Recommendations from the WHO guideline for the prevention, diagnosis, and treatment of infertility[†]

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Abstract

Background: The field of sexual and reproductive health care, including family planning has progressed in the last several decades. Significant progress has also been made in the field of medically assisted reproduction. Globally one in six people experience infertility in their lifetime. However, many countries do not include the prevention, diagnosis, and treatment of infertility in health policies, financing and services, and many do not have national clinical guidelines for the prevention, diagnosis and treatment of infertility.
Objective: To determine what interventions are recommended for prevention, diagnosis and treatment of infertility among individuals and couples.
Design, setting: The guideline was developed according to the WHO handbook for guideline development. A Guideline Development Group (GDG) was assembled and included a multidisciplinary and regionally diverse set of clinicians, policymakers, researchers,

[†] This article has been co-published with permission in *Human Reproduction* and *Fertility and Sterility*. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style.
[‡] A full list of all members of the GDG and their declared interests is included at the end of this document and as Supplementary Tables S2 and S3.
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Disclaimer: This manuscript reports a summary of recommendations from a WHO guideline. All reasonable precautions have been taken by WHO to verify the information contained in the guideline publication. However, the published material is being distributed without warranty of any kind, either expressed or implied.
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implementers and representatives of patient groups (n=30). The GDG prioritised key recommendation questions to address in the guideline. New systematic reviews were conducted, or existing reviews updated, to inform the recommendations. The GRADE approach was used to assess the certainty of the evidence and to guide the formulation of recommendations.

Main outcome measures: The GDG interpreted evidence and made judgments about the balance between benefits and harms (including patients' values) as well as costs, feasibility, acceptability, and equity. The recommendations were drafted, reviewed by an External Review Group (ERG) comprising 30 members, and approved by the WHO.

Results: The guideline makes good practice statements related to the general management of infertility (n=6) including (i) selection of tests, (ii) listening to individuals and couples with infertility, (iii) choosing treatment decisions, (iv) clinical follow-up, and (v) documenting outcomes of treatment. In relation to prevention, it provides recommendations related to the provision of information about fertility and infertility (n=1) and reduction of infertility risk from sexually transmitted infections (STIs; n=1), lifestyle factors (n=1), and tobacco use (n=1). In terms of diagnosis, recommendations for diagnosing infertility caused by ovulatory dysfunction (n=3), tubal disease (n=1), or uterine cavity abnormalities (n=5) among females are provided. For males, the guideline provides recommendations regarding when a semen test should be repeated (n=2). Also included is a recommendation for diagnosing unexplained infertility (n=1). Regarding treatment, the guideline provides recommendations related to the treatment of polycystic ovary syndrome (PCOS, n=6), tubal disease (n=5), uterine septae (n=1), varicocele (n=4), and unexplained infertility (n=6). Based on available evidence, the GDG did not make a recommendation for or against the use of antioxidant supplements in males. Most recommendations were conditional because relevant evidence was either absent, or of low or very low certainty. Critical research gaps were identified.

Conclusions: The World Health Organization (WHO) made 40 recommendations and six good practice statements for the prevention, diagnosis and treatment of infertility. By centring equity, science, and the imperative to provide fertility care as part of universal health coverage, the guideline aims to support countries in delivering high-quality, equitable, and effective healthcare for all. Although the guideline is primarily intended for use by health care professionals, it is an important source for policymakers to inform national guidelines and to inform the work of professional patient support, including advocacy organizations, funding and philanthropic agencies, civil society, professional societies and other nongovernmental organizations that provide social, financial and technical support to reproductive health programmes. The recommendations do not cover all aspects of infertility and fertility care, but subsequent editions of the guideline will expand the scope of recommendations. (Fertil Steril® 2026;125:359-73. ©2025 by American Society for Reproductive Medicine.)

Keywords: Infertility, pregnancy, guideline, recommendations, World Health Organization

INTRODUCTION

Infertility is a disease of the male and female reproductive systems, defined as the failure to achieve a pregnancy after 12 months of regular unprotected sexual intercourse (1, 2). Globally, approximately one in six people of reproductive age experience infertility at some stage in their lives (3). Lifetime prevalence of infertility is 17.5%, while period prevalence is 12.6%. In addition, infertility prevalence does not differ significantly between high-income (17.8%) and low- and middle-income countries (LMICs) (16.5%), or according to world regions, indicating that infertility is a global public health issue affecting people from all regions and countries (3).

A large World Health Organization (WHO) multi-country study involving 8500 couples in 25 countries found that infertility was due to female factors alone in 30.6%, both male and female factors in 26.3%, and male factors alone in 18.7% of cases (4, 5). No cause was found in 10.8% of cases (4, 5). The remaining 13.3% got pregant during study investigations. Based on this WHO study, male factors contributed wholly or in part to 45.1% of infertility cases. The most common identifiable causes of female infertility included anovulatory and oligo-ovulatory disorders (26.1%), endometriosis (4.8%), pelvic (including uterine) adhesions (14.8%), bilateral tubal blockage (17.7%), acquired tubal abnormalities (11.6%), and hyperprolactinemia (6.7%); rates of infertility due to tubal causes were higher in LMICs compared to high-income countries (4-6). Among males, identifiable causes of infertility included varicocele (13.1%), primary testicular failure (12%), and accessory gland infection (7.1%). Abnormal semen parameters (morphology and motility) were identified in 9.7% of males diagnosed with infertility (5). However, these multi-country data are relatively old and new patterns may have emerged across high-income, middle-income, and low-income settings.

Individuals and couples have the right to decide the number, timing, and spacing of their children (7); however, there is a gap between desired and actual fertility for many people in many settings (8). Addressing infertility is an important part of enabling individuals and couples to achieve their fertility preferences. WHO recognizes that the provision of high-quality services for family-planning, including fertility care services, is one of the core elements of reproductive health. The WHO guideline on infertility aims to provide recommendations related to prevention, as well as diagnosis and treatment of female-factor (tubal, ovulatory dysfunction, and uterine causes), male-factor, and unexplained-factor infertility (9). Because the recommendations in the guideline are based on current best evidence and the values and preferences of individuals and couples, it may help people to receive high-quality care and achieve their fertility preferences. This article presents a summary of the guideline recommendations.

MATERIALS AND METHODS

The guideline was developed in accordance with the 2014 WHO handbook for guideline development (10). In 2018, a WHO steering group was convened to facilitate the scoping of the recommendation questions. A Guideline Development

Group (GDG) was established, which included 30 members from different regions and with expertise in different topics related to the prevention, diagnosis, and treatment of infertility, and consisted of clinicians, researchers, implementers, and patient groups. GDG members completed and regularly updated a WHO declaration of interests (DOI) form. All declared interests are shown in Supplementary Tables S1 and S2. The votes of four GDG members were not counted on specific recommendations in which a conflict of interest existed.

The GDG met virtually on many occasions to brainstorm and prioritize questions. Outcomes identified as critical and important for decision-making included live birth rates, ongoing pregnancy rates, clinical pregnancy rates, quality of life, multiple pregnancy, miscarriage, and preterm birth. To inform the recommendations, systematic reviews of randomized and non-randomized studies were conducted *de novo* or existing reviews were updated. Searches spanned 1990 to December 2019 in MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and LILACS. Additional searches up to 2023 were conducted for selected questions. Cochrane methods for systematic reviews (11) were followed, and subgroup analyses conducted when data were available for key covariates such as body mass index (BMI) or semen parameters. A search was conducted in the Retraction Watch Database (12) for retracted studies included in the systematic reviews. Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (13), based on considerations of risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose–response, and opposing confounding. Certainty of evidence was graded as high, moderate, low, or very low. Evidence about benefits and harms was summarized in the GRADE summary of findings tables and Evidence Profiles. Evidence to decision framework tables (EtDs) were produced for each recommendation and presented to the GDG using GRADEpro online software (www.gradepro.org/).

The GDG met virtually to review and interpret the evidence, and to make judgments about the balance of desirable and undesirable consequences of the options. Consequences included the balance of benefits, harms, patients' values, certainty of evidence, costs and resources, feasibility, acceptability, and equity. Using the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations are presented using the wording '*WHO recommends* …', while conditional recommendations are worded as '*WHO suggests* …'. Strong and conditional recommendations have different implications (Table 1). Based on GRADE guidance (14), good practice statements were made in topics where the GDG agreed that the guidance was necessary, but a review of the evidence was not warranted because the benefits of the practice were unequivocal and other factors (such as equity) would not have an impact.

All decisions on recommendations were reached by discussion and consensus in virtual meetings, informed by GDG votes in GRADEPro online software indicating agreement or disagreement with recommendation statements drafted by topic leaders, the strength of the recommendations, judgments in all EtD domains, and any remarks. Recommendations with <80% agreement underwent discussion and revisions, whereas recommendations with ≥80% agreement were presented to the GDG for confirmation and a plan for addressing minor comments to improve the clarity of recommendation and accompanying EtDs. Implementation considerations were written according to discussions and comments made by the GDG. Algorithms were developed to illustrate the recommendations. The full guideline document was circulated to the GDG, reviewed and approved. An External Review Group (ERG) that included 30 clinical experts, policymakers, and patient advocates reviewed the

TABLE 1

Implications of the strengths of GRADE recommendations.

Implications	Strong recommendation WHO recommends …	Conditional recommendation WHO suggests …
For patients	• Most individuals in this situation would want the recommended course of action and only a small proportion would not. • Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	• Most individuals should receive the recommended course of action. • Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	• Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. • Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and the involvement of various stakeholders.

GRADE, Grading of Recommendations, Assessment, Development and Evaluation; WHO, World Health Organization.

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TABLE 2

General approach to management of infertility.

For males and females being evaluated and managed for infertility, it is good practice to:

• select diagnostic tests based on the clinical findings from medical history and physical examination to ensure that evaluation is systematic and cost-effective; • listen to individuals and couples, respect their preferences, discuss if psychological and social or peer support is needed, and if needed, provide it or refer patients for it; • base treatment decisions on benefits and harms, patient values and preferences, feasibility, costs and availability of resources; • consider the cost-effectiveness of treatment (e.g. least expensive, but effective treatments should be provided initially); • discuss the plan for clinical follow-up and management of potential risks that may occur during infertility treatment; • document the outcomes of pregnancies resulting from infertility treatment.	*Good practice statement*

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TABLE 3

Prevention of infertility.

For the general population of reproductive age, WHO suggests providing information about fertility and infertility using low-cost strategies or whenever there is opportunity. • Low-cost strategies may include information in digital or paper format when opportunities occur in schools, at primary health care centres or at reproductive health (contraceptive, sexual health) clinics. • Information adapted to local contexts and audiences, including how to reduce risk factors for infertility, lifestyle modification, age-related fertility decline/potential, and timely medical consultation, may increase the likelihood of information uptake and beneficial outcomes.	*Conditional recommendation, very low certainty of evidence*
For individuals and couples with infertility, WHO suggests providing low-cost lifestyle advice before and during infertility treatment. • Lifestyle advice may include advice to change diet, alcohol intake, smoking, physical activity and/or weight management.	*Conditional recommendation, low certainty of evidence*
WHO recommends that brief advice (between 30 s and 3 min per encounter) be consistently provided by health care providers as a routine practice to all tobacco users accessing any health care settings. • This is an existing WHO recommendation for the general population that also applies to individuals and couples who are planning a pregnancy, attempting to achieve a pregnancy or with infertility, given the association between infertility and current or previous history of smoking. • Assessment of lifestyle, including the use of tobacco, is part of medical history when evaluating individuals and couples for infertility. • Brief advice is advice to stop using tobacco—usually taking only a few minutes—given to all tobacco users, usually during a routine consultation or interaction. • Brief advice should include informing individuals and couples that (i) use of tobacco, particularly smoking, is associated with a higher risk of infertility; (ii) the risk of infertility due to tobacco smoking is higher among women; and (iii) a range of interventions to assist in cessation of tobacco use exist. • Brief advice should include the 5 As: *asking* about tobacco use; *advising* to make a quit attempt; *assessing* readiness to quit; *assisting* in making a quit plan; and *arranging* a follow-up. Advice should be tailored or personalized based on individual circumstances. • All adults interested in quitting smoking should be offered or referred to interventions to assist in tobacco cessation as recommended by existing WHO guidelines for preventing tobacco use uptake, promoting tobacco cessation or diagnosing and treating tobacco dependence.	*Strong recommendation, moderate certainty of evidence*
Couples and individuals planning or attempting to achieve pregnancy who are accessing any health care settings should be routinely informed about sexually transmitted infections (STIs), including the risk of infertility when STIs are untreated. Couples and individuals should be encouraged to seek prompt care and treatment if they have symptoms of STIs. • If symptoms of an STI are present, or if infection is confirmed, WHO guideline recommendations on the management of STIs are available.	*Good practice statement*

WHO, World Health Organization.

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TABLE 4

Diagnosis of female-, male-, and unexplained-factor infertility (see Figs 1, 2, and 3).

Female-factor infertility: Ovulatory disfunction	
For females with infertility but normal findings on history-taking (including regular menstrual cycles) and physical examination, WHO suggests presumptive confirmation of ovulation by measuring the level of mid-luteal serum progesterone rather than performing an ultrasound scan. For females in whom the initial mid-luteal serum progesterone indicates no ovulation, a repeat measurement is suggested to minimize the risk of an inaccurate diagnosis of anovulation. • Mid-luteal serum progesterone levels are assessed ~7 days before the expected onset of the next menses, noting that the specific cycle day can vary based on the length of the menstrual cycle. • A repeat mid-luteal serum progesterone measurement could be performed in a subsequent menstrual cycle, considering the turnaround time for tests and cycle-to-cycle variations.	*Conditional recommendation, very low certainty of evidence*
For females with infertility and suspected anovulation or oligo-ovulation, it is good practice to assess reproductive hormones related to the hypothalamic–pituitary–ovarian (HPO) axis (such as FSH and LH, and in some clinical presentations, estradiol (E2) and testosterone [T]). Additional testing (e.g. thyroid-stimulating hormone (TSH), prolactin [PRL]) may also be indicated based on the clinical presentation. The choice of diagnostic tests should be based on clinical findings from a comprehensive medical history and physical examination to ensure that evaluation is systematic and cost-effective.	*Good practice statement*
For females with infertility in whom other causes of anovulation and oligo-ovulation have been ruled out, WHO suggests that a diagnosis of low ovarian reserve should be based on age rather than diagnostic tests. If ovarian reserve diagnostic testing is conducted, WHO suggests using antral follicle count (AFC), anti-Müllerian hormone (AMH) or Day 2 or 3 FSH. • Age is the most important predictor of ovarian reserve. Therefore, ordering an ovarian reserve test in addition to age assessment may not substantially improve the accuracy of diagnosing low ovarian reserve (as assessed by poor response to stimulation). Note that the ability of age to predict ovarian reserve may be limited in some clinical scenarios, such as cases of premature ovarian insufficiency. • Selection of the test to assess ovarian reserve should be based on relative acceptability, availability, and resources in local contexts.	*Conditional recommendation, very low certainty of evidence*
Female-factor infertility: Tubal disease	
For females with infertility and suspected tubal disease, WHO suggests using either hysterosalpingogram (HSG) or hysterosalpingo contrast sonography (HyCoSy) to assess tubal patency. • When selecting whether to use HSG or HyCoSy to assess tubal patency, consider feasibility, the availability of trained health care providers and the potential for allergy.	*Conditional recommendation, low certainty of evidence*
Female-factor infertility: Uterine cavity disorder	
For females with infertility who are suspected to have a uterine cavity disorder, WHO suggests assessing the uterine cavity with saline infusion sonohysterography (SIS) rather than 3-dimensional ultrasound (3D US). • In settings where 3D US is already available within the existing resources, 3D US may be the preferred option.	*Conditional recommendation, low certainty of evidence*
For females with infertility who are suspected to have a uterine cavity disorder, WHO suggests assessing the uterine cavity with 3D US rather than 2-dimensional ultrasound (2D US) where resources are available.	*Conditional recommendation, low certainty of evidence*
For females with infertility who are suspected to have a uterine cavity disorder, WHO suggests assessing the uterine cavity with saline infusion sonohysterography (SIS) rather than 2D US.	*Conditional recommendation, low certainty of evidence*
For females with infertility due to suspected uterine cavity disorder, WHO suggests assessing the uterine cavity with saline infusion sonohysterography (SIS) rather than hysterosalpingogram (HSG).	*Conditional recommendation, very low certainty of evidence*
For females with infertility who are suspected to have a uterine cavity disorder, WHO suggests assessing the uterine cavity with either 2D US or hysterosalpingogram (HSG). • Health care providers may choose to use 2D US rather than HSG when resources are limited. Follow-up would be required for women who are negative on 2D US but still suspected of uterine cavity disorder because of high rates of false negatives.	*Conditional recommendation, very low certainty of evidence*
Male-factor infertility	
For males (in couples with infertility) with one or more semen parameters outside the WHO reference ranges, WHO suggests repeating the semen analysis after a minimum of 11 weeks.	*Conditional recommendation, very low certainty of evidence*
For males (in couples with infertility) with all semen parameters within the WHO reference ranges, WHO suggests not repeating the semen analysis. • The latest edition of the WHO laboratory manual for the examination and processing of human semen provides WHO reference ranges for semen parameters and details about the standardized procedures for semen collection and analysis.	*Conditional recommendation, very low certainty of evidence*
Unexplained-factor infertility	
WHO suggests making a diagnosis of unexplained infertility in a couple when all the following have occurred: • failure to achieve a pregnancy after 12 months of regular unprotected sexual intercourse; • normal physical examination and medical history in both the male and female; • presumptive confirmation of ovulation *and* patent tubes in the female partner; and • semen parameters that are within the WHO reference ranges in the male partner.	*Conditional recommendation, very low certainty evidence*

WHO, World Health Organization.

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recommendations and provided feedback on critical implementation considerations. The guideline was approved by WHO.

RESULTS

The GDG made a total of 40 recommendations and good practice statements, which are related to different aspects of infertility.

General approach to management of infertility

Good practice statements (n = 6) provide guidance on the general management of infertility including: (i) selection of tests, (ii) listening to individuals and couples with infertility, (iii) choosing treatment decisions, (iv) clinical follow-up, and (v) documenting outcomes of treatment as shown in Table 2.

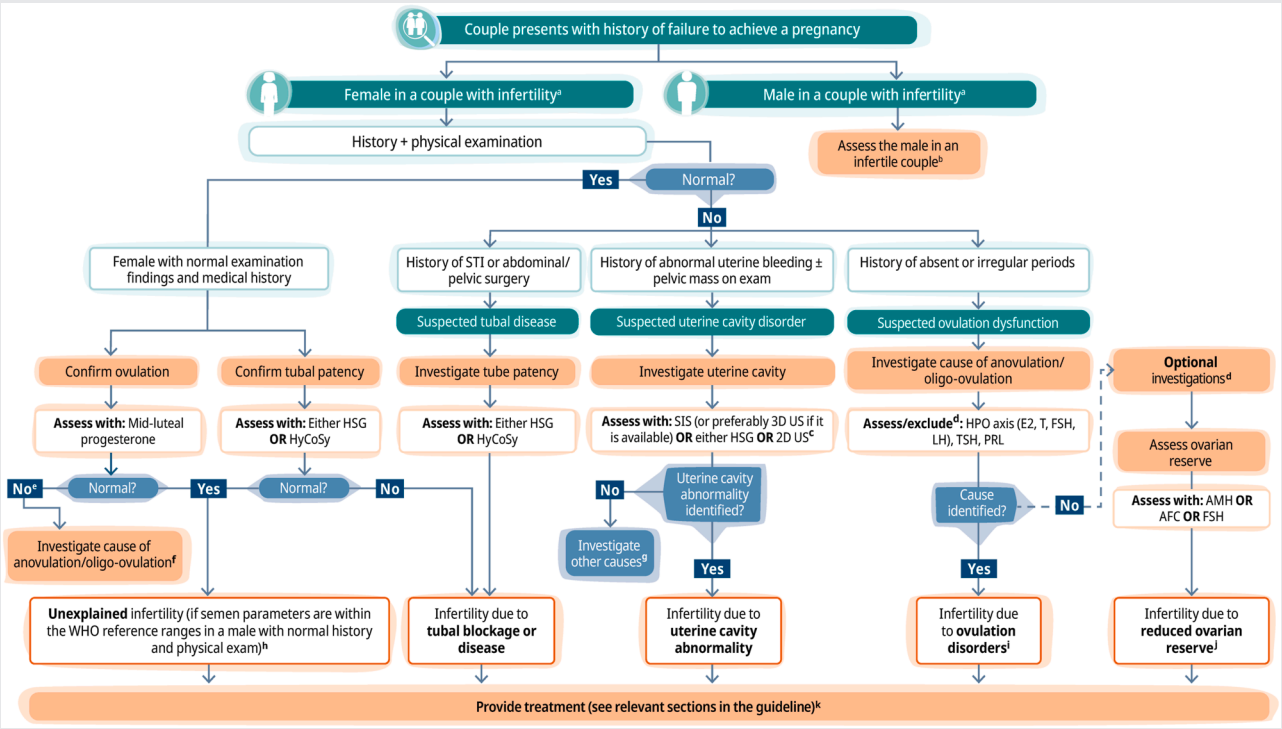
Prevention of infertility

In relation to prevention, the guideline provides recommendations related to the provision of information about fertility and infertility (n = 1) as well as reduction of infertility risk from sexually transmitted infections (STIs; n = 1), lifestyle factors (n = 1), and tobacco use (n = 1) as shown in Table 3.

Diagnosis of infertility

In terms of diagnosis, recommendations for diagnosing infertility caused by ovulatory dysfunction (n = 3), tubal disease (n = 1), or uterine cavity abnormalities (n = 5) among females are provided. For males, the guideline provides recommendations regarding when a semen test should be repeated (n = 2). Also included is a recommendation for diagnosing unexplained infertility (n = 1) (Table 4). An algorithm that elaborates recommendations related to diagnosis

FIGURE 1



Diagnostic algorithm for female-factor and unexplained-factor infertility. [a]Infertility is defined as failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. [b]See Section 5.7 in the full guideline (9). [c]See detailed diagnostic algorithm for uterine factors in Fig. 2 in this manuscript and Figure 5.2. in the full guideline (9) [d]Based on clinical findings; see Good Practice Statements in Chapter 3 in the full guideline (9). [e]Repeat if initial test result shows anovulation. [f]Follow the pathway for investigating the cause of anovulation or oligo-ovulation shown on the right side of this chart. [g]Such as adenomyosis or endometriosis. [h]See recommendation on semen analysis in Section 5.7 in the full guideline (9). [i]Such as polycystic ovarian syndrome (PCOS), functional hypothalamic amenorrhoea, premature ovarian insufficiency (POI), hypothyroidism, hyperthyroidism, hyperprolactinaemia, among others. See Sections 5.1–5.4 in the full guideline (9) [j]For example, due to advanced age, ovarian surgery, POI. [k]See Chapters 6–10 in the full guideline for treatment recommendations (9). 2D US, 2-dimensional ultrasound; 3D US, 3-dimensional ultrasound; AFC, antral follicle count; AMH, anti-Müllerian hormone; E2, estradiol; HPO, hypothalamic–pituitary–ovarian; HSG, hysterosalpingogram; HyCoSy, hysterosalpingo contrast sonography; PRL, prolactin; SIS, saline infusion sonohysterography; STI, sexually transmitted infection; T, testosterone; TSH, thyroid-stimulating hormone; WHO, World Health Organization.

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of female-factor and unexplained-factor infertility is shown in Fig. 1. Algorithms were developed to illustrate the recommendations related to the assessment of the uterine cavity (Fig. 2) as well as male-factor infertility (Fig. 3) which are represented in Table 4.

Treatment of infertility

Regarding treatment, the guideline provides recommendations related to the treatment of female-factor infertility, caused by polycystic ovary syndrome (PCOS, n = 6), tubal disease (n = 5), uterine septae (n = 1). Recommendations related to the treatment of female-factor infertility are shown in the following Table 5. Given its complexity, a treatment algorithm was developed to illustrate recommendations for anovulatory infertility due to PCOS (Fig. 4).

Recommendations related to the treatment of male-factor infertility are shown in the following Table 6. Most of these relate to the management of varicocele (n = 4). Based on available evidence, the GDG did not make a recommendation for or against the use of antioxidant supplements in males.

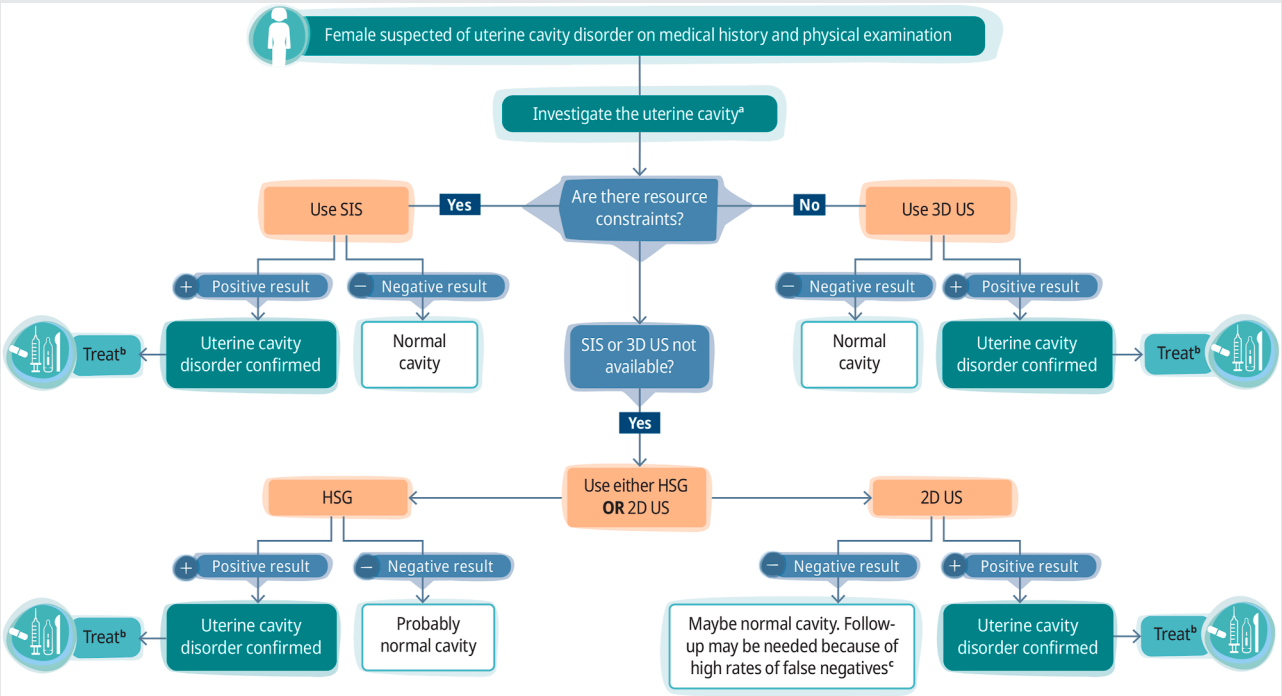
Recommendations (n = 6) and associated treatment algorithm related to the treatment of unexplained infertility is shown in the following Table 7 and Fig. 5, respectively.

DISCUSSION

This is a summary of the first WHO guideline for the prevention, diagnosis, and treatment of infertility (9), which aims to improve the implementation of evidence-based interventions related to infertility. Although the guideline is primarily intended for use by health care professionals involved in the provision of fertility care (including physicians, embryologists, nurses, midwives, laboratory specialists, and other health care providers), it will be an important source for other interest holders. Policymakers responsible for the development of national health (and other) policies, services, and financing can use these recommendations to inform national guidelines. In addition, the guideline can be used to inform the work of professional patient support organization, as well as advocacy groups, funding and philanthropic agencies, civil society, professional societies, and other nongovernmental organizations that provide social, financial, and technical support to reproductive health programmes. The guideline can also be used as an advocacy tool for evidence-based fertility care for everyone.

The recommendations in the guideline have been developed for a global audience, while many others are mostly country-or continent-specific. Its recommendations use a population perspective that considers resource considerations,

FIGURE 2



Diagnostic algorithm for the assessment of the uterine cavity. [a]See Fig. 1 of this manuscript and Figure 5.1 in the full guideline (9) for the overall diagnostic algorithm of female-factor infertility. [b]See recommendations for the treatment of uterine-factor infertility in Table 2 of this article and Chapter 8 in the full guideline (9). [c]See Table 5.7 in the full guideline (9) for the comparison of 3D US, SIS, 2D US, and HSG with hysteroscopy for the diagnosis of uterine cavity disorders. 2D US, 2-dimensional ultrasound; 3D US, 3-dimensional ultrasound; HSG, hysterosalpingogram; SIS, saline infusion sonohysterography.

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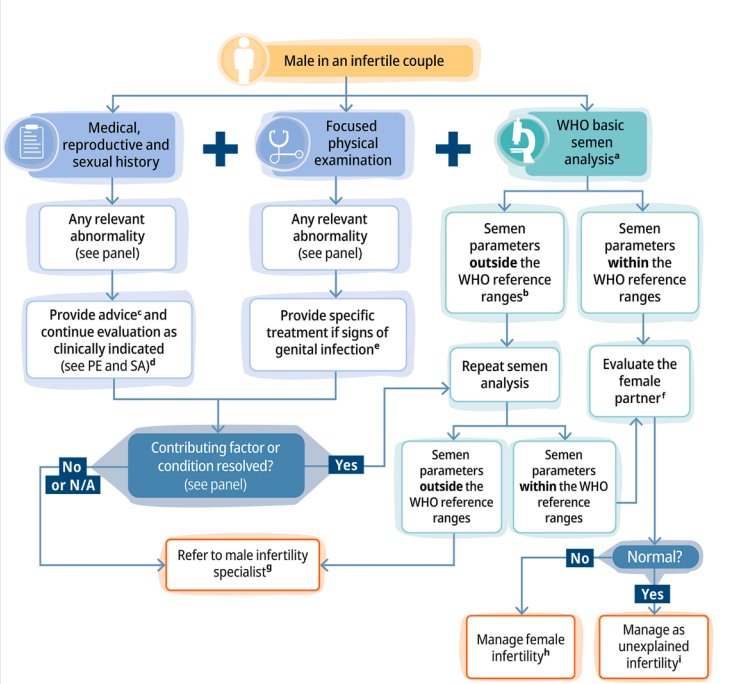
FIGURE 3



History	Components
1 Medical history	• Age • Systemic diseases (e.g. diabetes, cirrhosis, hypertension) • Sexually transmitted diseases, tuberculosis, viral infections, genital and systemic bacterial infections, history of fever, respiratory infection, anosmia • Cancers (e.g. testicular cancer, lymphoma, leukaemia) • Galactorrhoea, visual disturbances
2 Reproductive history	• Age of partner, length of time attempting to conceive • Contraceptive methods and duration • Previous pregnancy or miscarriage (current partner or another partner) • Previous treatments • Treatments or evaluations of female partner
3 Sexual history	• Potency, libido, lubricant use • Orgasm, ejaculation, timed intercourse, frequency of sex or masturbation
4 Childhood and development	• Cryptorchidism, hernia, testicular trauma, testicular torsion, infection (e.g. mumps) • Sexual development, puberty onset
5 Previous surgery or treatment	• Orchidopexy, herniorrhaphy, orchiectomy (e.g. testicular cancer, torsion) • Retroperitoneal and pelvic surgery (e.g. prostatectomy) • Other inguinal, scrotal or perineal surgery • Bariatric surgery, bladder neck surgery, transurethral resection of the prostate
6 Family history	• Cystic fibrosis, endocrine diseases • Infertility in the family
7 Gonadotoxin exposure	• Endocrine-disrupting chemicals (e.g. phthalates, bisphenol A, some pesticides, among others) • Some medication (e.g. chemotherapy agents) • Some organic solvents, heavy metals • High temperatures, ionizing radiation (e.g. high doses above recommended therapeutic or occupational levels)
8 Current health status/lifestyle	• Obesity/diet, metabolic syndrome • Anabolic steroids, tobacco smoking, alcohol

Physical exam	Components
1 Overall body characteristics	• Poor virilization, gynaecomastia • Obesity, BMI
2 Inguinal and genital areas	• Scar
3 Penis	• Hypospadias, epispadias, phimosis, curvature
4 Testes	• Location, size, consistency, pain/nodules/tenderness
5 Ductal structures (vas, epididymis)	• Present/absent • Normal/signs of obstruction or inflammation
6 Spermatic cord/scrotum	• Varicocele, hydrocele, cysts

Diagnostic algorithm for male-factor infertility. [a]See the WHO laboratory manual for the examination and processing of human semen (sixth (15) or latest edition). [b]Consider post-ejaculate urinalysis to rule out retrograde ejaculation if low (or no) semen ejaculate volume; see WHO laboratory manual for the examination and processing of human semen (sixth (15) or latest edition). [c]See Chapter 4 in the full guideline (9), for details on information provision. [d]Evaluation should include PE and SA regardless of history findings. [e]See Chapter 4 in the full guideline (9) and the WHO guideline for the management of sexually transmitted infections (16). [f]Female evaluation is essential and should proceed regardless of semen analysis outcome; see Fig. 1 in this article and Chapter 5 in the full guideline (9) for the evaluation of the female. [g]Healthcare provider with appropriate qualifications; for example, urologist, clinical andrologist, or reproductive medicine specialist with relevant qualifications. [h]See Chapters 6, 7, and 8 in the full guideline (9). [i]See Section 5.8 and Chapter 10 in the full guideline (9). N/A, not applicable; PE, physical examination; SA, semen analysis; WHO, World Health Organization.

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acceptability, feasibility, and impact on equity, in addition to traditional evidence analysis of balance between benefits and harms. It builds upon older manuals for the examination of infertile couples which were published by WHO several decades ago (17), recognizing that diagnosis and treatment have vastly improved over the last few decades. The guideline also incorporates prevention, as well as the diagnosis and treatment of male, female, and unexplained infertility, offering a single source for recommendations and intervention recommendations for both biological sexes, while emphasising a comprehensive approach.

We scoped and prioritized topics considering clinical areas where guidance was most needed, evidence was likely to be available, possibility for global reach and relevance, and the fact that resources to address recommendation questions were not infinite. This prioritization approach may raise some controversies on why we did not evaluate or recommend the most advanced diagnostic or treatment options, or why some topics were scheduled for future editions. However, the multi-country, multi-continent, and multidisciplinary GDG worked well in this respect, bringing insights regarding feasibility, impact on equity, and specific implementation considerations. Feedback from the ERG was taken seriously and each suggestion addressed on its own merit.

The guideline recommendations represent consensus from experts from all over the world who worked together for many years. The recommendations were strictly based on current best evidence. High standards, sticking with the

TABLE 5

Treatment of female-factor infertility (see Fig. 4).

Ovulatory dysfunction	
For females with infertility due to ovulatory dysfunction caused by polycystic ovary syndrome (PCOS), WHO suggests using letrozole over clomiphene citrate or metformin. Using letrozole alone rather than with metformin is suggested.	*Conditional recommendation, low certainty of evidence for letrozole compared to clomiphene citrate, low certainty evidence for letrozole compared with metformin alone, and very low certainty of evidence for letrozole compared to letrozole with metformin*
Where off-label use of letrozole is not permitted, use of clomiphene citrate with metformin rather than clomiphene citrate alone or metformin alone is suggested.	*Conditional recommendation, moderate certainty of evidence for clomiphene citrate compared to clomiphene with metformin, very low certainty of evidence for clomiphene citrate compared to metformin*
As part of management of polycystic ovary syndrome (PCOS), it is good practice to advise patients on lifestyle interventions such as a healthy diet, regular physical activity and/or weight management.	*Good practice statement*
For females with infertility due to ovulatory dysfunction caused by polycystic ovary syndrome (PCOS) who have been unsuccessful with oral pharmacological therapies such as letrozole or clomiphene citrate with metformin, WHO suggests using gonadotrophins over laparoscopic ovarian drilling (LOD).	*Conditional recommendation, low certainty of evidence*
For females with infertility due to ovulatory dysfunction caused by polycystic ovary syndrome (PCOS) who have been unsuccessful with pharmacological therapies such as letrozole, clomiphene citrate with metformin or gonadotrophins, WHO suggests IVF rather than expectant management.	*Conditional recommendation, very low certainty of evidence*
For females with infertility due to ovulatory dysfunction caused by hyperprolactinaemia, WHO suggests using cabergoline over bromocriptine.	*Conditional recommendation, low certainty of evidence*
Tubal disease	
For females aged <35 years with mild-to-moderate tubal disease (Hull and Rutherford grades I and II), WHO suggests surgery rather than IVF. • After surgery, a reasonable minimum time to wait to achieve pregnancy before pursuing other interventions, such as IVF, is 1 year. • This recommendation does not apply to females who have had previous tubal sterilization.	*Conditional recommendation, very low certainty of evidence*
For females aged <35 years with severe tubal disease (Hull and Rutherford grade III), WHO suggests IVF rather than surgery • This recommendation does not apply to females who have had previous tubal sterilization.	*Conditional recommendation, very low certainty of evidence*
For females aged ≥35 years with any tubal disease, WHO suggests IVF rather than surgery.	*Conditional recommendation, very low certainty of evidence*
For females with tubal factor infertility due to hydrosalpinx, WHO suggests either salpingectomy or tubal occlusion before provision of IVF. • When selecting whether to use salpingectomy or tubal occlusion, consider feasibility, availability of trained health care providers and presence of adhesions.	*Conditional recommendation, very low certainty evidence*
For females with tubal factor infertility caused by hydrosalpinx, WHO suggests either salpingectomy or tubal occlusion rather than transvaginal aspiration of hydrosalpingeal fluid before provision of IVF. • In settings where salpingectomy and tubal occlusion are not available or feasible, transvaginal aspiration may be offered.	*Conditional recommendation, very low certainty of evidence*
Uterine cavity disorder	
For females with infertility and uterine septum who have no history of recurrent pregnancy loss, WHO suggests that hysteroscopic septum resection (septoplasty) not be performed.	*Conditional recommendation, low certainty of evidence*

WHO, World Health Organization.

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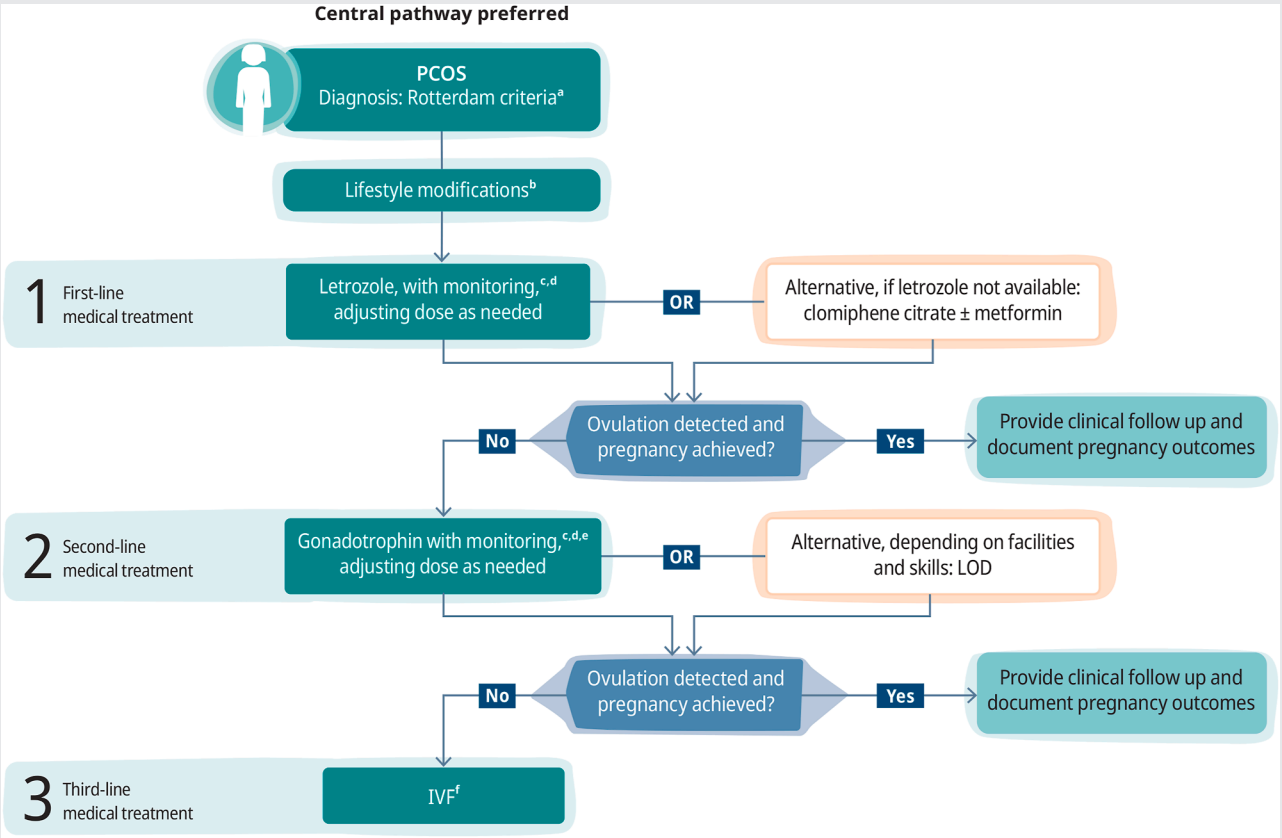
FIGURE 4



Treatment algorithm for anovulatory infertility due to PCOS. [a]Baseline investigations: 1. Diagnosis of PCOS according to the Rotterdam criteria (endocrine profile and pelvic ultrasound scan). See Chapter 6.1 in the full guideline (9). 2. Additional assessment tests may be required, including during the pre-pregnancy period. See Chapter 3 in the full guideline (9). 3. Consider assessing tubal patency. See Chapter 5.5 in the full guideline (9). 4. Assess the male partner, including semen analysis. See Chapter 5.7 in the full guideline (9). [b]Such as a healthy diet, regular physical activity and/or weight management. [c]Use repeated cycles based on shared decision-making considering age and resources. [d]Monitor patients regularly (with ultrasound as needed) and manage potential risks that may occur during treatment. See Chapter 3 and Chapter 6.1 in the full guideline (9). [e]If capacity for side-effect management exists. [f]Use IVF as third-line medical treatment unless other factors (e.g. male factors or tubal factor infertility) exist and manage potential risks (such as OHSS) that may occur during treatment. See Chapter 3 and Chapter 6.1 in the full guideline (9). LOD, laparoscopic ovarian drilling; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome. This algorithm was adapted from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome (18).

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evidence, and management of conflict-of-interests, safeguard credibility of these and other WHO recommendations (19, 20). Some recommendations are similar to recommendations from other groups (such as the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE)), while others differ from these and have the potential to change existing practice. Similarities and differences aside, a WHO guideline on infertility should be seen as strengthening the field because WHO guidelines tend to have wide reach and are often acceptable in many settings (10, 21). The guideline provides much-needed comments and guidance on presumptive confirmation of ovulation, clinical varicocele, use of ICSI for unexplained factors, among other clinical areas, and identifies evidence gaps related to the impact of antioxidant supplements among males, optimal numbers of IVF and IUI cycles, and key patient outcomes.

Many recommendations were based on low or very low certainty evidence. Despite very comprehensive searches for evidence, we identified relatively few studies from LMICs. Additionally, there was a dearth of studies on patient values, preferences, and acceptability of different interventions. We identified a need for studies to focus on patient-relevant outcomes such as time to pregnancy and live births (22). Data on the costs and cost-effectiveness of interventions were suboptimal for most interventions and very few studies assessed the feasibility of introducing interventions in different settings. Some studies had been retracted and were excluded from our evidence synthesis (23). Future studies will need

TABLE 6

Treatment of male-factor infertility.	
For males with infertility and one or more semen parameters that are outside the WHO reference ranges who are attempting to achieve pregnancy with or without medically assisted reproduction, the WHO infertility Guideline Development Group (GDG) did not make a recommendation for or against the use of antioxidant supplements. • Optimal nutrition is important during the pre-pregnancy period for the couple; however, the effects of antioxidant supplements for males with specific male-factor pathologies in couples with infertility are currently not known.	No recommendation
Varicocele	
For males with infertility and clinical varicocele, WHO suggests surgical or radiological treatment over expectant management. • Males with clinical varicocele and semen parameters that are outside the WHO reference ranges are more likely to benefit from receiving treatment for varicocele, compared to men with semen parameters within the WHO reference ranges. • This recommendation applies to males with varicoceles in couples with infertility who are not undergoing treatment with ART.	*Conditional recommendation, low certainty of evidence*
For males with infertility undergoing treatment of varicocele, WHO suggests using either surgical or radiological treatment. • When selecting whether to use surgical or radiological treatment, consider feasibility, the availability of trained health care providers and patient preferences regarding the type of treatment procedure. • This recommendation applies to males with varicoceles in couples with infertility who are not undergoing treatment with ART.	*Conditional recommendation, very low certainty of evidence*
For males with infertility undergoing surgical treatment of varicocele, WHO suggests using microscopic surgery rather than other surgical procedures. • Subinguinal microsurgery is a common surgical varicocelectomy procedure, while other surgical procedures include non-microscopic open approaches (such as inguinal and retroperitoneal) and laparoscopic methods. • In settings where the expertise to perform microscopic surgery is not available, other surgical techniques may be used. • This recommendation applies to males with varicocele in couples with infertility who are not undergoing treatment with ART.	*Conditional recommendation, very low certainty of evidence*
For males with infertility undergoing non-microscopic surgical treatment of varicocele, WHO suggests using either inguinal or retroperitoneal surgical procedures. • When selecting whether to use an inguinal or retroperitoneal surgical procedure, consider feasibility and the availability of trained health care providers. • This recommendation applies to males with varicocele in couples with infertility who are not undergoing treatment with ART.	*Conditional recommendation, very low certainty of evidence*

WHO, World Health Organization.

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to address these issues to effectively inform subsequent editions of the guideline.

Given that this is the first WHO guideline on the prevention, diagnosis, and treatment of infertility, it does not cover all aspects of infertility due to various constraints (e.g. resources). It is anticipated that subsequent editions of this guideline will have an expanded scope, allowing future recommendations to address topics that are not currently included. These include management of other personal risk factors (such as obesity, low body weight, excessive intake of alcohol, and other substances, including use of cannabis, vapes, and e-cigarettes or non-smoked/smokeless tobacco products, among others), sexual dysfunction as well as non-personal risk factors (e.g. environmental and workplace factors), fertility preservation in the context of gonadotoxic therapy, third-party reproduction (donor gametes, surrogacy), fertility care for individuals with pre-existing medical conditions that affect fertility (such as endometriosis and fibroids), hypothalamic amenorrhea, or those with obstructive, congenital, accessory gland, genital or hormonal abnormalities associated with male infertility, as well as psychosocial support for people with infertility. In males, future guidance will be needed for advanced sperm function testing, sperm retrieval techniques for obstructive and non-obstructive azoospermia, ART modalities, and non-invasive therapeutic approaches beyond antioxidant supplements. Management of PCOS involves a wide array of interventions (18) some of which are not scoped in the guideline, indicating future need for expanded scope. Guidance is also needed on the use of adjunct IVF 'add-ons', whose use is widespread (24), and how to further minimize multiple pregnancies. New and experimental interventions in infertility are emerging, including use of artificial intelligence, equipment technology, medical treatments, among others. WHO will track these and other developments for potential consideration in subsequent updates of the guideline.

The publication of the guideline recommendations will add confidence and strengthen arguments for policymakers to integrate fertility care in their reproductive health programs and agendas. For effective use of these recommendations, it is essential that the health systems at the country level create an enabling environment for the prevention, diagnosis, and treatment of infertility. This may include, for example, ensuring that infertility is included in relevant government

TABLE 7

Treatment of unexplained infertility (see Fig. 5).

First line management	
For couples with unexplained infertility, WHO suggests expectant management rather than unstimulated IUI (U-IUI). • Expectant management refers to monitoring the couple with the expectation that pregnancy will be achieved without medical intervention. It includes providing advice on lifestyle and the most fertile days of the menstrual cycle, and monitoring if pregnancy will occur; however, no medical intervention is provided. • The duration of expectant management was typically 3–6 months in studies informing this recommendation.	*Conditional recommendation, low certainty of evidence*
For couples with unexplained infertility, WHO suggests expectant management rather than ovarian stimulation with timed intercourse. • Expectant management refers to monitoring the couple with the expectation that pregnancy will be achieved without medical intervention. It includes providing advice on lifestyle and the most fertile days of the menstrual cycle, and monitoring if pregnancy will occur; however, no medical intervention is provided. • The duration of expectant management was typically 3–6 months in studies informing this recommendation.	*Conditional recommendation, low certainty of evidence*
Second-line management	
For couples with unexplained infertility, where expectant management has been unsuccessful, WHO suggests stimulated IUI (S-IUI) with either clomiphene citrate or letrozole. • When selecting whether to use clomiphene citrate or letrozole, consider the applicable national laws and regulations related to off-label use of letrozole. • The optimal number of S-IUI cycles is unknown; in the studies used to inform this recommendation, different numbers of cycles were provided, ranging from one to six, with more recent studies providing three to six cycles.	*Conditional recommendation, low certainty of evidence*
For couples with unexplained infertility, where expectant management has been unsuccessful, WHO suggests stimulated IUI (S-IUI) with either clomiphene citrate or letrozole rather than with gonadotrophins. • The optimal number of S-IUI cycles is unknown; in the studies used to inform this recommendation, different numbers of cycles were provided, ranging from one to six, with more recent studies providing three to six cycles.	*Conditional recommendation, very low certainty of evidence*
Third-line management	
For couples with unexplained infertility, where stimulated IUI (S-IUI) has been unsuccessful, WHO suggests IVF rather than expectant management.	*Conditional recommendation, low certainty of evidence*
For couples with unexplained infertility undergoing IVF after S-IUI has been unsuccessful, WHO recommends using IVF alone rather than IVF with intracytoplasmic sperm injection (ICSI).	*Strong recommendation, low certainty of evidence*

WHO, World Health Organization.

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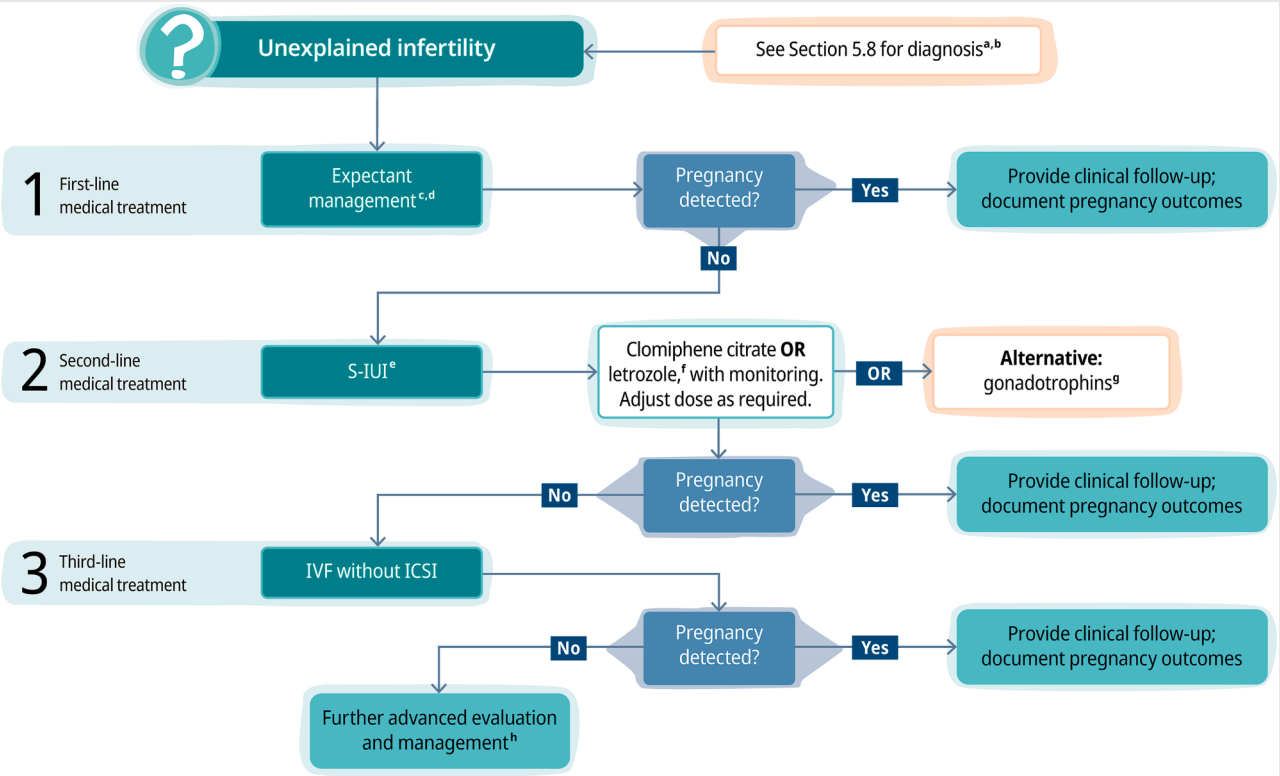
departments, health and other policies (e.g. educational or social), strategic plans, services and financing, as well as ensuring that fertility care medications are included in essential medicines lists, training is provided for health care providers on infertility, health information systems are modified to incorporate data on infertility, and national clinical guidelines are developed on infertility. Ultimately, the impact of a guideline depends on the extent to which it informs the standards of clinical care, and in turn improves patient outcomes. A basic metric of tracking this impact is by monitoring how these recommendations are adapted by countries. Countries can adapt the recommendations to suit their national needs, based on local contexts, through inclusive engagement of all local partners, including national and subnational governments, civil society, patient organizations, and professional societies of various health care providers involved in fertility care.

To enhance the uptake of the recommendations, this guideline will be disseminated through a broad network of partners, including ministries of health, international development agencies, academic institutions, professional societies, and non-governmental organizations, including non-state actors in official relations with WHO such as the American Society of Reproductive Medicine (ASRM), International Committee for Monitoring Assisted Reproductive Technologies (ICMART), and International Federation of Fertility Societies (IFFS), in collaboration with the European Society of Human Reproduction and Embryology (ESHRE), and the International Federation of Gynecology and Obstetrics (FIGO) among others. Translation of the guideline is essential (10), as is making it available in digital or online and other digital formats to improve usability (25, 26). Monitoring and evaluation should be built into the implementation process to provide important lessons to continually improve implementation. Recommendations in the guideline complement—and should be interpreted and implemented alongside—existing WHO normative guidance related to the examination and processing of human semen (15), tobacco cessation in adults (27), and management of symptomatic sexually transmitted infections (16) and antenatal care (28). We welcome collaborations with all partners on all aspects of the recommendations contained in the guideline, as we all work together to advance universal access to fertility care for all.

FIGURE 5



Treatment algorithm for unexplained infertility. [a]Infertility is defined as failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. [b]Criteria for the diagnosis of unexplained infertility: • failure to achieve a pregnancy after 12 months of regular unprotected sexual intercourse; • normal physical examination and medical history in both the male and female; • presumptive confirmation of ovulation and patent tubes in the female partner; and • semen parameters that are within the WHO reference ranges in the male partner. See Chapter 5.8 in the full guideline (9). [c]Expectant management refers to monitoring the couple with the expectation that pregnancy will be achieved without medical intervention. It includes providing advice on lifestyle and the most fertile days of the menstrual cycle, and monitoring if pregnancy will occur; however, no medical intervention is provided. [d]The duration of expectant management was typically 3–6 months in studies informing this recommendation. [e]The optimal number of S-IUI cycles is unknown; in the studies used to inform this recommendation, different numbers of cycles were provided, ranging from one to six, with more recent studies providing three to six cycles. [f]If off-label use of letrozole is allowed. [g]If capacity for side-effect management exists. [h]Individualized approach or under research conditions. S-IUI, stimulated intrauterine insemination; IVF, in vito fertilization; ICSI, intracytoplasmic sperm injection.

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SUPPLEMENTARY DATA

Supplementary data are available at *Human Reproduction* online.

DATA AVAILABILITY

The data underlying this manuscript are available in the full guideline as well as several Web Annexes containing literature reports and evidence to decision tables. These are available on the WHO website www.who.int at the following links:

Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. ISBN: 9789240115774. Licence: CC BY-NC-SA 3.0 IGO.

Guideline for the prevention, diagnosis and treatment of inferility: summary of recomendations. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B0995599

Web Annex A. Evidence to decision tables for approach to the evaluation and management of infertility. In: Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09575. Licence: CC BY-NC-SA 3.0 IGO.

Web Annex B. Evidence to decision tables for prevention of infertility. In: Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09576. Licence: CC BY-NC-SA 3.0 IGO.

Web Annex C. Evidence to decision tables for diagnosis of infertility. In: Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09577. Licence: CC BY-NC-SA 3.0 IGO.

Web Annex D. Evidence to decision tables for treatment of infertility due to male factors. In: Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World

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Web Annex E. Evidence to decision tables for treatment of infertility due to male factors. In: Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09578. Licence: CC BY-NC-SA 3.0 IGO.

Web Annex F. Evidence to decision tables for treatment of couples with unexplained infertility. In: Guideline for the prevention, diagnosis, and treatment of infertility. Geneva: World Health Organization; 2025. https://doi.org/10.2471/B09579. Licence: CC BY-NC-SA 3.0 IGO.

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Members of the ERG

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AUTHORS' ROLES

N.S. and G.M. drafted the manuscript. All named authors reviewed and provided critical inputs and approved the final version. All GDG members agreed to publish the final version.

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CONFLICT OF INTEREST

Full details of declared conflicts of interest of all named authors are shown in Supplementary Table S1; those for members of the GDG who are not named authors are shown in Supplementary Table S2; those for members of the ERG are shown in Supplementary Table S3.

DISCLAIMER

The authors alone are responsible for the views expressed in this manuscript, which do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

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