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**ESHRE Pages**

# Evidence-based guideline: unexplained infertility†

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## ABSTRACT

**STUDY QUESTION:** What is the recommended management for couples presenting with unexplained infertility (UI), based on the best available evidence in the literature?

**SUMMARY ANSWER:** The evidence-based guideline on UI makes 52 recommendations on the definition, diagnosis, and treatment of UI.

**WHAT IS KNOWN ALREADY:** UI is diagnosed in the absence of any abnormalities of the female and male reproductive systems after 'standard' investigations. However, a consensual standardization of the diagnostic work-up is still lacking. The management of UI is traditionally empirical. The efficacy, safety, costs, and risks of treatment options have not been subjected to robust evaluation.

**STUDY DESIGN, SIZE, DURATION:** The guideline was developed according to the structured methodology for ESHRE guidelines. Following formulation of key questions by a group of experts, literature searches, and assessments were undertaken. Papers written in English and published up to 24 October 2022 were evaluated.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** Based on the available evidence, recommendations were formulated and discussed until consensus was reached within the guideline development group (GDG). Following stakeholder review of an initial draft, the final version was approved by the GDG and the ESHRE Executive Committee.

**MAIN RESULTS AND THE ROLE OF CHANCE:** This guideline aims to help clinicians provide the best care for couples with UI. As UI is a diagnosis of exclusion, the guideline outlined the basic diagnostic procedures that couples should/could undergo during an infertility work-up, and explored the need for additional tests. The first-line treatment for couples with UI was deemed to be IUI in combination with ovarian stimulation. The place of additional and alternative options for treatment of UI was also evaluated. The GDG made 52 recommendations on diagnosis and treatment for couples with UI. The GDG formulated 40 evidence-based recommendations—of which 29 were formulated as strong recommendations and 11 as weak—10 good practice points and two research only recommendations. Of the evidence-based recommendations, none were supported by high-quality evidence, one by moderate-quality evidence, nine by low-quality evidence, and 31 by very low-quality evidence. To support future research in UI, a list of research recommendations was provided.

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**LIMITATIONS, REASONS FOR CAUTION:** Most additional diagnostic tests and interventions in couples with UI have not been subjected to robust evaluation. For a large proportion of these tests and treatments, evidence was very limited and of very low quality. More evidence is required, and the results of future studies may result in the current recommendations being revised.

**WIDER IMPLICATIONS OF THE FINDINGS:** The guideline provides clinicians with clear advice on best practice in the care of couples with UI, based on the best evidence currently available. In addition, a list of research recommendations is provided to stimulate further studies in the field. The full guideline and a patient leaflet are available in www.eshre.eu/guideline/UI.

**STUDY FUNDING/COMPETING INTEREST(S):** The guideline was developed by ESHRE, who funded the guideline meetings, literature searches, and dissemination of the guideline in collaboration with the Monash University led Australian NHMRC Centre of Research Excellence in Women's Health in Reproductive Life (CREWHIRL). The guideline group members did not receive any financial incentives; all work was provided voluntarily. D.R. reports honoraria from IBSA and Novo Nordisk. B.A. reports speakers' fees from Merck, Gedeon Richter, Organon and Intas Pharma; is part of the advisory board for Organon Turkey and president of the Turkish Society of Reproductive Medicine. S.B. reports speakers' fees from Merck, Organon, Ferring, the Ostetric and Gynaecological Society of Singapore and the Taiwanese Society for Reproductive Medicine; editor and contributing author, Reproductive Medicine for the MRCOG, Cambridge University Press; is part of the METAFOR and CAPE trials data monitoring committee. E.B. reports research grants from Roche diagnostics, Gedeon Richter and IBSA; speaker's fees from Merck, Ferring, MSD, Roche Diagnostics, Gedeon Richter, IBSA; E.B. is also a part of an Advisory Board of Ferring Pharmaceuticals, MSD, Roche Diagnostics, IBSA, Merck, Abbott and Gedeon Richter. M.M. reports consulting fees from Mojo Fertility Ltd. R.J.N. reports research grant from Australian National Health and Medical Research Council (NHMRC); consulting fees from Flinders Fertility Adelaide, VinMec Hospital Hanoi Vietnam; speaker's fees from Merck Australia, Cadilla Pharma India, Ferring Australia; chair clinical advisory committee Westmead Fertility and research institute MyDuc Hospital Vietnam. T.P. is a part of the Research Council of Finland and reports research grants from Roche Diagnostics, Novo Nordics and Sigrid Juselius foundation; consulting fees from Roche Diagnostics and organon; speaker's fees from Gedeon Richter, Roche, Exeltis, Organon, Ferring and Korento patient organization; is a part of NFOG, AE-PCOS society and several Finnish associations. S.S.R. reports research grants from Roche Diagnostics, Organon, Theramex; consulting fees from Ferring Pharmaceuticals, MSD and Organon; speaker's fees from Ferring Pharmaceuticals, MSD/Organon, Besins, Theramex, Gedeon Richter; travel support from Gedeon Richter; S.S.R. is part of the Data Safety Monitoring Board of TTRANSPORT and deputy of the ESHRE Special Interest Group on Safety and Quality in ART; stock or stock options from IVI Lisboa, Clínica de Reprodução assistida Lda; equipment/medical writing/gifts from Roche Diagnostics and Ferring Pharmaceuticals. S.K.S. reports speakers' fees from Merck, Ferring, MSD, Pharmasure. HRV reports consulting and travel fees from Ferring Pharmaceuticals. The other authors have nothing to disclose.



**Keywords:** unexplained infertility / guideline / evidence-based / medically assisted reproduction / IUI / IVF / pregnancy / ESHRE / ART

## Introduction

Approximately 30% of infertile couples are considered to experience 'unexplained infertility' (UI) (2019, 2020). This controversial diagnosis is made when no abnormalities of the female and male reproductive systems are identified. UI is inevitably a diagnosis by exclusion, following otherwise 'standard' investigations. However, a consensual standardization of the diagnostic work-up is still lacking. The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) defined UI as 'infertility in couples with apparently normal ovarian function, fallopian tubes, uterus, cervix and pelvis and with adequate coital frequency; and apparently normal testicular function, genito-urinary anatomy and a normal ejaculate. The potential for this diagnosis is dependent upon the methodologies used and/or those methodologies available' (Zegers-Hochschild *et al.*, 2017).

The proportion of couples with UI is related to the extent of diagnostic examination performed to uncover putative causes for unsuccessful attempts at pregnancy (ESHRE Capri Workshop Group, 2004). Furthermore, the criteria for labelling specific features as 'normal' are heterogeneous. Finally, apart from the clearly recognized causes of infertility, several undetectable defects in the reproductive process might prevent conception.

In the absence of an identified cause, the management of UI is traditionally empirical. The efficacy, safety, costs, and risks of treatment options have not been subjected to robust evaluation.

## Materials and methods

The guideline was developed according to a well-documented methodology that is universal to ESHRE guidelines (Vermeulen *et al.*, 2019). The guideline development group (GDG) was composed of members of the ESHRE Special Interest Group (SIG) Reproductive Endocrinology, SIG Andrology, SIG Safety and Quality in ART, SIG Nurses and Midwives, and a patient representative from Fertility Europe. This guideline was developed in collaboration with Monash University NHMRC Centre for Research Excellence in Women's Reproductive Health.

In short, 21 key questions were formulated by the GDG, of which four were answered as narrative questions, and 17 as PICO (Patient, Intervention, Comparison, Outcome) questions. For each PICO question, databases (PUBMED/MEDLINE and Cochrane library) were searched from inception to 24 October 2022, for publications written in English. From the literature searches, studies were selected on the basis of their relevance

to the PICO questions, assessed for quality, and summarized in evidence tables (Supplementary File S1). At GDG meetings, the evidence and draft recommendations were presented by the assigned GDG member and discussed until consensus was reached within the group. Each recommendation was labelled as strong or conditional and a grade was assigned based on the strength of the supporting evidence (High ⊕⊕⊕⊕, Moderate ⊕⊕⊕◯, Low ⊕⊕◯◯, Very low ⊕◯◯◯). Good practice points (GPPs) based on clinical expertise were added, where relevant, to clarify the recommendations or to provide further practical advice. Two 'research only' recommendations were also made for tests which should only be applied within the context of research.

Strong recommendations should be applied to most patients, while weak recommendations require discussion and shared decision-making.

For some of the narrative questions, a similar literature search was conducted. Collected data were summarized in a narrative summary and conclusions were formulated.

The draft guideline along with an invitation to participate in the stakeholder review were published on the ESHRE website between 12 December 2022 and 30 January 2023. All comments were processed by the GDG, either by adapting the content of the guideline and/or by responding to the reviewer. The review process was summarized in the review report, which is published on the ESHRE website (www.eshre.eu/Guidelines). The list of experts who contributed to the stakeholder review is included in Supplementary File S2. Overall, 31% of the 260 comments resulted in an amendment to the guideline text. A flowchart on diagnosis and management of UI is also available on the ESHRE website.

This guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

# Results

## Key questions and recommendations

The current document summarizes all the key questions and the recommendations from the guideline on 'Unexplained Infertility'. Further background information and the supporting evidence for each recommendation can be found in the full version of the guideline available at www.eshre.eu/guideline/UI.

## Definition

The GDG defines UI as follows: infertility in couples with apparently normal ovarian function, fallopian tubes, uterus, cervix and pelvis, age ≤40 years and with adequate coital frequency; and apparently normal testicular function, genito-urinary anatomy, and a normal ejaculate.

As per the ICMART definition of infertility, couples should have at least 12 months of regular, unprotected sexual intercourse before investigations are initiated.

The GDG recommends routinely taking a medical, reproductive and sexual history from both the male and female partner.

The GDG considers a regular menstrual cycle to be 24–38 days, up to 8 days in duration, and shortest to longest cycle variation of <7–9 days (Munro *et al.*, 2018).

The GDG recommends at least one basic semen examination, according to World Health Organization (WHO) criteria, performed by a laboratory which subscribes to an external quality control programme. If the result from first basic semen analysis is below the lower fifth percentile reference limit as per WHO criteria (6th edition), a second analysis should be performed after a 3-month interval.

## Diagnosis

### Confirmation of ovulation

| | |
|---|---|
| In women with regular menstrual cycles, tests for confirmation of ovulation are not routinely recommended. | GPP |
| 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 (Gregoriou *et al.*, 1990; Bischof *et al.*, 1991; Martinez *et al.*, 1991; Guermandi *et al.*, 2001) | Conditional ⊕◯◯◯ |

### Oocyte/corpus luteum quality

| | |
|---|---|
| In women with regular menstrual cycles, it is suggested not to routinely measure midluteal serum progesterone levels (Hull *et al.*, 1982). | Conditional ⊕◯◯◯ |
| In women investigated for infertility, endometrial biopsy for histological examination is not recommended in the absence of other indications (Coutifaris *et al.*, 2004; Edi-Osagie *et al.*, 2004). | Strong ⊕⊕◯◯ |

### Ovarian reserve

| | |
|---|---|
| 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 6–12 months (Scott *et al.*, 1993; Rosen *et al.*, 2011; Hagen *et al.*, 2012; Casadei *et al.*, 2013; Murto *et al.*, 2013; Hvidman *et al.*, 2016; Depmann *et al.*, 2017; Greenwood *et al.*, 2017; Steiner *et al.*, 2017; Yücel *et al.*, 2018; Nguyen *et al.*, 2022). | Strong ⊕⊕◯◯ |

### Tubal factor

| | |
|---|---|
| Hysterosalpingo-contrast-sonography (HyCoSy) and hysterosalpingography (HSG) are valid tests for tubal patency compared to laparoscopy and chromopertubation (Broeze *et al.*, 2011; Wang and Qian, 2016; Alcázar *et al.*, 2020). | Strong ⊕⊕⊕◯ |
| HSG and HyCoSy are comparable in diagnostic capacity, thus selection of the technique depends on the preference of the clinician and the patient. | GPP |
| 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 (Mol *et al.*, 1997). | Conditional ⊕◯◯◯ |
| In patients at high risk for tubal abnormality, visual demonstration of tubal patency is necessary. | GPP |

## Uterine factor

| | |
|---|---|
| Ultrasound, preferably 3D, is recommended to exclude uterine anomalies in women with unexplained infertility (Jurkovic *et al.*, 1995; Caliskan *et al.*, 2010; Ludwin *et al.*, 2013). | Strong ⊕○○○ |
| MRI is not recommended as a first-line test to confirm a normal uterine structure and anatomy in women with unexplained infertility. | Strong ⊕○○○ |
| If ultrasound assessment of the uterine cavity is normal, no further evaluation is needed (Fatemi *et al.*, 2010; Almog *et al.*, 2011; Bakas *et al.*, 2014; Makled *et al.*, 2014; Yang *et al.*, 2019). | Strong ⊕○○○ |

## Laparoscopy

| | |
|---|---|
| Routine diagnostic laparoscopy is not recommended for the diagnosis of unexplained infertility (Tanahatoe *et al.*, 2003, 2005; Lavy *et al.*, 2004). | Strong ⊕○○○ |

## Cervical/vaginal investigations

| | |
|---|---|
| The post-coital test is not recommended in couples with unexplained infertility (Oei *et al.*, 1995). | Strong ⊕⊕○○ |
| Vaginal microbiota testing could be considered in couples with unexplained infertility only in a research setting. | Research only |

## Male genito-urinary anatomy

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|---|---|
| Testicular imaging is not recommended when semen analysis according to WHO criteria is normal (Lotti *et al.*, 2021). | Strong ⊕○○○ |

## Male additional tests

| | |
|---|---|
| Testing for anti-sperm antibodies in the semen is not recommended when semen analysis according to WHO criteria is normal (Ayvaliotis *et al.*, 1985; Lähteenmäki, 1993; Rajah *et al.*, 1993; Pagidas *et al.*, 1994; Lähteenmäki *et al.*, 1995; Vazquez-Levin *et al.*, 1997; Bozhedomov *et al.*, 2015; Barbonetti *et al.*, 2020). | Strong ⊕○○○ |
| Testing for sperm DNA fragmentation is not recommended when semen analysis according to WHO criteria is normal (O'Neill *et al.*, 2018; Borges *et al.*, 2019; Repalle *et al.*, 2022). | Strong ⊕○○○ |
| Sperm chromatin condensation test is not recommended when semen analysis according to WHO criteria is normal. | Strong ⊕○○○ |
| Sperm aneuploidy screening is not recommended when semen analysis according to WHO criteria is normal. | Strong ⊕○○○ |
| Serum hormonal testing is not required when semen analysis according to WHO criteria is normal. | Strong ⊕○○○ |
| Human papillomavirus (HPV) testing of semen is not recommended when semen analysis according to WHO criteria is normal. | Strong ⊕○○○ |
| Microbiology testing of semen is not recommended when semen analysis according to WHO criteria is normal. | Strong ⊕○○○ |

## Systemic additional tests

| | |
|---|---|
| Testing for anti-sperm antibodies in serum of either males or females with unexplained infertility is not recommended (Menge *et al.*, 1982; Mardesic *et al.*, 2000; Monem and Moalla, 2003; Yasin *et al.*, 2016). | Strong ⊕○○○ |
| Testing for coeliac disease in women with unexplained infertility can be considered (Tersigni *et al.*, 2014). | Conditional ⊕⊕○○ |
| Testing for thyroid antibody and other autoimmune conditions (apart from coeliac disease) in women with unexplained infertility is not recommended (Poppe *et al.*, 2002; Abalovich *et al.*, 2007; Kilic *et al.*, 2008). | Strong ⊕○○○ |
| TSH measurement is considered good practice in pre-conception care. | GPP |
| No additional thyroid evaluation in women is recommended if TSH is within the normal range (Duran *et al.*, 2013; Unuane *et al.*, 2013; Orouji Jokar *et al.*, 2018; Rehman *et al.*, 2020). | Strong ⊕○○○ |
| Testing for thrombophilia in women with unexplained infertility is not recommended (Behjati *et al.*, 2006; Bellver *et al.*, 2008; Coulam and Jeyendran, 2009; Casadei *et al.*, 2010; Fatini *et al.*, 2012; Steinvil *et al.*, 2012; Kydonopoulou *et al.*, 2017; Milenkovic *et al.*, 2020). | Strong ⊕○○○ |
| Measurement of oxidative stress in semen of males with unexplained infertility should only be considered in the context of research. | Research only |
| Measurement of oxidative stress in women with unexplained infertility is not recommended (Veena *et al.*, 2008; Pekel *et al.*, 2015; Lazzarino *et al.*, 2021; Şentürk *et al.*, 2021). | Strong ⊕⊕○○ |
| Genetic or genomic tests are currently not recommended in couples with unexplained infertility (Trková *et al.*, 2000; Papanikolaou *et al.*, 2005; Witkin *et al.*, 2010; Sahmani *et al.*, 2011; Vani *et al.*, 2012; Suganya *et al.*, 2015; Salas-Huetos *et al.*, 2016; Rull *et al.*, 2018; Ertosun *et al.*, 2022). | Strong ⊕○○○ |
| Testing for vitamin D deficiency in women is not recommended for diagnosis of unexplained infertility (Rudick *et al.*, 2012; Lopes *et al.*, 2017; Butts *et al.*, 2019; Güngör *et al.*, 2022; Ko *et al.*, 2022). | Strong ⊕○○○ |
| Prolactin testing in women is not recommended (Subramanian *et al.*, 1997; Veena *et al.*, 2008; Orouji Jokar *et al.*, 2018; Qu *et al.*, 2020). | Strong ⊕○○○ |
| BMI measurement in women is considered good practice in pre-conception care. | GPP |

# Treatment

## Expectant management

| | |
|---|---|
| IUI with ovarian stimulation is recommended as a first-line treatment for couples with unexplained infertility (Fisch *et al.*, 1989; Bhattacharya *et al.*, 2008; Pandian *et al.*, 2015; Ayeleke *et al.*, 2020). | Strong ⊕○○○ |
| The GDG advises to base the decision to start active treatment on prognosis in couples with unexplained infertility. | GPP |

### Active treatment

| | |
|---|---|
| IUI with ovarian stimulation is recommended as a first-line treatment for couples with unexplained infertility (Agarwal and Mittal, 2004; Bhattacharya *et al.*, 2008; Ayeleke *et al.*, 2020; Harira 2018; Ibrahim *et al.*, 2012). | Strong ⊕◯◯◯ |
| To avoid multiple pregnancies and ovarian hyperstimulation syndrome (OHSS), care is needed by using gonadotrophin treatment only in a low-dose regimen with adequate monitoring. | GPP |
| IVF is probably not recommended over IUI with ovarian stimulation in couples with unexplained infertility (Pandian *et al.*, 2015; Nandi *et al.*, 2022). | Conditional ⊕◯◯◯ |
| 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 |
| ICSI is not recommended over conventional IVF in couples with unexplained infertility (Bhattacharya *et al.*, 2001; Foong *et al.*, 2006; Dang *et al.*, 2021). | Strong ⊕◯◯◯ |

### Mechanical–surgical procedures

| | |
|---|---|
| Hysteroscopy for the detection and possible correction of intrauterine abnormalities not seen at routine imaging is not recommended (Casini *et al.*, 2006; Seyam *et al.*, 2015). | Strong ⊕⊕◯◯ |
| 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 (Wang *et al.*, 2020). | Conditional ⊕⊕◯◯ |
| Endometrial scratching should not be offered for unexplained infertility (Parsanezhad *et al.*, 2013; Senocak *et al.*, 2017; Ghuman *et al.*, 2020; Jafarabadi *et al.*, 2020; Yildiz *et al.*, 2021; Wong *et al.*, 2022). | Strong ⊕⊕◯◯ |

**If incidentally minimal to mild endometriosis is found at laparoscopy, this is not further considered unexplained infertility by the GDG.**

### Alternative therapeutic approaches

| | |
|---|---|
| Adjunct oral antioxidant therapy to women undergoing fertility treatment is probably not recommended (Showell *et al.*, 2020). | Conditional ⊕◯◯◯ |
| Adjunct oral antioxidant therapy to males undergoing fertility treatment is probably not recommended. | Conditional ⊕◯◯◯ |
| Acupuncture in women is probably not recommended (Guven *et al.*, 2020). | Conditional ⊕⊕◯◯ |
| Inositol supplementation in women is probably not recommended (Montanino Oliva *et al.*, 2020). | Conditional ⊕◯◯◯ |
| Psychological support, including psychotherapy, is recommended for patients when needed. | GPP |
| A healthy diet and regular exercise, supported by behavioural therapy when necessary, are recommended. | GPP |

### Quality of life

| | |
|---|---|
| Healthcare professionals should be aware that<br>• There is probably no difference in quality of life (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.<br>• 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 (Kowalcek *et al.*, 2001; Santoro *et al.*, 2016; Warchol-Biedermann, 2021). | Conditional ⊕◯◯◯ |

## Discussion

The current paper presents the 52 recommendations on management of UI from the evidence-based guideline on 'Unexplained Infertility'. This guideline covers all aspects of the definition, diagnosis and treatment of couples with UI. The guideline was written by a multidisciplinary group of experts in reproductive endocrinology, reproductive surgery, and andrology, along with a nurse and a patient representative and developed in collaboration with the Monash University led NHMRC Centre of Research Excellence in Women's Health in Reproductive Life (CREWHIRL).

Notwithstanding the importance and relevance of the topic, research data on many key aspects are scarce. As a basis for the current guideline, a formal literature review was conducted. Most studies on diagnosis were old, with often incomplete reporting of methodology. Review of additional tests for establishing the diagnosis of UI was plagued by heterogeneity of the study population and lack of standardization of assays. The literature on the diagnosis of a putative male cause for unexplained infertility was complicated by the interchangeable use of the terms unexplained and idiopathic male infertility.

The recommendation against laparoscopy as a routine procedure in the diagnostic infertility work-up generated considerable debate during the stakeholder review. Therefore, this topic, which was extensively analysed during the previous meetings, was further reconsidered. The GDG agreed that HSG and HyCoSy/HyFoSy do not detect mild endometriosis, adhesions, or subtle tubal lesions. However, there are insufficient good quality data to suggest that clinically relevant diagnoses will be missed by omitting a laparoscopy in patients at low risk for tubal pathology. As evidence is lacking to justify routine laparoscopy for every patient with otherwise UI given possible surgical and anaesthesiological risks, the recommendation was retained. Nevertheless, clinicians are advised to counsel women at high risk for tubal pathology (a history of pelvic inflammatory disease, previous ectopic pregnancy) or endometriosis about the benefits and risks of laparoscopy.

The GDG received several comments on the relatively minor role of investigations of the male partner in the standard diagnostic work-up for UI. The literature on most of the possible additional tests proposed for the male partner in the last decades was reviewed in the guideline development process. Insufficient evidence was found to suggest the diagnostic benefit of these investigations in men with normal semen parameters according to WHO criteria (6th edition). The tests under scrutiny were characterized by limited capacity to discriminate between

couples who would benefit from a specific medically assisted reproduction (MAR) technique; inconsistent and heterogenous cut-offs and unvalidated thresholds; lack of reliable predictive value in terms of reproductive outcomes; and lack of proven value in informing clinical decision making. Hence, recommendations in favour of their routine use in the initial evaluation of couples with UI were not adequately supported, taking into account their possible economic and psychological burden.

Nevertheless, the GDG acknowledges that the quality of data is generally very low and that the male factor is neglected in the scientific literature. It was decided to amend the former version of the guideline by underlining that more research is needed in this area. Re-focusing research efforts on addressing gaps in the understanding of male infertility, such as identifying new aetiological causes, clinical diagnostics, and MAR treatment options, will enable the development of more personalized therapeutic options to manage couple's infertility and improve reproductive outcomes. Furthermore, a statement was added on the importance to investigate the general and reproductive history of the male, with particular attention to sexual dysfunction. Should any abnormality emerge, physical examination, and appropriate investigations would be warranted. However, in these circumstances, the diagnosis of UI would no longer be applicable, and further specifications would fall outside the scope of the present guideline.

Very few high-quality randomized controlled trials were available to the GDG to make sound recommendations with regard to treatment of couples with unexplained infertility. The GDG also received criticism for not including a section on prognosis-based treatment in the guideline. This feedback was held in high regard and a new section was included in the guideline. In brief, it was reported that prognostic models, as well as patients' preference, can help the decision-making on a treatment plan in couples with UI. Overall, in the case of expectant management, the most important prognostic factors are age, duration of infertility, previous treatment, and previous pregnancies. It is, however, important to note that none of the currently available prediction models is fully evolved. Promising models are currently under development, however, they need to be implemented and validated before legitimately entering into common use.

Research gaps were detected in several areas, and the top three topics are documented in a list of recommendations for further research (Supplementary File S3).

Despite the limitations of guidelines in general, and the limitations in the evidence supporting the current guideline, the GDG is confident that this document will help best practice in the management of couples with UI.

## Supplementary data

Supplementary data are available at *Human Reproduction* online.

## Data availability

The data underlying this article are available in the article and in its supplementary material.

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## Authors' roles

D.R. chaired the GDG and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. N.L.C., as methodological expert, performed all literature searches for the guideline, provided methodological support, and coordinated the guideline development. All other authors, listed in alphabetical order, as GDG members, contributed equally to the manuscript, by drafting key questions, synthesizing evidence, writing the different parts of the guideline, and discussing recommendations until consensus within the group was reached.

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## Conflict of interest

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