushing

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with expectant management	Risk with tubal flushing with WSCM				
Live birth rate (Wang et al. 2020)	205 per 1,000	**225 per 1,000 (147 to 330)**	OR 1.13 (0.67 to 1.91)	334 (1 RCT)	⨁⨁◯◯ Low[a,b]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of inconsistency because only 1 RCT.
b. Small sample size with a low event rate

ENDOMETRIAL INJURY/SCRATCH

Endometrial scratching compared to no endometrial scratching for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: Endometrial scratching
Comparison: No endometrial scratching

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no endometrial scratching	Risk with endometrial scratching				
Live birth (Wong et al. 2022)	65 per 1,000	**89 per 1,000 (34 to 220)**	OR 1.39 (0.50 to 4.03)	220 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Ongoing PR (Yildiz et al. 2021)	48 per 1,000	**0 per 1,000 (0 to 0)**	not estimable	96 (1 RCT)	⨁⨁◯◯ Low[c,d]	
Ongoing PR (Ghuman et al. 2020) and (Wong et al. 2022)	82 per 1,000	**85 per 1,000** (31 to 370)	OR 1.04 (0.50 to 2.20)	370 (2 RCTs)	⨁⨁◯◯ Low[e]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Serious risk of inconsistency or imprecision because only 1 RCT or small sample size.
b. Small number of events, and the optimal information size was not met.
c. Serious risk of bias due to incomplete reporting of methodology.
d. Small number of patients with a small event rate, no calculation of optimal information size provided.
e. Serious inconsistency, imprecision and indirectness between the two studies in the meta-analysis

3.4 Alternative therapeutic approaches

PICO Question: What is the effectiveness of alternative therapeutic approaches?

Antioxidants

Antioxidants compared to placebo/no treatment for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: Antioxidants
Comparison: Placebo/no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with Antioxidants				
Live birth rate (Showell et al. 2020)	200 per 1,000	300 per 1,000	OR 1.71 (0.22, 13.41)	30 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Possible risk of bias in the single relevant study which is a small pilot trial (Espino et al. 2019).
b. Very small sample size, and the cumulative effect crosses the line of no effect.
c. Serious inconsistency because only 1 study.

Acupuncture

No evidence identified following integrity assessment.

Nutraceuticals (inositol)

Inositol compared to placebo for unexplained infertility

Patient or population: Couples with unexplained infertility
Intervention: Inositol
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Inositol				
Live birth rate (Montanino Oliva et al. 2020)	70 per 1,000	0 per 1,000 (0 to 0)	not estimable	86 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. Possible risk of selection and performance bias due to incomplete reporting of methodology.
b. Serious inconsistency because only 1 study.
c. Low number of patients and a low number of events.

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6. RESEARCH INTEGRITY PROCESS

Evidence synthesis is underpinned by the assumption that published evidence is derived from sound research practices and trustworthy data. However, the last decade has seen a rise in “problematic studies”, with retracted studies being the most conspicuous [1, 2]. This implies that problematic studies are either increasing in number and/or that there is increased awareness of them among the scientific community. Although there is no universal definition, a “problematic study” generally refers to a study with questionable data or findings, irrespective of its retraction status. This could result from scientific misconduct, poor research practices, or naïve but honest error(s), all of which have significant and far-reaching consequences including jeopardising the validity of systematic reviews and undermining patient and public trust in scientific research.

Tools and policies have been introduced in response to this increasingly recognised issue, including by the Cochrane collaboration [3] and others (e.g. RIA [4] TRACT [5]), aiming to incorporate research integrity assessments as routine steps in systematic reviews and publishing processes. However, no process has yet been established to ensure the authenticity and accuracy of evidence in the context of guideline development. This is a critical gap since guidelines can directly influence patient care, often on a global scale.

To address this gap, we developed the *Research Integrity for Guideline Development (RIGID)* framework - a transparent, unbiased, and rigorous process to identify and manage problematic studies encountered during the guideline development process. The RIGID framework, outlined below, is a complementary but critical process to be integrated alongside risk of bias and GRADE assessments to ensure that recommendations are based on high-quality, authentic and accurate evidence. The framework was successfully piloted in a previous international guideline, endorsed by leading experts from 39 organisations globally [6-9].

Here, we have applied the RIGID framework to all RCTs in this guideline adaptation, as summarised in the six steps below. For other study designs, integrity assessments were not applied; however, studies by authors with a large number of retractions were not included in the guideline or considered in the formulation of recommendations. This methodology was not applied by ESHRE and that used by the Australian ADAPTE group resulted in several studies being excluded. The exclusion of these studies did not change the overall direction of the recommendations.

All moderate and high risk studies excluded from the guideline are tabulated with reasons/ integrity scores and/or contact log in technical documents or supplemental material for transparency (see Tables II-III below).

Table I. Summary of instructions (READER) to implement the six steps of the RIGID framework

Phase	Description of Process
1. Review	Review the literature using standard systematic review processes, in line with approved evidence synthesis methodologies (e.g. Cochrane) and compile a list of eligible studies.
2. Exclude	Exclude any studies that have been retracted or listed on the Retraction Watch Database, and note any studies that have an 'Expression of Concern' or are 'Under Investigation' by journal editors or publishers.
3. Assess	Assess the integrity of the remaining studies using a well-developed tool (e.g. RIA [10] or TRACT [5]) and allocate each study an initial integrity risk rating of low, moderate or high risk for integrity concerns*.
4. Discuss	Discuss results of the integrity assessment with members of the integrity committee and place votes to reach consensus on the integrity risk rating allocation for each study.
5. Establish contact	Establish contact with authors of any studies ranked as moderate or high risk for integrity concerns to source the required information/ clarification. Low risk studies are included in the evidence synthesis informing the guideline.
6. Re-assess	Using the RIGID algorithm, re-assess studies for inclusion following a suitable timeline. Studies are categorised as 'Included' where authors have provided a satisfactory response, 'Awaiting Classification' where authors have responded with an intention to supply the requested information within a specified time; or 'Not Included' where authors have not responded to contact attempt(s).

RIA, Research Integrity Assessment; RIGID, Research Integrity in Guideline Development; TRACT, Trustworthiness of Randomised Clinical Trials. *Classification as moderate or high risk does not imply fraudulent data or research misconduct. These classifications suggest that one or more critical issues were identified that require clarification (and may indeed be adequately justified) before guideline development groups can be confident in using these studies to inform recommendations with direct impact to patient care.

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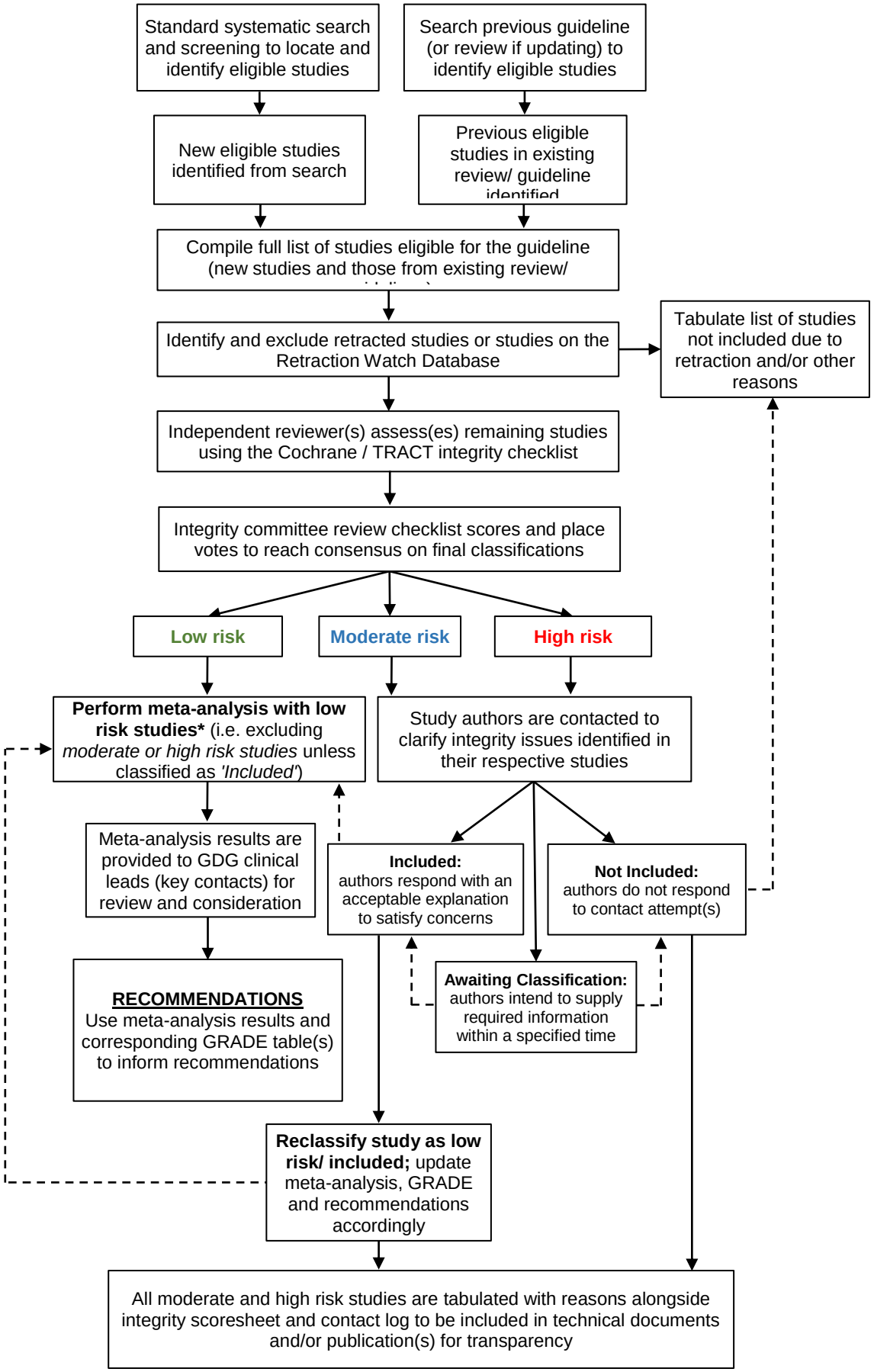

Figure I. Research Integrity in Guideline Development (RIGID) Framework: A process for incorporating research integrity assessments into evidence synthesis for guideline development. GDG, guideline development group; **GRADE,** Grading of Recommendations, Assessment, Development and Evaluations; **TRACT,** Trustworthiness in Randomised Controlled Trials. *meta-analysis should not be performed until all authors have been contacted and, time-permitting, where relevant studies have been re-classified

Table II. Integrity assessment for RCTs in the ESHRE guideline Australian adaptation, conducted following the RIGID framework (Mousa et al. 2023) and using the TRACT checklist (Mol, et al. 2023)

Author, year	Governance			Author group			Plausibility of intervention		Timeframe			Drop outs		Baseline Characteristics		Outcomes		Total Score	Voting Record	Final Consensus Decision
	Absent or retrospective registration	Discrepant registration	Absent or vague ethics	Low # or ratio of authors	Retraction watch base	Large # RCTs	Implausible intervention	Illogical methods	Fast recruitment	Fast follow-up	No LTFU	Ideal numbers	No or few (<5) BL data	Implausible data	Perfectly balanced	Larger effect size than other RCTs	Conflicting outcomes			
Bhattacharya, 2008	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x8	Included
Fisch, 1989	No	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	3	Unanimous x8	Included
Harira, 2018	Yes	No	Yes	Yes	No	No	No	No	Yes	No	Yes	No	No	Yes	No	No	No	6	Unanimous x8	Not Included
Ibrahim, 2012	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No	No	7	Unanimous x8	Not Included
Agarwal & Mittal, 2004	No	No	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	4	x2 low (HT, MC) x6 mod (WL, BM, AM, RW, RN, MF)	Not Included
Foong, 2016	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	1	Unanimous x8	Included
Dang, 2021	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	2	Unanimous x8	Included
Bhattacharya, 2001	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x8	Included
Seyam, 2015	No	No	No	No	Yes	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	4	Unanimous x8	Not Included
Casini, 2006	No	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No	No	No	No	3	Unanimous x8	Not Included
Van Welie, 2021	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x8	Included
Ghuman, 2020	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	1	Unanimous x8	Included
Jafarabadi, 2020	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	6	Unanimous x8	Not Included
Maged, 2016	Yes	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	No	5	Unanimous x8	Not Included

Parsanezhad, 2013	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	3	x5 mod (AM, RW, WL, BM, MF) x2 low (MC, HT)	Not Included
Senocak, 2017	Yes	No	No	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	5	Unanimous x8	Not Included
Wong. 2022	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x8	Included
Yildiz, 2021	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x8	Included
Guven, 2020	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No	6	Unanimous x8	Not Included
Montanino Oliva, 2020	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x8	Included

NB: Categories are not weighted equally; some studies may be ranked as Awaiting Classification or Not Included due to more critical concerns, despite achieving a low score on the checklist. Final decisions are made by the integrity committee on the basis of a majority vote. Studies classified as 'Awaiting Classification' are where author(s) have responded indicating an intention to clarify the concerns raised. Studies classified as 'Not included' are those where the author(s) did not respond to emails requesting clarifications for concerns raised.

Table III. Integrity assessment for studies identified via systematic reviews, conducted using the TRACT checklist (Mol, et al. 2023)

Author, year	Governance			Author group			Plausibility of intervention		Timeframe			Drop outs		Baseline Characteristics		Outcomes		Total Score	Voting Record	Final Consensus Decision
	Absent or retrospective registration	Discrepant registration	Absent or vague ethics	Low # or ratio of authors	Retraction watch base	Large # RCTs	Implausible intervention	Illogical methods	Fast recruitment	Fast follow-up	No LTFU	Ideal numbers	No or few (<5) BL data	Implausible data	Perfectly balanced	Larger effect size than other RCTs	Conflicting outcomes			
Arcaini 1996	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x7	Included
Arici 1994	No	No	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	3	Unanimous x7	Included
Bhattacharya 2008	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x7	Included
Chung 1995	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x7	Included
Crosignani 1991	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x7	Included
Deaton 1990	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x7	Included
Farquhar 2018	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x7	Included
Goverde 2000	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x7	Included
Guzick 1999	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x7	Included
Janko 1998	No	No	Yes	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	3	Unanimous x7	Included
Karlstrom 1993	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x7	Included
Melis 1995	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	1	Unanimous x7	Included
Murdoch 1991	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	2	Unanimous x7	Included
Steures 2006	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	3	Unanimous x7	Included
Cicek 2012	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No	4	x4 mod (AM, HT, RW, MF), x3 high (WL, RN, MF)	Not Included
Espino 2019	Yes	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	4	Unanimous x7	Included

NB: Categories are not weighted equally; some studies may be ranked as Awaiting Classification due to more critical concerns, despite achieving a low score on the checklist. Final decisions are made by the integrity committee on the basis of a majority vote. Studies classified as 'Awaiting Classification' are where author(s) have responded indicating an intention to clarify the concerns raised. Studies classified as 'Not included' are those where the author(s) did not respond to emails requesting clarifications for concerns raised.

7. Australian version UI Guideline

Summary table

No.	Question	ESHRE	Australian
1	Definitions		
Q1.1 NR	Narrative question: after how many months of unprotected intercourse should a couple be defined as infertile?	A comprehensive review of 237 studies on unexplained infertility found that 85 studies used the timing of unprotected intercourse in their UI definitions, with 46.5% specifying 1 year, 39.5% specifying 2 years, and 14% specifying 3 years, aligning to some extent with ICMART's guideline that recommends at least 12 months of unprotected intercourse before initiating fertility interventions.	Changed to a PP to align to NHMRC format. PP It is recommended that at least 12 months of unprotected intercourse is required to define infertility. Added: PP In Australia, it is recognised that clinical investigations may commence earlier in the case of a couple who are older or who may want more than one child.
Q1.2 NR	Narrative question: Should frequency of sexual intercourse affect the definition of UI?	No, the frequency of sexual intercourse should not rigidly affect the definition of infertility, given that the concept of "regular" coital frequency is highly variable and influenced by multiple individual and societal factors. Hence, in couples	Changed to CR format to align to NHMRC format PP Whilst frequency of intercourse should not affect the definition of infertility, in couples seeking to conceive, it could be reasonable to advise to increase sexual intercourse to at least every 2-3 days within the fertility window to the extent that such suits their own preference.

		seeking to conceive, it could be reasonable to advise to increase sexual intercourse to at least every 2-3 days within the fertility window to the extent that such suits their own preference.	
Q1.3 NR	Narrative question: should female or male partner's age affect the definition of UI?	Out of 237 studies on unexplained infertility, only 49 consider the female partner's age, suggesting varying upper age limits, while the ICMART definition omits age; however, data indicates that adding an age limit could refine the diagnosis, as the false positive rate for UI spikes from 10% to 80% in women under 35 and over 40, respectively, and male age is noted as a less significant factor at extreme ages.	Changed to PP format to align to NHMRC format PP Female age is a consideration in UI, with male age a less significant factor at more extreme age.
Q1.4. NR	Narrative question: Should couples with mild infertility factors be included in the definition of UI?	Mild male factor is excluded from the diagnosis of unexplained infertility. The GDG proposed that results from a basic semen examination below the lower 5th percentile reference limit (and its 95% confidence interval) should be considered as clinically	Changed to PP format to align to NHMRC format PP- A semen analysis below the lower 5th percentile should be considered as clinically relevant for further investigation, whilst anything outside this range, should be considered as excluding unexplained infertility.

		relevant for decision making about further clinical investigation. However, anything outside this reference excludes unexplained infertility.	
2	**Diagnosis**		
	In women with regular menstrual cycles, tests for confirmation of ovulation are not routinely recommended.	PP	Unchanged
2.1.1	In women with regular menstrual cycles, if confirmation of ovulation is warranted, tests such as urinary LH measurements, ultrasound monitoring or mid-luteal progesterone measurement can be used.	Conditional ⊕	Unchanged
2.2.1	In women with regular menstrual cycles, it is suggested not to routinely measure midluteal serum progesterone levels.	Conditional ⊕	Unchanged
2.2.2	In women investigated for infertility, endometrial biopsy for histological examination is not recommended in the absence of other indications.	Strong ⊕⊕	Unchanged
2.3.1	In women with regular menstrual cycles, ovarian reserve testing is	Strong ⊕⊕	Unchanged

	not required to identify the aetiology of infertility or to predict the probability of spontaneous conception over 6 to 12 months.		
2.4.1	Hysterosalpingo-contrast-sonography (HyCoSy) and hysterosalpingography (HSG) can be recommended as valid tests for tubal patency compared to laparoscopy and chromopertubation.	Strong ⊕⊕⊕	Unchanged
7	HSG and HyCoSy are comparable in diagnostic capacity, thus selection of the technique depends on the preference of the clinician and the patient.	GPP	
8	Chlamydia antibody testing for tubal patency could be considered a non-invasive test to differentiate between patients at low and at high risk for tubal occlusion.	Conditional ⊕	Unchanged
9	In patients at high-risk for tubal abnormality, visual demonstration of tubal patency is necessary.	GPP	Unchanged?
10	Ultrasound, preferably 3D, is recommended to exclude uterine anomalies in women with unexplained infertility.	Strong ⊕	Conditional Ultrasound, preferably 3D, is probably recommended to exclude uterine anomalies in women with unexplained infertility.
11	MRI is not recommended as a first-line test to confirm a normal uterine structure and anatomy in women with unexplained infertility.	Strong ⊕	Conditional MRI is probably not recommended as a first-line test to confirm a normal

			uterine structure and anatomy in women with unexplained infertility.
12	If ultrasound assessment of the uterine cavity is normal, no further evaluation is needed.	Strong ⊕	Conditional If ultrasound assessment of the uterine cavity is normal, further evaluation is probably not needed.
13	Routine diagnostic laparoscopy is not recommended for the diagnosis of unexplained infertility.	Strong ⊕	Conditional Routine diagnostic laparoscopy is probably not recommended for the diagnosis of unexplained infertility. PP: Consideration should be given to discuss the benefits and harms of laparoscopy for diagnosing minimal to mild endometriosis.
14	The post-coital test is not recommended in couples with unexplained infertility.	Strong ⊕⊕	Conditional The post-coital test is probably not recommended in couples with unexplained infertility.
15	Vaginal microbiota testing could be considered in couples with unexplained infertility only in a research setting.	Research only	
16	Testicular imaging is not recommended when semen analysis according to WHO criteria is normal.	Strong ⊕	Conditional Testicular imaging is probably not recommended when semen analysis according to WHO criteria is normal.
17	Testing for anti-sperm antibodies in the semen is not recommended when semen analysis according to WHO criteria is normal.	Strong ⊕	Conditional Testing for anti-sperm antibodies in the semen is probably not recommended when semen analysis according to WHO criteria is normal.
18	Testing for sperm DNA fragmentation is not recommended when semen analysis according to WHO criteria is normal.	Strong ⊕	Conditional

			Testing for sperm DNA fragmentation is probably not recommended when semen analysis according to WHO criteria is normal.
19	Sperm chromatin condensation test is not recommended when semen analysis according to WHO criteria is normal. Strong ⊕	Strong ⊕	Conditional Sperm chromatin condensation test is probably not recommended when semen analysis according to WHO criteria is normal.
20	Sperm aneuploidy screening is not recommended when semen analysis according to WHO criteria is normal.	Strong ⊕	Conditional Sperm aneuploidy screening is probably not recommended when semen analysis according to WHO criteria is normal.
21	Serum hormonal testing is not recommended when semen analysis according to WHO criteria is normal.	Strong ⊕	Conditional Serum hormonal testing is probably not recommended when semen analysis according to WHO criteria is normal.
22	HPV testing of semen is not recommended when semen analysis according to WHO criteria is normal.	Strong ⊕	Conditional HPV testing of semen is probably not recommended when conventional semen analysis according to WHO criteria is normal.
23	Microbiology testing of semen is not recommended when semen analysis according to WHO criteria is normal.	Strong ⊕	Conditional Microbiology testing of semen is probably not recommended when semen analysis according to WHO criteria is normal.
24	Testing for anti-sperm antibodies in serum of either males or females with unexplained infertility is not recommended.	Strong ⊕	Conditional Testing for anti-sperm antibodies in serum of either males or females with unexplained infertility is probably not recommended.
25	Testing for coeliac disease in women with unexplained infertility can be considered.	Conditional ⊕⊕	Unchanged
26	Testing for thyroid antibody and other autoimmune conditions (apart from coeliac disease) in women with unexplained infertility is not recommended.	Strong ⊕	Conditional Testing for thyroid antibody and other autoimmune conditions (apart from coeliac disease) in women with unexplained infertility is probably not recommended.

27	TSH measurement is considered good practice in pre-conception care.	GPP	Unchanged
28	No additional thyroid evaluation in women is recommended if TSH is within the normal range.	Strong ⊕	Strong retained unchanged
29	Testing for thrombophilia in women with unexplained infertility is not recommended.	Strong ⊕	Conditional: Testing for thrombophilia in women with unexplained infertility is probably not recommended.
30	Measurement of oxidative stress in semen of males with unexplained infertility should only be considered in the context of research.	Research only	
31	Measurement of oxidative stress in women with unexplained infertility is not recommended.	Strong ⊕⊕	Conditional Measurement of oxidative stress in women with unexplained infertility is probably not recommended.
32	Genetic or genomic tests are currently not recommended in couples with unexplained infertility.	Strong ⊕	Conditional Genetic or genomic tests are currently probably not recommended in couples with unexplained infertility.
33	Testing for vitamin D deficiency in women is not recommended for diagnosis of unexplained infertility.	Strong ⊕	Conditional Testing for vitamin D deficiency in women is probably not recommended for diagnosis of unexplained infertility.
34	Prolactin testing in women is not recommended.	Strong ⊕	Conditional Prolactin testing in women is probably not recommended.
35	BMI evaluation in women is considered good practice in preconception care.	GPP	
36	IUI with ovarian stimulation is recommended as a first-line treatment for couples with unexplained infertility.	Strong	Conditional IUI with ovarian stimulation is probably recommended as a first-line treatment for couples with unexplained infertility

			PP: Start active treatment on prognosis including female age, duration infertility, sperm motility and prior pregnancy in couples with unexplained infertility, acknowledging evolving evidence.
37	The GDG advises to base the decision to start active treatment on prognosis in couples with unexplained infertility.	GPP	
38	IUI with ovarian stimulation is recommended as a first-line treatment for couples with unexplained infertility	Strong ⊕	Unchanged.
39	To avoid multiple pregnancies and OHSS, care is needed by using gonadotrophin treatment only in a low-dose regimen with adequate monitoring.	GPP	
40	IVF is probably not recommended over IUI with ovarian stimulation in couples with unexplained infertility.	Conditional ⊕	Taking into consideration a couples aspiration of family size, age of the female partner, duration of infertility and consideration of ability to access IUI centre (remote based coupled may favour IVF for convenience)
41	It is expected that the decision to use IVF is individualized by patient characteristics such as age, duration of infertility, previous treatment and previous pregnancy.	GPP	
42	ICSI is not recommended over conventional IVF in couples with unexplained infertility.	Strong	Unchanged
43	Hysteroscopy for the detection and possible correction of intrauterine abnormalities not seen at routine imaging is not recommended.	Strong ⊕⊕	Research recommendation ⊕ VERY LOW Hysteroscopy for the detection and possible correction of intrauterine abnormalities not seen at routine imaging, requires further research.
44	HSG (i.e., tubal flushing) with an oil-soluble contrast medium is preferable over a water-soluble contrast medium. Risks and benefits of tubal flushing with oil-soluble contrast medium should be discussed with all couples with unexplained infertility.	Conditional ⊕⊕	Strong

	If incidentally minimal to mild endometriosis is found at laparoscopy, this is not further considered unexplained infertility by the GDG.		
45	Endometrial scratching should not be offered for unexplained infertility.	Strong ⊕⊕	Conditional ⊕ Endometrial scratching should probably not be offered for unexplained infertility.
46	Adjunct oral antioxidant therapy to women undergoing fertility treatment is probably not recommended.	Conditional ⊕	Unchanged
47	Adjunct oral antioxidant therapy to males undergoing fertility treatment is probably not recommended.	Conditional ⊕	Unchanged
48	Acupuncture in women is probably not recommended	Conditional ⊕⊕	Research recommendation only
49	Inositol supplementation in women is probably not recommended.	Conditional ⊕	Unchanged
50	Psychological support, including psychotherapy, is recommended for patients when needed.	GPP	
51	A healthy diet and regular exercise, supported by behavioural therapy, when necessary, are recommended.	GPP	
52	Healthcare professionals should be aware that - there is probably no difference in QoL between women with unexplained infertility versus women in couples with known causes of infertility, except when the cause of infertility is PCOS, where the QoL is lower. - QoL is probably higher in men from a couple with unexplained infertility compared to men from a couple with known causes of infertility except when the cause of infertility is men with a partner with PCOS, then the men from a couple with unexplained infertility have a lower QoL.	Conditional ⊕	Unchanged PP: It should be acknowledged that couples with UI may experience considerable impact on their QoL and they can be offered support and therapeutic counselling.

8. GRADE EVIDENCE TO RECOMMENDATIONS TABLES

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 1.1-NR

After how many months of unprotected intercourse should a couple be defined as infertile?

Recommendation	**Narrative question: after how many months of unprotected intercourse should a couple be defined as infertile?** **A comprehensive review of 237 studies on unexplained infertility found that 85 studies used the timing of unprotected intercourse in their UI definitions, with 46.5% specifying 1 year, 39.5% specifying 2 years, and 14% specifying 3 years, aligning to some extent with ICMART's guideline.**	**PP: At least 12 months of unprotected intercourse is recommended before initiating fertility interventions.** **Discussion on context in Australia, it is recognised that clinical investigation may commence earlier in the case of a couple who are older or may want more than one child.**
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	Narrative review	NA
Summary of evidence & justification for the recommendation and for	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable - narrative

differences between strength and GRADE certainty		
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	An economic evaluation was outside the scope of the current review.
Impact on health equity	Would the option reduce or increase health equity in Australia?	Nil
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Nil
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Nil
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation –1.2 – NR

Should frequency of sexual intercourse affect the definition of UI?

Recommendation	**Narrative question: should frequency of sexual intercourse affect the definition of ui?**	**No, the frequency of sexual intercourse should not rigidly affect the definition of infertility, given that the concept of "regular" coital frequency is highly variable and influenced by multiple individual and societal factors.**
GRADE strength of the recommendation	NA	Add PP: In couples seeking to conceive, it could be reasonable to advise to increase sexual intercourse to at least every 2-3 days within the fertility window to the extent that such suits their own preference.
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	NA	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable - narrative
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a	An economic evaluation was outside the scope of the current review.

	recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	The PP may impact those with health issues, age or limit opportunity for frequent sexual activity.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	PP: will be more acceptable in Australia Encouraging sexual intercourse at least every 2-3 days can sometimes be stressful for individuals.
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Area of research need: Investigating fertility and reproductive health in populations not using contraception, including those transitioning off long-term contraceptive methods, within the Australian context.

Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – NR

Should female or male partner's age affect the definition of UI?

Recommendation	**Narrative question: should female or male partner's age affect the definition of UI?**	**Out of 237 studies on unexplained infertility, only 49 consider the female partner's age, suggesting varying upper age limits, while the ICMART definition omits age; however, data indicates that adding an age limit could refine the diagnosis, as the false positive rate for UI spikes from 10% to 80% in women under 35 and over 40, respectively, and male age is noted as a less significant factor at extreme ages.**
GRADE strength of the recommendation	NA	Agreed
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	Narrative review NA	
Summary of evidence & justification for the	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and	Integrity assessment not applicable - narrative

recommendation and for differences between strength and GRADE certainty	justification for the recommendation. Any integrity study issues will also be considered here	
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	An economic evaluation was outside the scope of the current review.
Impact on health equity	Would the option reduce or increase health equity in Australia?	Nil
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Nil
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Nil
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil

Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Further research into age related infertility in females
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – NR

Should couples with mild infertility factors be included in the definition of UI?

Recommendation	**Narrative question: should couples with mild infertility factors be included in the definition of UI?**	**Mild male factor is excluded from the diagnosis of unexplained infertility**
GRADE strength of the recommendation	NA Consider the below criteria to inform strength of recommendation.	Minor change
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	NA narrative review	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- narrative
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	An economic evaluation was outside the scope of the current review.
Impact on health equity	Would the option reduce or increase health equity in Australia?	Nil
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Nil
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Nil

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Further research into age related infertility in females
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.1.1

Which is the reliability and convenience of methods to confirm regular ovulation?

Recommendation	**PICO QUESTION: Which is the reliability and convenience of methods to confirm regular ovulation?**	**PP In women with regular menstrual cycles, tests for confirmation of ovulation are not routinely recommended.**
GRADE strength of the recommendation	NA	Unchanged
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	NA - PP	Reference for 22-35 days Munro reference defining regular cycles
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	See ESHRE guideline and note Munro et al - Reference for 22-35 days Munro reference defining regular cycles "The GDG considers a regular menstrual cycle to be 24 to 38 days, up to 8 days in duration and shortest to longest cycle variation of less than 7 to 9 days (Munro et al., 2018)." Integrity assessment not applicable -PP
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Kits and US have a cost
Impact on health equity	Would the option reduce or increase health equity in Australia?	Regional access issues noted but it is not mandatory, kits are accessible broadly but if requested equity of access for monitoring should be considered for regional Australians. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Nil

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.1.1

Which is the reliability and convenience of methods to confirm regular ovulation?

Recommendation	**PICO QUESTION: Which is the reliability and convenience of methods to confirm regular ovulation?**	**In women with regular menstrual cycles, if confirmation of ovulation is warranted, tests such as urinary LH measurements, ultrasound monitoring or mid-luteal progesterone measurement could be used.**
GRADE strength of the recommendation	STRONG CONDITIONAL WEAK Consider the below criteria to inform strength of recommendation.	Unchanged
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	

Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	See ESHRE guideline and note Munro et al - Reference for 22-35 days Munro reference defining regular cycles "The GDG considers a regular menstrual cycle to be 24 to 38 days, up to 8 days in duration and shortest to longest cycle variation of less than 7 to 9 days (Munro et al., 2018)."- altered in the text Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Kits and US have a cost
Impact on health equity	Would the option reduce or increase health equity in Australia?	Regional access issues noted but it is not mandatory, kits are accessible broadly but if requested equity of access for monitoring should be considered for regional Australians. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian

		Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	May empower couples to manage timing and frequency of intercourse
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Access barriers in regional areas, health literacy for assay kits
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Indigenous
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Nil

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.2.1

What is the reliability of parameters detecting good oocyte/ corpus luteum quality?

Recommendation	**PICO QUESTION: WHAT IS THE RELIABILITY OF PARAMETERS DETECTING GOOD OOCYTE/ CORPUS LUTEUM QUALITY?**	**In women with regular menstrual cycles, it is suggested not to routinely measure midluteal serum progesterone levels.**
GRADE strength of the recommendation	STRONG CONDITIONAL WEAK Consider the below criteria to inform strength of recommendation.	Unchanged
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Given the limited information on an association between luteal progesterone levels and spontaneous pregnancy this is an area that requires further research.

strength and GRADE certainty		Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Nil
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Yes, it is feasible- no issues
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Oocyte quality primarily affected by maternal age which is the primary predictor
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Nil
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil

Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Given the limited information on an association between luteal progesterone levels and spontaneous pregnancy this is an area that requires further research.
Any revision of recommendations, strength or if justified, wording (including consensus vote)		No

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.2

What is the reliability of parameters detecting good oocyte/ corpus luteum quality?

Recommendation	**Pico question: What is the reliability of parameters detecting good oocyte/ corpus luteum quality?**	**In women investigated for infertility, endometrial biopsy for histological examination is not recommended in the absence of other indications.**
GRADE strength of the recommendation	STRONG CONDITIONAL WEAK	No change * This recommendation does not apply to women having an indication for endometrial biopsy, such as endometrial hyperplasia.

	Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕◯◯ LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	This recommendation does not apply to women having an indication for endometrial biopsy, such as endometrial hyperplasia. Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	No.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	N/A
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be	This recommendation does not apply to women having an indication for endometrial biopsy, such as endometrial hyperplasia.

	considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.3

Should one or more tests of ovarian reserve be included in the diagnostic work-up?

Recommendation	**PICO QUESTION: Should one or more tests of ovarian reserve be included in the diagnostic work-up?**	**In women with regular menstrual cycles, ovarian reserve testing is not required to identify the aetiology of infertility or to predict the probability of spontaneous conception over 6 to 12 months.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL	No Change – Justification changed. GDG determined that this PICO question cannot be determined by an RCT and is reliant on observational cohort studies which are automatically rated as lower quality. GDG determined this was a strong recommendation considering the benefits of risks versus harms as uptake would increase if this was conditional.
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕◯◯ LOW Consider the certainty ratings that underpin this recommendation.	See above
Summary of evidence & justification for the recommendation and	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects	Strong recommendation retained on vote – 1 vote for conditional as observational data, all others vote for strong.

for differences between strength and GRADE certainty	and justification for the recommendation. Any integrity study issues will also be considered here	Different justification to ESHRE Evidence was reviewed – cohort studies AMH or other ovarian reserve tests were not appropriate for a diagnosis of UI and did not predict the probability of natural spontaneous conception over 6 to 12 months Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	NIL
Impact on health equity	Would the option reduce or increase health equity in Australia?	
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes. Patient preference should be considered as part of making a reproductive life plan.
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	NIL
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Consideration of shortening of menstrual cycles and family history of EM and ovarian surgery or other risk factors of reduced ovarian reserve
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address	

	concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	As cohort studies exclude women very low AMH – need more research in women with very low AMH.
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.4

What is the accuracy of commonly used tests of tubal patency?

Recommendation 8	**PICO QUESTION: What is the accuracy of commonly used tests of tubal patency?**	**Hysterosalpingo-contrast-sonography (HyCoSy) and hysterosalpingography (HSG) are valid tests for tubal patency compared to laparoscopy and chromopertubation.**

GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Unchanged
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕⊕◯ MODERATE Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	SR observational studies HyCoSy and HSG are highly sensitive and specific and comparable to laparoscopy and dye for tubal pathology patency occlusion Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Tests are available largely limited to metro area – both tests are currently largely unavailable in rural centre.
Impact on health equity	Would the option reduce or increase health equity in Australia?	-Limited access in remote and rural areas -Particularly indigenous populations with a possible higher incidence of tubal disease Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian

		Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes -HyCoSy has the additional benefit of providing information on urterine structure and pelvis anatomy -Oil based HSG offers additional therapeutic value -Less invasive and less costly for the patient compared to laparoscopy
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system?	Less accessible outside major metro areas – radiologists have adequate training – further training in fertility specific radiological investigations for radiologists
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	These tests may not be appropriate in women vaginismus Caution should be exercised in patient's at high risk of STIs.
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	See feasibility above Consideration of cost benefits of oil-based vs water based HSG
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil

Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Urgent national requirement for further research on epidemiology diagnosis and management of infertility in Indigenous Australian populations.
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.4

What is the accuracy of commonly used tests of tubal patency? CAT vs Laparoscopy

Recommendation	**PICO QUESTION: What is the accuracy of commonly used tests of tubal patency? CAT vs Laparoscopy**	**PP HSG and HyCoSy are comparable in diagnostic capacity, thus selection of the technique depends on the preference of the clinician and the patient.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL GPP Consider the below criteria to inform strength of recommendation.	Unchanged
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence		PP
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	SR of observational studies shows CAT to have a lower sensitivity but equal specificity to HyCoSy/HSG compared with laparoscopy dye Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Low
Impact on health equity	Would the option reduce or increase health equity in Australia?	-Increased health equity blood tests more accessible -Consider in indigenous populations with a possible higher incidence of tubal disease
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes Increase health equity blood tests more acceptable
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system?	Nil

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Consider in indigenous populations with a possible higher incidence of tubal disease and less access to other tests of tubal patency More acceptable in women with vaginismus and past history sexual abuse/trauma Consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts. Aboriginal and Torres Strait Islander people face a disproportionate burden of risk factors contributing to infertility, highlighting the urgent requirement for interventions in culturally responsive education, healthcare models, policy revisions, and research. It's worth noting that while a higher proportion of ATSI individuals reside in rural areas, substantial absolute numbers still inhabit urban centres, underscoring the significance of achieving accessible, timely, and equitable care across diverse geographical contexts.
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Clinician preferences may be for formal visual tubal patency testing prior to IUI
Monitoring	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil

Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Urgent national requirement for further research on epidemiology diagnosis and management of infertility in Indigenous Australian populations.
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.4

What is the accuracy of commonly used tests of tubal patency?

Recommendation	**PICO QUESTION: What is the accuracy of commonly used tests of tubal patency?**	**Chlamydia antibody testing for tubal patency could be considered a non-invasive test to differentiate between patients at low and at high risk for tubal occlusion.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Unchanged

CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Consider higher rates of STIs in high risk groups including Aboriginal and Torres Strait Islander people.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system?	
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Urgent national requirement for further research on epidemiology diagnosis and management of infertility in Indigenous Australian populations
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.4

What is the accuracy of commonly used tests of tubal patency?

Recommendation 8	**PICO QUESTION: What is the accuracy of commonly used tests of tubal patency?**	**PP In patients at high-risk for tubal abnormality, visual demonstration of tubal patency is necessary.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL	Unchanged

	GPP Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	NA	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	SR observational studies HyCoSy and HSG are highly sensitive and specific and comparable to laparoscopy and dye for tubal pathology patency occlusion Integrity assessment not applicable - GPP
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Tests are available largely limited to metro area – both tests are currently largely unavailable in rural centres
Impact on health equity	Would the option reduce or increase health equity in Australia?	Limited access in remote and rural areas Particularly indigenous populations with a possible higher incidence of tubal disease. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally

		responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes HyCoSy has the additional benefit of providing information on uterine structure and pelvis anatomy Oil based HSG offers additional therapeutic value Less invasive and less costly for the patient compared to laparoscopy
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system?	Less accessible outside major metro areas – radiologists have adequate training – further training in fertility specific radiological investigations for radiologists
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	These tests may not be appropriate in women vaginismus Caution should be exercised in patient's at high risk of STIs.
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	See feasibility above Consideration of cost benefits of oil-based vs water based HSG
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Urgent national requirement for further research on epidemiology diagnosis and management of infertility in Indigenous Australian populations (refs?)

Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.5

Which diagnostic procedures should be performed to confirm a normal uterine structure/anatomy, uterine wall/myometrium? 3D vs 2D ultrasound

Recommendation	**PICO QUESTION: Which diagnostic procedures should be performed to confirm a normal uterine structure/anatomy, uterine wall/myometrium? 3D vs 2D ultrasound**	**Ultrasound, preferably 3D, could be recommended to exclude uterine anomalies in women with unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE Consider the below criteria to inform strength of recommendation.	Change level of recommendation CONDITIONAL (Australian recommendation) because of the very low certainty of evidence
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	⊕◯◯◯ VERY LOW
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Strength of recommendation changed due to very low-quality evidence 3 prospective cohort observational studies showed 3D to be superior to 2D US in diagnosing uterine anomalities with no extra invasiveness or pain or cost to the patient. But 3D US may not be available in every radiological clinic Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Test available largely limited to metro area – test currently largely unavailable in rural centres 3D equipment more expensive and requires training (high quality and well conducted tests)
Impact on health equity	Would the option reduce or increase health equity in Australia?	Limited access to 3D US equipment and it's high quality performance for indigenous populations and in regional and remote areas Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely,

		preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes 3D US has the additional benefit of providing information on uterine structure
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system?	Less accessible outside major metro areas – radiologists have adequate training – further training in fertility specific radiological investigations for radiologists
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Transvaginal 2D or 3D US may not be appropriate in women vaginismus and women with history of sexual abuse/trauma
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	See feasibility above Consideration of cost
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Urgent national requirement for further research on epidemiology diagnosis and management of infertility in Indigenous Australian populations (refs?) Further studies are needed to compare these two interventions in order to diagnose uterine wall/myometrial abnormalities such as fibroids/adenomyosis as the evidence is predominantly in diagnose congenital abnormalities.

Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation -2.5

Which diagnostic procedures should be performed to confirm a normal uterine structure/anatomy, uterine wall/myometrium? - MRI

Recommendation	**PICO QUESTION: Which diagnostic procedures should be performed to confirm a normal uterine structure/anatomy, uterine wall/myometrium? - MRI**	**MRI is not recommended as a first-line test to confirm a normal uterine structure and anatomy in women with unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL - Consider the below criteria to inform strength of recommendation.	Unchanged as no evidence found
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	Not applicable	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	No evidence MRI is expensive and time consuming Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	MRI is expensive and time consuming compared to US
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low access to MRI in non-
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Low acceptability - 10% have claustrophobbia and less expensive
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system?	High cost compared to the US
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	MRI may be preferable in women vaginismus and women with history of sexual abuse/trauma
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	See feasibility above Consideration of cost

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.5

Which additional diagnostic procedures should be performed to confirm an anatomically normal uterine cavity?

Recommendation	**Pico question: Which additional diagnostic procedures should be performed to confirm an anatomically normal uterine cavity?**	**If ultrasound assessment of the uterine cavity is normal, no further evaluation may be needed.**
GRADE strength of the recommendation	STRONG - ESHRE	Conditional – Strength of recommendation changed due to very low quality evidence

	CONDITIONAL - Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Evidence was reviewed – 1 RCT 4 cohort studies Normal US, hysteroscopy low level of additional findings Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil, cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	If low quality initial US, then pathology may be missed especially regional/ remote/ rural
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Ultrasound might miss pathology of questionable significance in up to 10% of cases
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system?	Nil

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Nil
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Further studies to explore whether treatment of pathologies of questionable significance improves outcomes
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation -2.6

Should women undergo a laparoscopy before being diagnosed with UI?

Recommendation	**PICO QUESTION: Should women undergo a laparoscopy before being diagnosed with UI?**	**Routine diagnostic laparoscopy is probably not recommended for the diagnosis of unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Conditional – (Australian recommendation) due to very low quality evidence. New Practice Point PP: Consideration should be given to discuss the benefits and harms of laparoscopy for diagnosing minimal to mild endometriosis.
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	1 RCT that did not address the PICO question.
Summary of evidence & justification for the recommendation and for	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for	Australia is the first country to have a National Action Plan on Endometriosis and increased

differences between strength and GRADE certainty	the recommendation. Any integrity study issues will also be considered here	awareness and advocacy in one of the main pillars of the plan. Integrity assessment not applicable- observational data / irrelevant RCT
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact Metro-based patients, Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	This weak recommendation may lead to the under-diagnosis of women with minimal or mild endometriosis. There is evidence of benefit of surgically treating minimal or mild endometriosis to improve pregnancy outcomes. Women may prefer to have a laparoscopy in order to exclude minimal to mild endometriosis.

Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Yes
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	The Australian Federal Govt is investing in regional endo specific clinics to improve endo diagnosis and management.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Nil

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.7

What is the need for female lower genital tract investigations?- POST-COITAL TEST (PCT)

Recommendation	**PICO QUESTION: What is the need for female lower genital tract investigations?- POST-COITAL TEST (PCT)**	**The post-coital test is probably not recommended in couples with unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional Australia – very low to low evidence certainty The post-coital test is probably not recommended in couples with unexplained infertility.
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕◯◯ LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or	Nil

	save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.7

What is the need for female lower genital tract investigations?- VAGINAL MICROBIOTA TESTING

Recommendation	**PICO QUESTION: What is the need for female lower genital tract investigations?- VAGINAL MICROBIOTA TESTING**	**Vaginal microbiota testing could be considered in couples with unexplained infertility only in a research setting.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL	No change

	Research only Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence		
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.8

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: Is there added value of additional tests in the male with normal who semen analysis?**	**Testicular imaging is not recommended when semen analysis according to WHO criteria is normal.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Conditional Australia – very low to low evidence certainty
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or	Nil

	save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.9

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: Is there added value of additional tests in the male with normal who semen analysis?**	**Testing for anti-sperm antibodies in the semen is not recommended when semen analysis according to WHO criteria is normal.**

GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional Australia – changed to probable Testing for anti-sperm antibodies in the semen is probably not recommended when semen analysis according to WHO criteria is normal.
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil

Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil

Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.9

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: is there added value of additional tests in the male with normal who semen analysis?**	**Testing for sperm DNA fragmentation is not recommended when semen analysis according to WHO criteria is normal.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional Australia – very low to low evidence certainty Testing for sperm DNA fragmentation is probably not recommended when semen analysis according to WHO criteria is normal.

CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making

Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making. Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	DNA fragmentation research is required (clinical value)
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.9

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: is there added value of additional tests in the male with normal who semen analysis?**	**Sperm chromatin condensation test is probably not recommended when semen analysis according to WHO criteria is normal.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Conditional Australia – very low to low evidence certainty
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data

between strength and GRADE certainty		
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making. Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to

		lack of culturally responsive resources, and barriers such as low health literacy.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.9

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: Is there added value of additional tests in the male with normal who semen analysis?**	**Sperm aneuploidy screening is not recommended when semen analysis according to WHO criteria is normal.**

GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Conditional Australia – very low to low evidence certainty
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	Integrity assessment not applicable- observational data
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.

Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making. Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably Sperm aneuploidy screening is probably not recommended when semen analysis according to WHO criteria is normal.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.9

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: Is there added value of additional tests in the male with normal who semen analysis?**	**Serum hormonal testing is not recommended when semen analysis according to WHO criteria is normal.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Conditional Australia – very low to low evidence certainty
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable- observational data

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably Serum hormonal testing is probably not recommended when semen analysis according to WHO criteria is normal.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.9

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: Is there added value of additional tests in the male with normal who semen analysis?**	**HPV testing of semen is probably not recommended when conventional semen analysis according to WHO criteria is normal.**

GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Excessive numbers of leukocytes in the ejaculate (leukocytospermia, pyospermia) may be associated with infection and poor sperm quality (WHO, 2021). However, in the case of a normal physical examination and in the absence of symptoms associated with genitourinary tract infection, medical and reproductive history do not give indications for signs of infection, further microbiological culture of the semen is not usually warranted. Tests for discriminating specific leukocyte types from round immature germ cells are not part of the routine semen analysis according to the latest, sixth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen. These techniques are included in the 'extended examination' section of the manual. However, the clinical value of these specific tests is not clear and there are currently no evidence-based reference values for these tests in semen of fertile men (WHO, 2021). Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a	

	recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making. Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil

Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably HPV testing of semen is probably not recommended when conventional semen analysis according to WHO criteria is normal.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.9

Is there added value of additional tests in the male with normal who semen analysis?

Recommendation	**Pico question: Is there added value of additional tests in the male with normal who semen analysis?**	**Microbiology testing of semen is not recommended when semen analysis according to WHO criteria is normal.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Conditional Australia – very low to low evidence certainty
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Nil
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Downgrade strength to conditional and alter with probably Microbiology testing of semen is probably not recommended when semen analysis according to WHO criteria is normal.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**Testing for anti-sperm antibodies in serum of either males or females with unexplained infertility is probably not recommended.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Changed to conditional Strength of recommendation changed due to very low-quality evidence
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data

between strength and GRADE certainty		
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Informed choice a key consideration based on high quality information provision to patients.
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Conditional. Strength of evidence downgraded. Testing for anti-sperm antibodies in serum of either males or females with unexplained infertility is probably not recommended.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**Testing for coeliac disease in women with unexplained infertility could be considered.**
GRADE strength of the recommendation	STRONG	No Change

	CONDITIONAL Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕◯◯ LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and

		equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**Testing for thyroid antibody and other autoimmune conditions (apart from coeliac disease) in women with unexplained infertility is probably not recommended.**
GRADE strength of the recommendation	STRONG CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data

between strength and GRADE certainty		
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	

Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Informed choice a key consideration based on high quality information provision to patients.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Testing for thyroid antibody and other autoimmune conditions (apart from coeliac disease) in women with unexplained infertility is probably not recommended.

GRADE: Evidence to recommendation framework for an evidence-based recommendation 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**PP - TSH measurement is considered good practice in preconception care**

GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL GPP Consider the below criteria to inform strength of recommendation.	No change
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	NA	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable -GPP.
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making

Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Nil
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**No additional thyroid evaluation in women is recommended if TSH is within the normal range.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL GPP Consider the below criteria to inform strength of recommendation.	No change
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕⊕⊕ HIGH ⊕⊕⊕◯ MODERATE ⊕⊕◯◯ LOW ⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable -GPP.

between strength and GRADE certainty		
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	No impact as test not recommended
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Yes
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	No
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	No
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	

Any revision of recommendations, strength or if justified, wording (including consensus vote)		No change as strong evidence for this is general population also

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**Testing for thrombophilia in women with unexplained infertility is probably not recommended.**
GRADE strength of the recommendation	STRONG - ESHRE Consider the below criteria to inform strength of recommendation.	Change Conditional
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁⨁⨁⨁ HIGH ⨁⨁⨁◯ MODERATE	

	⊕⊕◯◯ LOW ⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Testing for thrombophilia in women with unexplained infertility is probably not recommended.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**Measurement of oxidative stress in women with unexplained infertility is not recommended.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕◯◯ LOW Consider the certainty ratings that underpin this recommendation.	Integrity assessment not applicable- observational data
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence.

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or	Nil

	an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Measurement of oxidative stress in women with unexplained infertility is probably not recommended.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: should there be additional evaluations of possible systemic cause of UI in the couple?**	**Genetic or genomic tests are currently not recommended in couples with unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional

CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Genetic or genomic tests are currently probably not recommended in couples with unexplained infertility.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**Testing for vitamin D deficiency in women is not recommended for diagnosis of unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data

strength and GRADE certainty		
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making.

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Testing for vitamin D deficiency in women is probably not recommended for diagnosis of unexplained infertility. Downgraded due to low strength of evidence.

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: should there be additional evaluations of possible systemic cause of UI in the couple?**	**Prolactin testing in women is not recommended.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Conditional

CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Downgraded due to low strength of evidence. Integrity assessment not applicable- observational data
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Some clinicians and patients may wish to use these tests and can do so using shared and informed decision making

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patient resources and education for shared decision making.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Consideration to be given to Aboriginal and Torres Strait Islanders may be disadvantaged due to lack of culturally responsive resources, and barriers such as low health literacy.
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		Prolactin testing in women is probably not recommended. Downgraded due to low strength of evidence.

GRADE: Evidence to recommendation framework for an evidence-based recommendation -2.10

Should there be additional evaluations of possible systemic cause of UI in the couple?

Recommendation	**PICO QUESTION: Should there be additional evaluations of possible systemic cause of UI in the couple?**	**BMI evaluation in women is considered good practice in pre-conception care.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	No change PP
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence		
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable - GPP

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Weight stigma should be considered for those living in a bigger body. HP ask permission to discuss weight before proceeding.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations,		

strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 3.1

What is the value of expectant management compared to active treatment for patients with UI?

Recommendation	**What is the value of expectant management compared to active treatment for patients with UI?**	**IUI with ovarian stimulation could be recommended as a first-line treatment for couples with unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Downgraded to conditional or “could”
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and	Downgraded due to low strength of evidence.

recommendation and for differences between strength and GRADE certainty	justification for the recommendation. Any integrity study issues will also be considered here	Four RCTs and three systematic reviews in total: Three RCTs not included due to moderate integrity risk ratings, hence only 1 RCT included. One SR included (Ayeleke et al. 2020) where all studies had low risk of integrity concerns except one. Other SRs for IVF enhanced by IPD evidence - no integrity assessment needed for IPD.
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	NIL
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes. Patient preference should be considered as part of making a reproductive life plan.
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	NIL
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Shortening of menstrual cycles and family history of EM and ovarian surgery or other risk factors of reduced ovarian reserve

Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	cohort studies exclude women very low AMH – an area needing more research - women with very low AMH
Any revision of recommendations, strength or if justified, wording (including consensus vote)		NO- this PICO question cannot be determined by an RCT and is reliant on observational cohort studies which are automatically rated as lower quality. However ,the GDG determined this was a strong recommendation considering the benefits of risks versus harms as uptake would increase if this was conditional.

GRADE: Evidence to recommendation framework for an evidence-based recommendation -PP

If active treatment is pursued, which type of active treatment for UI?

Recommendation	**Pico question: If active treatment is pursued, which type of active treatment for UI?**	**The GDG advises to base the decision to start active treatment on prognosis in couples with unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL GPP Consider the below criteria to inform strength of recommendation.	PP - NA
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence		No change GPP
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable - GPP

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	NIL
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes. Patient preference should be considered as part of making a reproductive life plan.
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	NIL
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Shortening of menstrual cycles and family history of EM and ovarian surgery or other risk factors of reduced ovarian reserve
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or	Nil

	an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation -3.1

If active treatment is pursued, which type of active treatment for UI?

Recommendation	**PICO QUESTION: If active treatment is pursued, which type of active treatment for UI?**	**IUI with ovarian stimulation is probably recommended as a first-line treatment for couples with unexplained infertility** **PP: The GDG advises to base the decision to start active treatment on prognosis including female age, duration infertility, sperm motility and prior pregnancy in couples with unexplained infertility, acknowledging evolving evidence.(link to prognosis testing)**

GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Conditional Australian recommendation Prediction scores consideration
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	All evidence considered, no change in evidence based on integrity assessment. One cohort study (Carosso) with low risk integrity rating considered Three RCTs - two with low risk integrity rating considered; the third was a cost analysis - no integrity assessment applicable Two SRs available but only one was assessed (Ayeleke et al. 2020) with all but one low risk studies; the other SR (Pandian et al. 2015) was replaced by IPD
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	There is a cost for IUI vs expectant management but it is less than IVF Multiple pregnancy is more common with ovarian stimulation with clomid and gonadotrophins and IVF and multiple embryo transfer, not with letrozole.
Impact on health equity	Would the option reduce or increase health equity in Australia?	Increase equity of access with lower cost option

Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes. Patient preference should be taken into account as part of making a reproductive life plan with shared decision making around other considerations.
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Yes
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	The age of the women and other prognostic factors as a subgroup
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Policy and accessibility needs to be improved including RTAC accreditation of labs.
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Yes ANZARD and policy makers should report IUI data
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		IUI with ovarian stimulation is probably recommended as a first-line treatment for couples with unexplained infertility PP: The GDG advises to base the decision to start active treatment on prognosis including female age, duration infertility, sperm motility and prior pregnancy in couples with unexplained infertility, acknowledging evolving evidence. (link to prognosis testing)

GRADE: Evidence to recommendation framework for an evidence-based recommendation – PP

What is the value of expectant management compared to active treatment for patients with UI?

Recommendation	**Pico question: What is the value of expectant management compared to active treatment for patients with UI?**	**To avoid multiple pregnancies and OHSS, care is needed by using gonadotrophin treatment only in a low-dose regimen with adequate monitoring.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL GPP Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁⨁⨁⨁ HIGH ⨁⨁⨁◯ MODERATE ⨁⨁◯◯ LOW ⨁◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	

Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable - GPP.
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an	

	impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation -3.2

If active treatment is pursued, which type of active treatment for UI?

Recommendation	**Pico question: If active treatment is pursued, which type of active treatment for UI?**	**IVF is probably not recommended over IUI with ovarian stimulation in couples with unexplained infertility.**
GRADE strength of the recommendation	STRONG -	Unchanged

	CONDITIONAL - ESHRE Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	All evidence considered, no change in evidence based on integrity assessment. One cohort study (Carosso) with low risk integrity rating considered Three RCTs - two with low risk integrity rating considered; the third was a cost analysis - no integrity assessment applicable Two SRs available but only one was assessed (Ayeleke et al. 2020) with all but one low risk studies; the other SR (Pandian et al. 2015) was replaced by IPD IPD on which a GDG member was an author and it will not change the direction of the recommendation

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost analysis – IUI vs IVF 4-6 IUI to 2-3 cycles of IVF, cost effective for live birth in favour for IUI including consideration of multiple birth costs will be higher in IUI than in IVF but overall it is still cheaper with IUI. Longer term costs to the patient of multiple pregnancy have not been fully captured.
Impact on health equity	Would the option reduce or increase health equity in Australia?	More affordable for IUI Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes. Patient preference should be considered as part of making a reproductive life plan. A further consideration is that IVF can generate frozen embryos and future pregnancies.
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	NIL, IUI accessibility and regional and remote without accredited clinics Cost increased.
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	no
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Informed decision making needed. Multiple pregnancy considerations with IUI

Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Yes ANZARD
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation - PP

What is the value of IVF versus ICSI?

Recommendation	**Pico question: what is the value of IVF versus ICSI?**	**It is expected that the decision to use IVF is individualized by patient characteristics such as age, duration of infertility, previous treatment and previous pregnancy.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL GPP	

	Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁⨁⨁⨁ HIGH ⨁⨁⨁◯ MODERATE ⨁⨁◯◯ LOW ⨁◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Integrity assessment not applicable - GPP
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.

Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 3.2

What is the value of IVF versus ICSI?

Recommendation	**Pico question: What is the value of IVF versus ICSI?**	**ICSI is not recommended over conventional IVF in couples with unexplained infertility.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Agreed with justification as a consensus across the GDG, having reviewed all the GRADE considerations and the evidence there was a consensus that this remains a strong recommendation
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁⨁⨁⨁ HIGH ⨁⨁⨁◯ MODERATE ⨁⨁◯◯ LOW ⨁◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Evidence was reviewed – three large RCTs- no evidence All three RCTs had low risk of integrity concerns and were considered in the recommendation

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Lower costs
Impact on health equity	Would the option reduce or increase health equity in Australia?	Nil
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes, except for failed fertilisation in 4% of couples which contributes to the stress
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Patients should be adequately counselled on IVF vs ICSI and risk of failed fertilisation prior to treatment
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	RCT of fertilising half of eggs with IVF and half ICSI
Any revision of recommendations,		

strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 3.3

What is the value of mechanical-surgical procedures?

Recommendation	**Pico question: What is the value of mechanical-surgical procedures?**	**Hysteroscopy for the detection and possible correction of intrauterine abnormalities not seen at routine imaging is not recommended.**
GRADE strength of the recommendation	STRONG - ESHRE CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change level of evidence Research recommendation Hysteroscopy for the detection and possible correction of intrauterine abnormalities not seen at routine imaging, requires further research.
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	Consider the certainty ratings that underpin this recommendation.	Changed to no evidence
Summary of evidence & justification for the recommendation and for	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and	Evidence was reviewed – both included studies were rated as moderate risk on the integrity process.

differences between strength and GRADE certainty	justification for the recommendation. Any integrity study issues will also be considered here	
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	
Impact on health equity	Would the option reduce or increase health equity in Australia?	.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	

Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 3.3

What is the value of mechanical-surgical procedures?

Recommendation	**PICO - What is the value of mechanical-surgical procedures?**	**HSG (i.e., tubal flushing) with an oil-soluble contrast medium is preferable over a water-soluble contrast medium. Risks and benefits of tubal flushing with oil soluble contrast medium should be discussed with all couples with unexplained infertility.**
GRADE strength of the recommendation	CONDITIONAL Consider the below criteria to inform strength of recommendation.	Change Strong
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	⊕⊕◯◯ LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Evidence was reviewed – reasonably solid evidence for oil over water soluble and negatives / adverse effects noted with oil-based contrast. The GDG determined this was a strong recommendation considering the benefits of risks versus harms as uptake would increase if this was conditional. No studies removed based on integrity - 1 low risk RCT and 1 SR (Wang et al. 2020) considered in recommendation
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Companies increased costs after efficacy studies
Impact on health equity	Would the option reduce or increase health equity in Australia?	Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Cost barriers may reduce access and rural and remote may have reduced access to services

Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Consideration of those women with shortening of menstrual cycles and family history of EM and ovarian surgery or other risk factors of reduced ovarian reserve.
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		However, the GDG determined this was a strong recommendation considering the benefits of risks versus harms as uptake would increase if this was conditional.

GRADE: Evidence to recommendation framework for an evidence-based recommendation –

What is the value of mechanical-surgical procedures?

Recommendation	**PICO: What is the value of mechanical-surgical procedures?**	**Endometrial scratching should probably not be offered for unexplained infertility**
GRADE strength of the recommendation	STRONG - conditional Consider the below criteria to inform strength of recommendation.	CONDITIONAL against
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁⨁◯◯ LOW Consider the certainty ratings that underpin this recommendation.	Downgraded to low certainty evidence
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Evidence was reviewed – seven studies - four studies removed on integrity check, 3 remaining showed no significant difference. Evidence certainty is low for all outcomes except pregnancy rate (very low), hence changed to conditional due to low certainty based on GRADE Here in removing 4 studies and no residual studies (3/3) showing consistent benefit hence this is more consistent

		evidence than in the ESHRE GDG and the Australian GDG deemed this is a strong rec. All three studies showed no significance difference so we have no evidence to show it does work
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Nil
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Nil
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an	Nil

	impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Nil
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 3.4

What is the effectiveness of alternative therapeutic approaches?

Recommendation	**Pico question: What is the effectiveness of alternative therapeutic approaches?**	**Adjunct oral antioxidant therapy to women undergoing fertility treatment is probably not recommended.**
GRADE strength of the recommendation	STRONG - conditional Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	⊕⊕⊕⊕ HIGH ⊕⊕⊕◯ MODERATE ⊕⊕◯◯ LOW ⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	In SR only two RCTs antioxidants in women- if excluded on integrity check then research rec No antioxidants in men – research rec
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Improved if not using unproven treatment
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes, shared decision making still need to be respected
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in	Nil

	relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Informed decision making
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 3.4

What is the effectiveness of alternative therapeutic approaches?

Recommendation	**Pico question: What is the effectiveness of alternative therapeutic approaches?**	**Adjunct oral antioxidant therapy to males undergoing fertility treatment is probably not recommended.**
GRADE strength of the recommendation	STRONG - conditional Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁⨁⨁⨁ HIGH ⨁⨁⨁◯ MODERATE ⨁⨁◯◯ LOW ⨁◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	In SR only two RCTs antioxidants in women- if excluded on integrity check then research rec No antioxidants in men – research rec

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Improved if not using unproven treatment
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes, shared decision making still need to be respected
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Informed decision making
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	

Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE template: Evidence to recommendation framework for an evidence-based recommendation – 3.4

What is the effectiveness of alternative therapeutic approaches?

Recommendation	**Pico question: What is the effectiveness of alternative therapeutic approaches?**	**Acupuncture in women is probably not recommended**
GRADE strength of the recommendation	STRONG - conditional Consider the below criteria to inform strength of recommendation.	No change
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕◯◯ LOW Acupuncture no evidence Consider the certainty ratings that underpin this recommendation.	⊕◯◯◯ VERY LOW

Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Antioxidants: Two eligible RCTs in SR by Showell et al. 2020 Acupuncture: RCT by Guyen et al. (2020) removed in integrity check - in acupuncture, no evidence. - Nutraceuticals: one RCT with low risk of integrity concerns (Montanino et al. 2020) Traditional Chinese medicine- only one case series, integrity assessment not applicable – research recommendation to ensure accurate information for informed decision making Very low certainty evidence
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Improved if not using unproven treatment
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes, shared decision making and patient preferences respected
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil

Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Assists informed decision making
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Further research on Acupuncture in women with UI
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation -3.4

What is the effectiveness of alternative therapeutic approaches?

Recommendation	**Pico question: What is the effectiveness of alternative therapeutic approaches?**	**Inositol supplementation in women is probably not recommended.**
GRADE strength of the recommendation	STRONG -	No change

	conditional Consider the below criteria to inform strength of recommendation.	
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⨁⨁⨁⨁ HIGH ⨁⨁⨁◯ MODERATE ⨁⨁◯◯ LOW ⨁◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Inositol one low risk RCT – no test of significance – we did the stats and no difference No studies were removed based on integrity assessment.
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Improved if not using unproven treatment
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes, Patient preferences to be respected and shared decision making still need to be respected

Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Informed decision making assisted
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Further research on inositol use in UI
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – PP

What is the effectiveness of alternative therapeutic approaches?

Recommendation	**PICO QUESTION: WHAT IS THE EFFECTIVENESS OF ALTERNATIVE THERAPEUTIC APPROACHES?**	**Psychological support, including psychotherapy, is recommended for patients when needed**
GRADE strength of the recommendation	STRONG - conditional GPP Consider the below criteria to inform strength of recommendation.	No change
CRITERIA	Instructions and considerations to address criterion	
GRADE certainty of the evidence	⊕⊕⊕⊕ HIGH ⊕⊕⊕◯ MODERATE ⊕⊕◯◯ LOW ⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Low quality evidence Integrity assessment not applicable - GPP

Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Improved if not using unproven treatment Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes, shared decision making and patient preferences respected
Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Assists informed decision making
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or	Nil

	an impact evaluation carried out alongside or before full implementation of the option in Australia?	
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation - PP

What is the effectiveness of alternative therapeutic approaches?

Recommendation	**Pico question: What is the effectiveness of alternative therapeutic approaches?**	**A healthy diet and regular exercise, supported by behavioural therapy when necessary, are recommended.**
GRADE strength of the recommendation	STRONG - conditional GPP Consider the below criteria to inform strength of recommendation.	No change
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	⊕⊕⊕⊕ HIGH ⊕⊕⊕◯ MODERATE ⊕⊕◯◯ LOW ⊕◯◯◯ VERY LOW Consider the certainty ratings that underpin this recommendation.	
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Low quality evidence Integrity assessment not applicable - GPP
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	Cost savings
Impact on health equity	Would the option reduce or increase health equity in Australia?	Improved if not using unproven treatment Low impact on Metro-based patients. Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	Yes, shared decision making and patient preferences respected

Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	Assists informed decision making
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	
Any revision of recommendations, strength or if justified, wording (including consensus vote)		

GRADE: Evidence to recommendation framework for an evidence-based recommendation – 4

Is there a difference in qol for patients with unexplained versus explained infertility?

Recommendation	**Pico question: Is there a difference in qol for patients with unexplained versus explained infertility?**	**Healthcare professionals should be aware that** **- there is probably no difference in QoL between women with unexplained infertility versus women in couples with known causes of infertility, except when the cause of infertility is PCOS, where the QoL is lower.** **- QoL is probably higher in men from a couple with unexplained infertility compared to men from a couple with known causes of infertility except when the cause of infertility is men with a partner with PCOS, then the men from a couple with unexplained infertility have a lower QoL.**
GRADE strength of the recommendation	STRONG - conditional Consider the below criteria to inform strength of recommendation.	No change PP It should be acknowledged that couples with UI may experience considerable impact on their QoL and they can be offered support and therapeutic counselling.
CRITERIA	Instructions and considerations to address criterion	

GRADE certainty of the evidence	⨁◯◯◯ VERY LOW Acupuncture no evidence Consider the certainty ratings that underpin this recommendation.	Very low
Summary of evidence & justification for the recommendation and for differences between strength and GRADE certainty	Consider the brief summary of evidence that underpins this rec, considering desirable and undesirable effects and justification for the recommendation. Any integrity study issues will also be considered here	Conflicting evidence - unclear PCOS studies – two RCTs - lower in PCOS Cohort studies males – unexplained had high scores than if there was male factor Old study – no difference between men and women for well-being Integrity assessment not applicable
Resource requirements	How large an investment of resources would implementation of the recommendation require or save? The greater the cost, the less likely it is that a recommendation should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.	maybe
Impact on health equity	Would the option reduce or increase health equity in Australia?	Those disadvantaged by geographic location and low SES have reduced health equity. In addition, consideration should be given to the persistent and pervasive disparities experienced by Australian Aboriginal and Torres Strait Islander communities in their unequal access to accessible, timely, preventative, culturally responsive, and equitable care across diverse geographical contexts.
Acceptability	Consider acceptability to key stakeholders and strategies to optimise this in translation	

Feasibility issues in Australia	Can the option be accomplished or brought about- identify specific Australian barriers related to our health or funding system	Nil
Subgroup considerations	What, if any, subgroups do we need to consider and what, if any, specific criteria in this framework should be considered in relation to those subgroups when implementing the recommendation? This includes CaLD and Indigenous groups	Nil
Implementation considerations	What should be considered when implementing the recommendation, including strategies to address concerns about acceptability and feasibility unique to Australia?	
Monitoring and evaluation considerations	What indicators should be monitored? Is there a need to evaluate the impacts of the option, either in a pilot study or an impact evaluation carried out alongside or before full implementation of the option in Australia?	Nil
Research priorities	Are there any important uncertainties in relation to any of the criteria that are a priority for further research?	Further research on QoL comparing couples with UI with other couples with diagnostic causes other that PCOS.
Any revision of recommendations, strength or if justified, wording (including consensus vote)		GPP It should be acknowledged that couples with UI may experience considerable impact on their QoL and they can be offered support and therapeutic counselling.