Guideline for the prevention, diagnosis and treatment of infertility

World Health Organization

human reproduction programme hrp
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Foreword

This first WHO *Guideline for the prevention, diagnosis and treatment of infertility* is grounded in the principles of equity, scientific rigour and respect for human rights. This guideline responds to the urgent need for evidence-based, person-centred, and universally accessible services for managing infertility as an integral part of sexual and reproductive health. Fertility care – which includes prevention, diagnosis and treatment of infertility – should be accessible to all who need it without stigma or discrimination.

The recommendations in this guideline are informed by the best available scientific evidence, generated through systematic reviews and robust evaluation of the benefits, harms, values, costs, feasibility and impact on equity. The guideline development process was multidisciplinary and inclusive, drawing on the expertise of clinicians, researchers, policy-makers and – critically – the lived experiences of people impacted by infertility.

Despite progress within sexual and reproductive health care, many countries still do not include the prevention, diagnosis or treatment of infertility in health policies, financing and services. There is also a pressing need for more research to better understand the epidemiology, causes and optimal management of infertility, with a particular focus on underserved and at-risk populations.

This guideline covers multiple topics and provides guidance to facilitate the provision of safe and effective services in clinical settings. Of course, infertility also involves decisions far beyond the clinic, including policy, social and non-clinical aspects, all of which must be addressed through evidence-informed interventions. The guideline calls for ongoing evidence generation to inform future editions so that fertility care continues to advance in line with scientific progress and the evolving needs of all people.

By centring equity, science and the imperative to provide fertility care as part of universal health coverage, this guideline aims to support countries in delivering high-quality, equitable and effective health care for all.

Dr Tedros Adhanom Ghebreyesus
Director-General, World Health Organization

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Abbreviations

2D US	two-dimensional ultrasound
3D US	three-dimensional ultrasound
4D US	four-dimensional ultrasound
AMH	anti-Müllerian Hormone
ART	assisted reproductive technologies
BMI	body mass index
CI	confidence interval
COI	conflict of interest
DOI	declaration of interest
DTA	diagnostic test accuracy
E2	estradiol
ERG	External Review Group
EtD	evidence to decision
FSH	follicle-stimulating hormone
GDG	Guideline Development Group
GnRH	gonadotrophin-releasing hormone
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HIC	high-income country
HOMP	high-order multiple pregnancy
HPO	hypothalamic–pituitary–ovarian
HSG	hysterosalpingogram
HyCoSy	hysterosalpingo contrast sonography
ICSI	intracytoplasmic sperm injection
IUI	intrauterine insemination
IVF	in vitro fertilization
LH	luteinizing hormone
LMIC	low- and middle-income country
LOD	laparoscopic ovarian drilling
OHSS	ovarian hyperstimulation syndrome
OR	odds ratio
OS	ovarian stimulation
PCOS	polycystic ovary syndrome
PICO	population, intervention, comparator, outcome
PRL	prolactin
RCT	randomized controlled trial
RD	risk difference
RR	relative risk
SDGs	Sustainable Development Goals
SIS	saline infusion sonohysterography
S-IUI	stimulated intrauterine insemination
STI	sexually transmitted infection
T	testosterone
TSH	thyroid-stimulating hormone
U-IUI	unstimulated intrauterine insemination
US	ultrasound
WHO	World Health Organization

Executive summary

Infertility is a disease of the male and female reproductive system defined as the failure to achieve a pregnancy after 12 months of regular unprotected sexual intercourse. Globally, approximately one in six people of reproductive age experience infertility at some stage in their lives. Lifetime prevalence of infertility does not differ between high-income and low- and middle-income countries, or according to world regions, indicating that infertility is a global public health issue affecting people from all regions and countries.

Individuals and couples have the right to decide the number, timing and spacing of their children; however, there is a gap between desired and actual fertility in many countries, implying constraints to people's ability to realize their reproductive goals because of a variety of reasons that may include infertility. Therefore, addressing infertility is an important part of enabling individuals and couples to achieve their fertility preferences.
The provision of high-quality services for family planning, including services to prevent, diagnose and treat infertility, is one of the core elements of reproductive health. However, access to fertility care remains a challenge in most countries. By acting urgently, countries have an opportunity to respond to the need for services for the prevention, diagnosis and treatment of infertility, and mitigate the many inequities in the availability, accessibility, acceptability and quality of fertility care.

This is the first WHO *Guideline for the prevention, diagnosis and treatment of infertility*, which aims to improve the implementation of evidence-based interventions related to infertility.

The objectives of this guideline are:

- to provide evidence-based recommendations for the prevention, diagnosis and treatment of infertility;
- to provide explicit explanations of all the relevant factors that guided the development of the recommendations in order to maximize the adaptation and implementation of the guideline in different settings;
- to provide a source for countries to adopt, adapt or update their national guidelines for the prevention, diagnosis and treatment of infertility.

This guideline is primarily intended for use by health care professionals (including physicians, embryologists, nurses, midwives, laboratory specialists and other health care providers) involved in the provision of fertility care.
This guideline is of interest to policy-makers responsible for the development of national health (and other) policies, services and financing because its recommendations use a population perspective that considers resource considerations, acceptability, feasibility and impact on equity.
This guideline may be used to inform the work of professional patient support, as well as 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 guideline can also be used as an advocacy tool for evidence-based fertility care for everyone.

This guideline was developed according to the methods outlined in the *WHO handbook for guideline development*. A Guideline Development Group (GDG) was assembled and included a multidisciplinary and regionally diverse set of clinicians, researchers, policy-makers, implementers and representatives of patient groups. Existing or new systematic reviews of the effects of the interventions related to the prevention, diagnosis and treatment of infertility were used to inform the recommendations. The GDG reviewed the evidence and made recommendations. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the evidence and formulate the recommendations. An External Review Group (ERG) reviewed the guideline.

The recommendations in this guideline cover the prevention of infertility, and the diagnosis and treatment of infertility due to female, male or unexplained factors. However, they do not cover all aspects of infertility and fertility care. It is anticipated that subsequent editions of this guideline will expand the scope of recommendations (see **section 12.2**).

Summary of recommendations

Table 1 presents all the recommendations included in this guideline, including the strength of the recommendation and certainty of the evidence supporting each recommendation. These recommendations are also presented in the relevant chapters of the guideline, accompanied by explanations for the judgements, appropriate diagnostic flow charts and treatment algorithms.

Table 1. Summary of recommendations and key guidance

General approach and management of infertility

Good practice statements on the general approach and 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 the medical history and physical examination to ensure that evaluation is systematic and cost-effective.** *(Good practice statement)*
- **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.** *(Good practice statement)*
- **base treatment decisions on benefits and harms, patient values and preferences, feasibility, costs and availability of resources.** *(Good practice statement)*
- **consider the cost-effectiveness of treatment (e.g. least expensive but effective treatments should be provided initially).** *(Good practice statement)*
- **discuss the plan for clinical follow-up and management of potential risks that may occur during infertility treatment.** *(Good practice statement)*
- **document the outcomes of pregnancies resulting from infertility treatment.** *(Good practice statement)*

Recommendations for the prevention of infertility

Recommendations for information provision on fertility and 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. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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.

Recommendations for information provision on fertility and infertility (cont.)

- 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.

For individuals and couples with infertility, WHO suggests providing low-cost lifestyle advice before and during infertility treatment. *(Conditional recommendation, low certainty of evidence)*

Remark:

- Lifestyle advice may include advice to change diet, alcohol intake, smoking, physical activity and/or weight management.

Recommendation for risk reduction from tobacco smoking

WHO recommends that brief advice (between 30 seconds and 3 minutes per encounter) be consistently provided by health care providers as a routine practice to all tobacco users accessing any health care settings. *(Strong recommendation, moderate certainty of evidence)*

Remarks:

- 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 5As: *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.

Recommendation for risk reduction from sexually transmitted infections

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. *(Good practice statement)*

Remark:

- If symptoms of an STI are present, or if infection is confirmed, WHO guideline recommendations on the management of STIs are available.

Recommendations for the diagnosis of female-factor infertility

Recommendations for the diagnosis of infertility due to ovulatory dysfunction

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. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- Mid-luteal serum progesterone levels are assessed approximately 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.

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 follicle-stimulating hormone (FSH) and luteinizing hormone (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)*

Recommendations for the diagnosis of infertility due to ovulatory dysfunction (cont.)

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 follicle-stimulating hormone (FSH). *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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.

Recommendation for the diagnosis of infertility due to 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. *(Conditional recommendation, low certainty of evidence)*

Remark:

- 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.

Recommendations for the diagnosis of infertility due to 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 three-dimensional ultrasound (3D US). *(Conditional recommendation, low certainty of evidence)*

Remark:

- In settings where 3D US is already available within the existing resources, 3D US may be the preferred option.

For females with infertility who are suspected to have a uterine cavity disorder, WHO suggests assessing the uterine cavity with three-dimensional ultrasound (3D US) rather than two-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 two-dimensional ultrasound (2D US). *(Conditional recommendation, low certainty of evidence)*

Recommendation for the diagnosis of infertility due to uterine cavity disorder (cont.)

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)*

Remark:

- 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.

Recommendations for the diagnosis of male-factor infertility

Recommendation for semen analysis

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. *(Conditional recommendation, very low certainty of evidence)*

Remark:

- 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.

Recommendation for the diagnosis of unexplained-factor infertility

WHO suggests making a diagnosis of unexplained infertility in a couple when all the following have occurred:

- failure to achieve 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 of evidence)

Recommendations for the treatment of female-factor infertility

Recommendations for the treatment of infertility due to 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 in vitro fertilization (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)*

Recommendations for the treatment of infertility due to 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 in vitro fertilization (IVF). *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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.

Recommendations for the treatment of infertility due to tubal disease (cont.)

For females aged < 35 years with severe tubal disease (Hull and Rutherford grade III), WHO suggests in vitro fertilization (IVF) rather than surgery. *(Conditional recommendation, very low certainty of evidence)*

Remark:

- This recommendation does not apply to females who have had previous tubal sterilization.

For females aged ≥ 35 years with any tubal disease, WHO suggests in vitro fertilization (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 in vitro fertilization (IVF). *(Conditional recommendation, very low certainty evidence)*

Remark:

- When selecting whether to use salpingectomy or tubal occlusion, consider feasibility, availability of trained health care providers and presence of adhesions.

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 in vitro fertilization (IVF). *(Conditional recommendation, very low certainty of evidence)*

Remark:

- In settings where salpingectomy and tubal occlusion are not available or feasible, transvaginal aspiration may be offered.

Recommendation for the treatment of infertility due to 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)*

Recommendations for the treatment of male-factor infertility

Recommendation on the use of antioxidants

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.

Remark:

- 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.

Recommendations for the treatment of varicocele

For males with infertility and clinical varicocele, WHO suggests surgical or radiological treatment over expectant management. *(Conditional recommendation, low certainty of evidence)*

Remarks:

- 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 varicocele in couples with infertility who are not undergoing treatment with assisted reproductive technology (ART).

For males with infertility undergoing treatment of varicocele, WHO suggests using either surgical or radiological treatment. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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 varicocele in couples with infertility who are not undergoing treatment with assisted reproductive technology (ART).

Recommendations for the treatment of varicocele (cont.)

For males with infertility undergoing surgical treatment of varicocele, WHO suggests using microscopic surgery rather than other surgical procedures. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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 assisted reproductive technology (ART).

For males with infertility undergoing non-microscopic surgical treatment of varicocele, WHO suggests using either inguinal or retroperitoneal surgical procedures. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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 assisted reproductive technology (ART).

Recommendations for the treatment of unexplained infertility

Recommendations for first-line management of couples with unexplained infertility

For couples with unexplained infertility, WHO suggests expectant management rather than unstimulated intrauterine insemination (U-IUI). *(Conditional recommendation, low certainty of evidence)*

Remarks:

- 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.

Recommendations for first-line management of couples with unexplained infertility (cont.)

For couples with unexplained infertility, WHO suggests expectant management rather than ovarian stimulation with timed intercourse. *(Conditional recommendation, low certainty of evidence)*

Remarks:

- 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.

Recommendations for second-line management of couples with unexplained infertility

For couples with unexplained infertility, where expectant management has been unsuccessful, WHO suggests stimulated intrauterine insemination (S-IUI) with either clomiphene citrate or letrozole. *(Conditional recommendation, low certainty of evidence)*

Remarks:

- 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.

For couples with unexplained infertility, where expectant management has been unsuccessful, WHO suggests stimulated intrauterine insemination (S-IUI) with either clomiphene citrate or letrozole rather than with gonadotrophins. *(Conditional recommendation, very low certainty of evidence)*

Remark:

- 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.

Recommendations for third-line management of unexplained infertility

For couples with unexplained infertility, where stimulated intrauterine insemination (S-IUI) has been unsuccessful, WHO suggests in vitro fertilization (IVF) rather than expectant management. *(Conditional recommendation, low certainty of evidence)*

For couples with unexplained infertility undergoing in vitro fertilization (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)*

Chapter 1 Introduction

This chapter provides background information on infertility, including its epidemiology and the need to strengthen global efforts to prevent, diagnose and treat it.

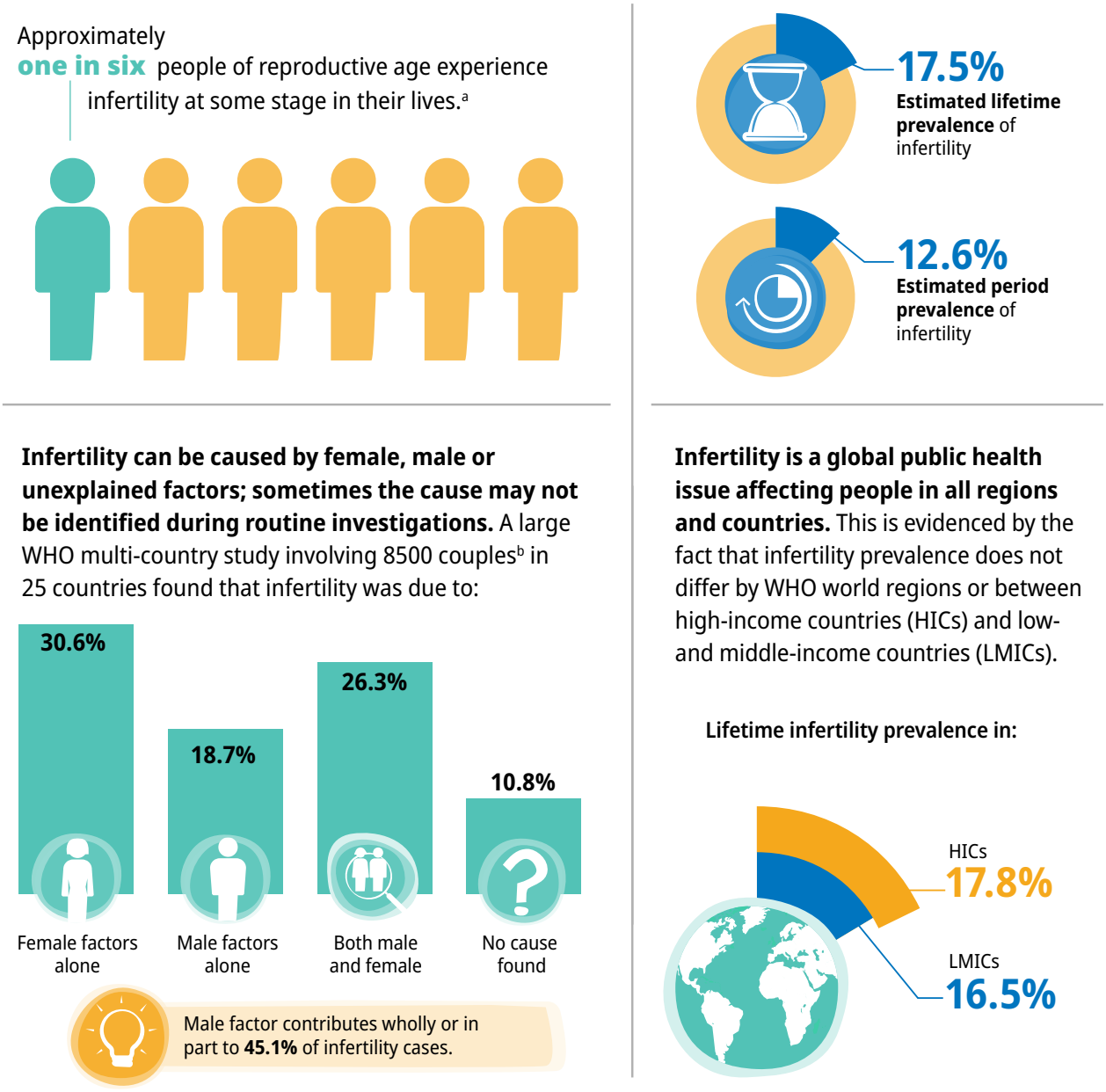
1.1 Epidemiology and global burden of infertility

Infertility is a disease of the male and female reproductive system, which is defined as the failure to achieve a pregnancy after 12 months of regular unprotected sexual intercourse *(1, 2)*. Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved, and secondary infertility is when at least one prior pregnancy has been achieved. Individuals and couples have the right to decide the number, timing and spacing of their children *(3)*. Persons of full age, without any limitation due to race, nationality or religion, have the right to marry and found a family *(4)*. However, there is a gap between desired and actual fertility in many settings *(5)*, implying constraints to people's ability to realize their reproductive goals because of several reasons that may include infertility. Therefore, addressing infertility is an important part of enabling individuals and couples to achieve their fertility preferences. Addressing infertility will enable individuals and couples to exercise their sexual and reproductive health and rights and achieve their desired family size.

Globally, approximately one in six people of reproductive age experience infertility at some stage in their lives *(6)*. Lifetime prevalence of infertility is 17.5%, while period prevalence is 12.6%. In addition, infertility prevalence does not differ significantly between high-income and low- and middle-income countries (LMICs), or according to world regions, indicating that infertility is a global public health issue affecting people in all regions and countries *(6)*. Although the overall period and lifetime prevalence is similar across regions, the distribution of the underlying risks of infertility (such as postpartum infections, unsafe abortions and some sexually transmitted infections [STIs]) can vary across countries and regions and potentially cause differences in the patterns of primary versus secondary infertility *(6–8)*. Using different definitions and methodological approaches, the numbers of people affected by infertility were estimated to be 186 million individuals in 2004 *(9)* and 48.5 million couples in 2010 *(10)*. (See **Fig. 1.1**).

Classically, each type of infertility can be attributed to congenital or acquired causes *(11)*. The former stem from abnormalities in the development of the genital tract in either males or females *(11)*. Infertility in both males and females can be associated with impairments affecting any portion of the hypothalamic–pituitary–gonadal axis and reproductive organs (i.e. testes, ducts and penis in males, and ovaries, uterus, fallopian tubes, cervix and vagina in females). In general terms, these reproductive impairments are often associated with congenital or acquired abnormalities, genetic aberrations, urogenital infections, malignancies, endocrine disturbances, gonadotoxic exposures, sexual dysfunction, immunological abnormalities, iatrogenic factors and other physiological factors such as age *(12, 13)*. In general, less is known about male causes of infertility than female causes; of those causes that can be identified in the male, fewer are amenable to corrective treatment.

Fig. 1.1. Epidemiology and global burden of infertility



[a] See more details in WHO infertility prevalence estimates 1990–2021 *(6)*.
[b] 13.3% became pregnant in the course of study investigations. See details in Cates et al., 1985 *(14)* and WHO, 1992 *(15)*.

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 *(14, 15)*. No cause was found in 10.8% of cases *(14, 15)*. The remaining 13.3% became pregnant during investigations. Based on this study, male factors contributed wholly or in part to 45.1% of infertility cases. In this study, 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%). In this study, rates of infertility due to tubal causes were higher in LMICs compared to high-income countries *(14–16)*.

Among males, identifiable causes of infertility included varicocele (13.1%), primary testicular failure (12.0%) and accessory gland infection (7.1%). Abnormal semen parameters (morphology and motility) were identified in 9.7% of males diagnosed with infertility *(14)*. In this study, male factors contributed wholly or in part to 45.1% of infertility cases *(14)*. However, these multi-country data are relatively old and new patterns may have emerged across high-income, middle-income and low-income settings (see **Annex 1. Distribution of the causes of infertility**).

In the absence of more recent epidemiological studies, there are knowledge gaps and uncertainty regarding the precise proportions of infertility caused by male, female, both male and female or unexplained factors in the general population of reproductive age. Many studies and systematic reviews quantifying the relative contributions of these factors are based on clinic samples *(17)* in single countries *(18)* or on samples with restricted inclusion criteria *(6)*, which together with the varying extents of selection and investigation of each partner, makes it difficult to determine an unbiased prevalence of these causes among global populations of reproductive age.

In terms of risk factors, the most consistent predictive factor of infertility is increasing female/maternal age *(19–22)*. In both males and females, infertility is also associated with lifestyle risk factors such as smoking *(23–26)*, excessive alcohol intake *(27, 28)*, obesity *(29)*, underweight *(30)*, as well as sexually transmitted, reproductive tract, and other pelvic infections *(31, 32)*, although evidence is not equally strong across these factors *(33)*. Exposure to environmental endocrine-disrupting chemicals can interfere with the reproductive system, resulting in poor quantity or quality of gametes, and potentially contributing to infertility *(34–37)*; however, definitive conclusions cannot be made based on the available data *(37)*. Several causal diagnoses may be present simultaneously and may be coincidental or causal (e.g. an STI-induced pathology in both male and female partners). The temporal or geographical contribution of specific etiological factors, such as postpartum or post-abortion infections, genital tuberculosis, schistosomiasis, iatrogenic causes and female genital mutilation is uncertain. For many etiologies, there are knowledge gaps in the natural history and sequence of intermediate sequelae that lead to infertility. In summary, the relative prevalence of the causes and risk factors for infertility differ from country to country *(16)* and there is a lack of comprehensive data in many countries.

The possibility for multiple factors to contribute to infertility in a couple, as well as variations in definition, data collection methods and outcomes reported in existing studies, continue to pose measurement challenges *(38, 39)*. Temporal epidemiological trends in infertility may also be modified by global efforts to address STIs, unsafe abortions and other risk factors, as well as demographic trends. Declining total fertility rates *(40, 41)*, rising maternal and paternal age at first birth *(42–44)* and possible temporal and geographical declines in reported semen parameters *(45, 46)*, could potentially contribute to a greater need for prevention, diagnosis and treatment of infertility; however, the influence of paternal age on fecundity, compared to maternal age *(47)*, is less certain; declines in semen parameters have not been observed universally among all male populations *(48)* and semen parameters per se are not a reliable diagnostic indicator of male fertility status *(49, 50)*.

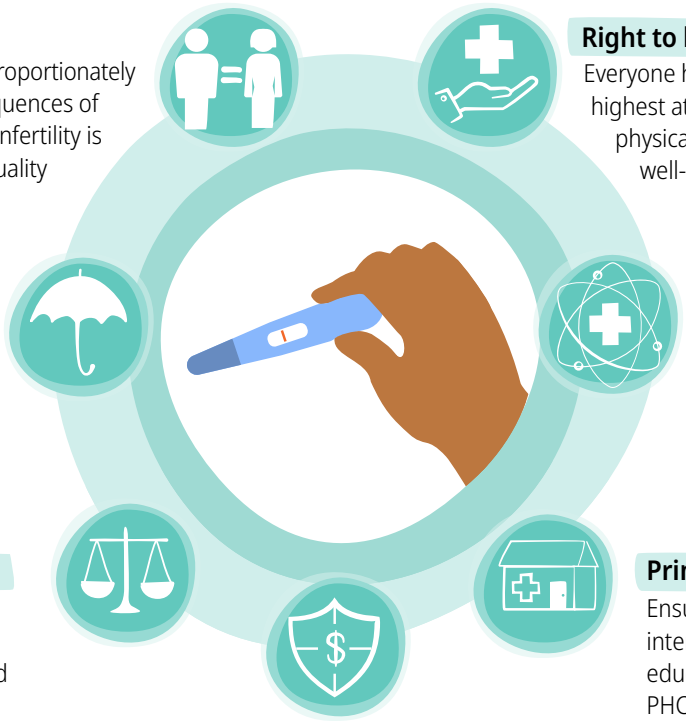
To quantify causes more clearly, it is necessary to distinguish between the inability to achieve pregnancy, the inability to carry a pregnancy to a live birth and the failure of a live birth to survive, all of which contribute to involuntary childlessness. Although infertility is an important cause of involuntary childlessness, other biomedical (e.g. pregnancy loss), biopsychosocial (e.g. sexual dysfunction) or non-biomedical (e.g. legal, regulatory, cultural or social) situations may impede individuals' ability to have children *(51, 52)*. Desire or intentions for parenthood in otherwise

fertile populations can be modified by multiple concerns *(53, 54)*. A wide variety of people may not be infertile, as they have biological reproductive capacity, but could need interventions to have children and fulfil their fertility preferences.[1]

Overall, better epidemiological data relating to the extent and causes of infertility, and the need for fertility care arising because of different reasons, are required to inform health (and other) policies and services.

1.2 The need to strengthen global efforts to prevent, diagnose and treat infertility

Fig. 1.2. Addressing infertility is central to human rights and global health aspirations



Gender equality
Women are often disproportionately affected by the consequences of infertility. Addressing infertility is relevant to gender equality

Right to health
Everyone has a right to enjoy the highest attainable standard of physical, mental and social well-being

Universal health coverage (UHC)
Prevention, diagnosis and treatment of infertility should be integrated into health services and systems

Right to enjoy the benefits of scientific progress and its applications
Interventions like assisted reproductive technologies (ARTs) have a role to play in addressing infertility

Equitable access to health care
Infertility should be consistently included in health policies, services and financing

Primary health care (PHC)
Ensuring that basic interventions such as fertility education are available at the PHC level will contribute to enhanced service coverage

Financial protection
Given the risk of large out-of-pocket costs for preventing, diagnosing or treating infertility, fertility care should be provided while upholding financial protection

The **Universal Declaration of Human Rights** (Article 16) states that "men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and found a family" *(4)*. A significant proportion of young adults in demographic health surveys express a desire

[1] Because of the need to refer to biological sex characteristics on clinical grounds, this guideline uses terms such as male and female (in its recommendations), and men and women (in text synthesizing research) to indicate biological sex assigned at birth, and uses "couples" to refer to heterosexual partnerships. However, a wide variety of people, including individuals who are single or who are in same-sex or gender-diverse relationships, may need services to fulfil their fertility preferences. Providers of fertility care should consider the needs of, and provide equal care to, all individuals.

for children *(55–58)* and infertility can prevent the ability of individuals to achieve their preferences regarding the number, timing and spacing of their children. Services for the prevention, diagnosis and treatment of infertility are an essential element of reproductive health care included in the 1994 International Conference on Population and Development call to action, to, among others, achieve universal access to a full range of reproductive health services *(59)*. A wide variety of individuals and couples may require infertility management and fertility care services *(60)*; individual circumstances should not lead to discrimination.

Addressing infertility is central to the achievement of the **right to health**. Every human being has a right to the enjoyment of the highest attainable standard of physical, mental and social well-being. Infertility has a negative impact on mental well-being, relationships and quality of life *(61, 62)* and is associated with a high prevalence of intimate partner violence *(63)*. Therefore, improving access to prevention, diagnosis and treatment of infertility is needed to mitigate the negative health and psychosocial consequences of infertility. The right to health is closely linked with the ***right to enjoy the benefits of scientific progress and its applications*** *(64)*. Although assisted reproductive technologies (ARTs) and a range of other interventions may have a role in partially compensating for postponement of births *(65-67)*, demographic changes and declines in total fertility rates should not be used as a basis for restricting or coercing access to fertility care and other reproductive services *(68)*; instead, health (and other) policies and services should be aimed at facilitating the achievement of people's fertility goals and preferences through a rights-based approach *(69)*.

Addressing infertility is also relevant to **gender equality**. Women are often disproportionately affected by the consequences of infertility *(62, 70, 71)* and tend to bear the blame for infertility in couples *(9, 72)*. Infertility also affects men's mental health and well-being *(73)*, yet its impact is often concealed because of stigma, masculine norms *(74)* and low participation of men in infertility studies and services *(75–77)*. Many social norms stigmatize infertility and affect reproductive decision-making in women and men. (See **Fig. 1.2**).

Addressing infertility is necessary to enhance **equitable access to health care**. Infertility is not consistently included in health policies, services and financing. Consequently, access to fertility care remains a challenge for many people. Although worldwide provision of in vitro fertilization (IVF) has increased over time *(78)*, there are marked disparities in the availability, accessibility, acceptability and quality of services for preventing, diagnosing and treating infertility between regions, countries and populations *(79, 80)*. Only about half of all couples with infertility seek any form of infertility services *(81)*, but this can vary from country to country *(82)*. Although many reasons prevent access to fertility care, cost is among the most common barriers, particularly in settings that do not have fully funded fertility care *(80, 83, 84)*. It is the responsibility of Member States to put in place legislative frameworks, determine eligibility criteria and facilitate equitable access to fertility care for those in need. Member States have an obligation to facilitate access to health care, including preventing infertility and enabling access to diagnostic and treatment services *(85, 86)*. By acting urgently, countries have an opportunity to respond to the need for services for the prevention, diagnosis and treatment of infertility and mitigate the many inequities in access to safe and effective fertility care.

Efforts to achieve **universal health coverage** should include measures to address the needs of people with infertility by integrating the prevention, diagnosis and treatment of infertility into sexual and reproductive health services and wider health systems. It is essential to ensure that services for infertility are available, accessible, acceptable and of good quality. This will require having supportive health (and other) policies to ensure that all people have access to services to prevent, diagnose and treat infertility that they need, when and where they

need them. However, in many countries, infertility services and policies are not prioritized or included in health systems, including services or financing *(87–89)*. Achieving universal health coverage will require provision of health financing, trained personnel, medicines, equipment, infrastructure and effective monitoring of services through robust health information systems. Ensuring that fertility care is provided while upholding **financial protection** is essential given the risk for catastrophic expenditures because of out-of-pocket costs. People often incur large out-of-pocket costs to access services for preventing, diagnosing or treating infertility *(83, 90)*. In addition, ensuring that basic fertility care interventions are available at the **primary health care** level will contribute to enhanced service coverage.

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Chapter 2 Rationale and methodology

This chapter presents information on the rationale, overall goals and methodology used to develop this guideline.

2.1 Rationale

This guideline responds to requests from Member States, organizations, institutions and health care providers for evidence-based norms and standards related to infertility. Despite the high burden of disease, infertility is often neglected *(1, 2)*. Management of infertility is continually evolving. Absence of clear guidelines contributes to inconsistent outcomes and variable practices and can exacerbate existing disparities. Implementation of best practices that emphasize cost-effective interventions is a key strategy to reduce disparities in access to services.

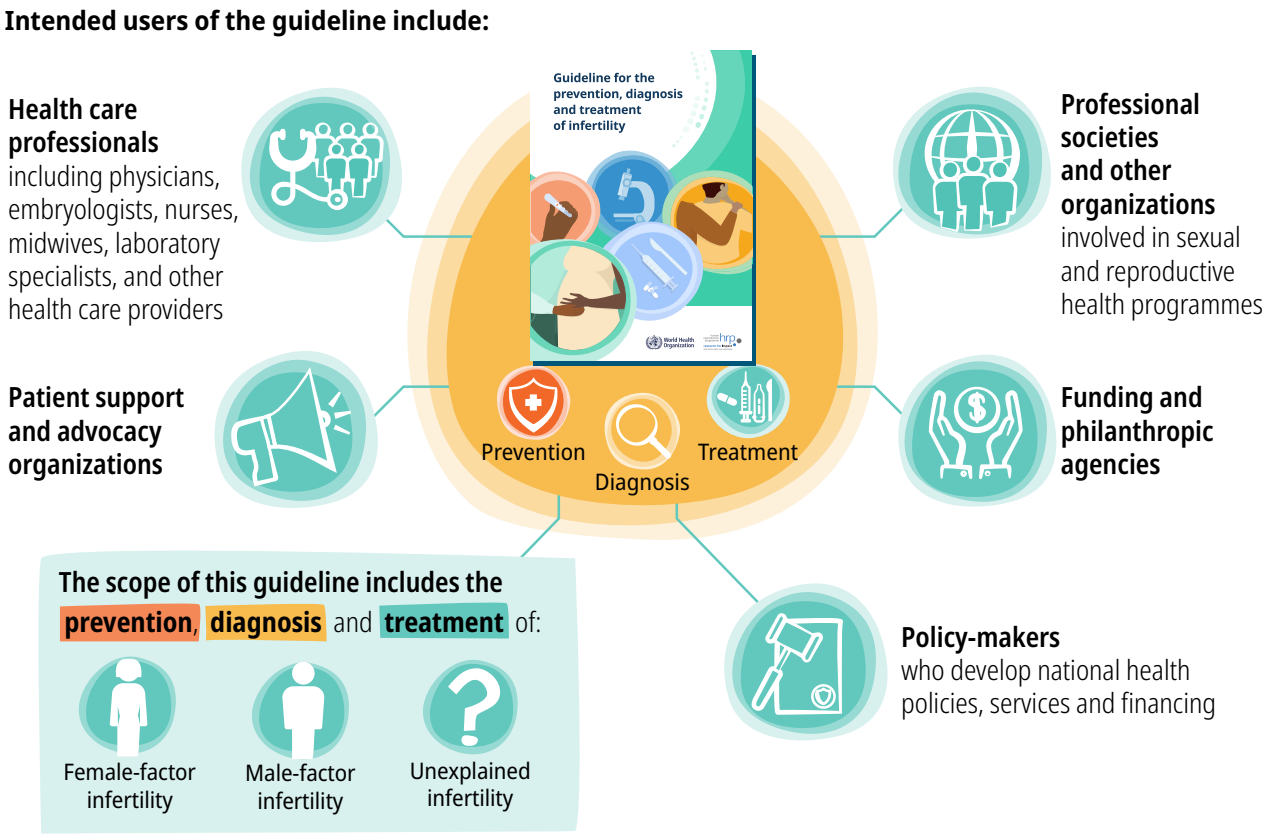
This guideline underscores the importance of infertility as a global public health issue. The prevention, diagnosis and treatment of infertility is an integral component of comprehensive sexual and reproductive health, and is aligned with Sustainable Development Goal (SDG) 3, which aims to ensure healthy lives and promote well-being for all at all ages, and SDG 5, which aims to achieve gender equality and empower all women and girls. Prevention, diagnosis and treatment of infertility is also needed to ensure universal access to sexual and reproductive health care, and to achieve universal health coverage.

2.2 Goals and objectives

The goal of this guideline is to provide evidence-informed guidance for the prevention, diagnosis and treatment of infertility to improve the standard of fertility care globally, with a focus on public health perspective. The objectives are:

- to provide evidence-based recommendations for the prevention, diagnosis and treatment of infertility;
- to provide explicit explanations of all the relevant factors that guided the development of the recommendations in order to maximize the adaptation and implementation of the guideline in different settings;
- to provide a source for countries to adopt, adapt or update their national guidelines for the prevention, diagnosis and treatment of infertility.

Fig. 2.1. Scope and audience



2.3 Scope

This guideline provides recommendations related to prevention, as well as diagnosis and treatment of female-factor (tubal, ovulatory dysfunction and uterine causes), male-factor and unexplained infertility.

Given that this is the first WHO guideline on the prevention, diagnosis and treatment of infertility, it does not cover all aspects of infertility and important gaps remain. It is anticipated that subsequent editions of this guideline will have an expanded scope, allowing it to address topics that are not included currently, including management of other risk factors (such as obesity, low body weight, excessive intake of alcohol and other substances (including use of cannabis, use of vapes and e-cigarettes, or non-smoked/smokeless tobacco products, among others) and sexual dysfunction, as well as non-individual 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), or with obstructive, congenital, accessory gland, genital or hormonal abnormalities associated with male infertility, as well as psychosocial support for people with infertility. These topics received relatively limited attention in this first version (based on initial scoping) and will be considered in subsequent editions.

2.4 Target audience

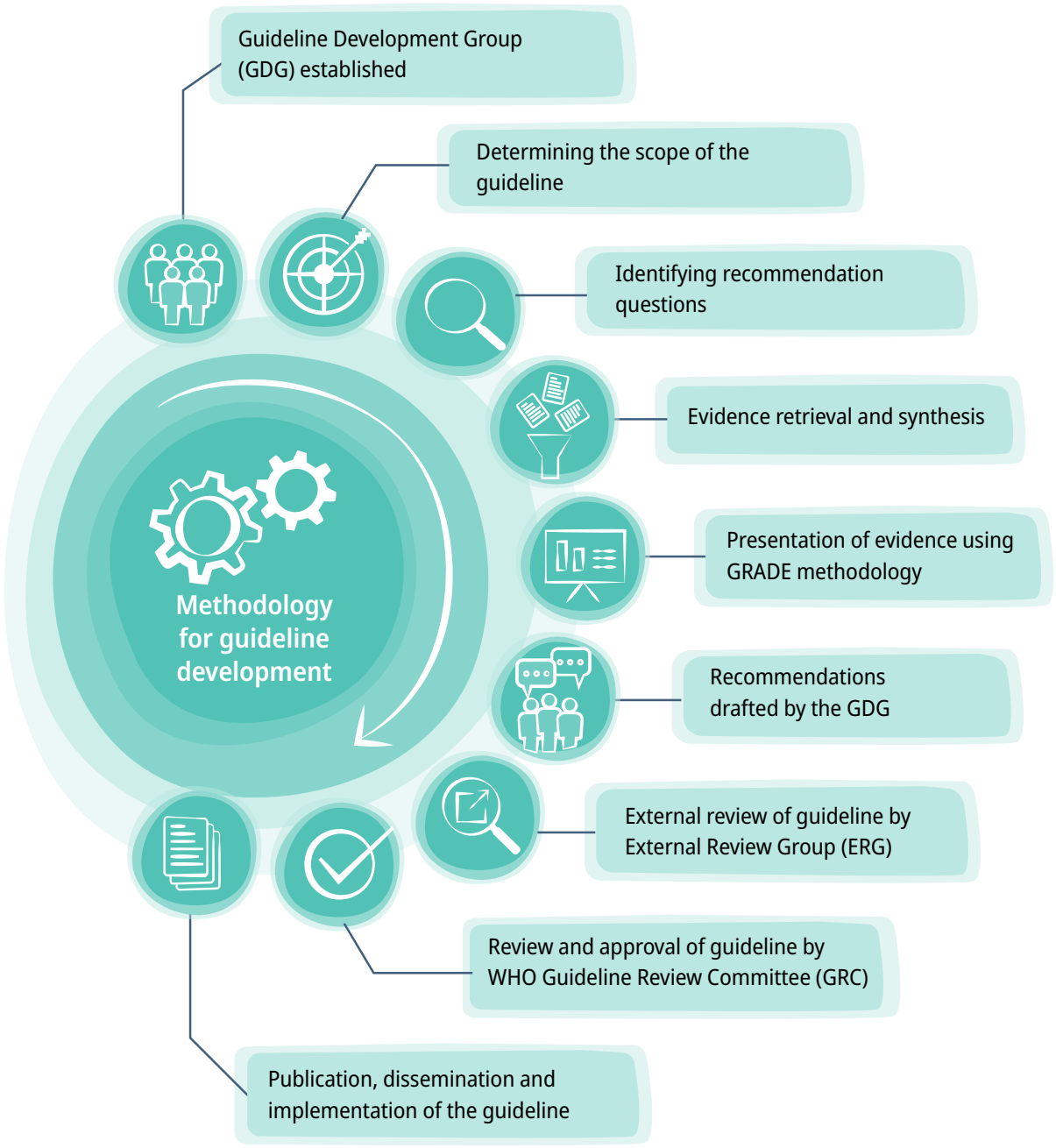
This guideline is primarily intended for use by health care professionals, including physicians, embryologists, nurses, midwives, laboratory specialists and other health care providers, involved in the care of individuals or couples with infertility in primary, secondary and tertiary settings in both the private and public sectors. This guideline is of interest to policy-makers responsible for the development of national health (and other) policies, services and financing, as its recommendations use a population perspective that considers resource needs, acceptability, feasibility and impact on equity. The recommendations have been developed through a public health lens. This guideline can be used to inform the financial and human resources required to deliver adequate, acceptable and equitable fertility care for all populations in need. In addition, this guideline may be used to inform the work of patient support and advocacy organizations, mental health professionals, funding and philanthropic agencies, civil society, professional societies and other nongovernmental organizations that provide social, financial and technical support to sexual and reproductive health programmes. The guideline can also be used as an advocacy tool to ensure adequate, acceptable and equitable fertility care for everyone. (See **Fig. 2.1**)

2.5 Guiding principles

The following principles have informed the development of this guideline and should guide the implementation of the recommendations:

- Development of the guideline **responds to unmet need for guidance for a specified audience**.
- Implementation of the guideline should inform and **contribute to national goals and relevant global targets**, including attainment of SDG 3 (to ensure healthy lives and promote well-being for all at all ages) and SDG 5 (to achieve gender equality and empower all women and girls).
- Implementation of the guideline should ensure that the prevention, diagnosis and treatment of infertility is considered an integral component of **sexual and reproductive health and rights** and should be aimed at achieving **universal health coverage**.
- Implementation of the guideline needs to be accompanied by efforts to promote and protect the **right to health** of people with or at risk of infertility.
- Implementation of the guideline should be based on a **public health approach** as a key strategy to reduce access disparities, by ensuring all populations in need of such services are reached with interventions to prevent, diagnose and treat infertility, including populations in low-resource settings.
- Implementation of the recommendations in this guideline should be informed by **local context**, including epidemiology and prevalence of infertility, the values and preferences of local populations or patients and feasibility, as well as the organization and capacity of the health system. Other contextual considerations may be related to demographic resilience, fertility and demographic trends, which require policies geared towards the achievement of universal access to sexual and reproductive health and rights.

Fig. 2.2. Methodology for guideline development



2.6 Methods

This guideline was developed in accordance with the 2014 WHO handbook for guideline development *(3)*. (See **Fig. 2.2**).

Guideline Development Group

A WHO steering group was convened to facilitate the scoping of the guideline, including priority topics related to the prevention, diagnosis and treatment of infertility. The steering group consisted of WHO staff members from different departments in WHO. A systematic review lead and guideline methodologist were appointed by the WHO steering group. The WHO steering group consulted with experts, clinicians,

researchers, patient organizations and other key stakeholders and established the WHO Infertility Guideline Development Group (GDG), which included 30 members from different regions and with expertise in different topics related to the prevention, diagnosis and treatment of infertility. The GDG consisted of clinicians, researchers, implementers and patient advocate groups (see **Annex 2. Members of the GDG**). A Chair and co-Chair were appointed to lead the GDG meetings. Two leaders were also assigned to each subtopic within the scope of the guideline.

External Review Group

An External Review Group (ERG) that included 30 clinical experts, policy-makers and patient advocates was established. The ERG reviewed the recommendations and provided feedback on critical implementation considerations (see **Annex 3. Members of the ERG**).

Determining the scope of the guideline and recommendation questions

In 2018, the WHO Infertility GDG met virtually to define the scope of this guideline. The WHO GDG provided input, which was used to brainstorm and prioritize questions. The questions were divided into subtopics: prevention and information provision, and diagnosis and treatment of infertility due to female factors, male factors and unexplained factors. Recommendation questions were developed using the population, intervention, comparator, outcome (PICO) framework, related to diagnostic tests, surgical and medical treatments, and information provision (see **Web Annexes A–F** for the guideline for the prevention, diagnosis and treatment of infertility). The GDG identified outcomes that included live birth rates, ongoing pregnancy rates, clinical pregnancy rates and quality of life, multiple pregnancy, miscarriage, preterm birth and other relevant adverse events. Based on input from a virtual meeting with the GDG, the WHO Steering Group finalized the prioritized PICO questions, which then formed the basis for systematic reviews.

Retrieval and synthesis of evidence

Systematic reviews were conducted by the Michael G. DeGroote Cochrane Canada Centre at McMaster University. The team took a hierarchical approach and searched for published systematic reviews, and then primary studies when no review was available, or updated a review when out-of-date. The systematic reviews assessed the benefits and harms of the interventions (and diagnostic tests), as well as acceptability, feasibility, equity and resource requirements. Searches for randomized or non-randomized studies were conducted from 1990 up to December 2019 in multiple databases including MEDLINE, Embase, Cochrane Central Register of Controlled Trials and LILACS. Additional searches up to 2023 were conducted for selected questions. Based on feedback from the GDG, targeted monitoring of evidence (and an updated search) was conducted for selected guideline questions in which new studies were likely to be published, allowing results from new studies to potentially be added to evidence summaries. If a study was published after the search and was identified by the GDG to likely have an impact on the recommendation, it was also incorporated into the review. Cochrane methods for conducting systematic reviews *(4)* were followed: using a comprehensive search strategy; duplicate screening of articles; duplicate assessment of risk of bias using study-design-specific tools; data abstraction by one investigator and verification by another; and synthesis through meta-analysis (using RevMan) when possible, otherwise performing a narrative synthesis. Subgroup analyses were conducted when data were available for key parameters that could affect outcomes such as body mass index (BMI) or semen parameters.

Because of concerns about the number of retracted papers in the field of reproductive medicine, a search was conducted in the Retraction Watch Database version 1.0.8.0 (https://retractiondatabase.org/) for studies included in the systematic reviews. When a study was retracted or under investigation, it was excluded from the pairwise meta-analyses and new calculations were made, or new analyses were sought in the case of network meta-analyses.

Presentation of the evidence

Tables to facilitate decision-making for recommendations (evidence to decision [EtD] frameworks) were produced for each recommendation and presented to the GDG using the GRADEpro online software (www.gradepro.org/). These tables include a summary of the problem – test (diagnostic) accuracy; summary of the evidence for benefits and harms (including for different subgroups); certainty of the evidence; relevant patient values and preferences; and other issues, such as cost, resources, feasibility, equity and acceptability. **Table 2.1** illustrates how each of the EtD factors influences a guideline recommendation.

Table 2.1. Evidence to decision framework

Domain	Favours strong recommendations	Favours conditional recommendations
Balance of benefits and harms	Benefits highly outweigh harms or vice versa	Benefits and harms are more closely balanced
Quality of evidence	Higher certainty	Lower certainty
Values/preferences regarding outcomes	Benefits to harms assessment not impacted by variability in values or preferences	Variability in values or preferences would impact benefits to harms assessment
Acceptability	Highly acceptable	Low or variable acceptability
Costs/resources	Cost-saving/cost-effective	Costly/cost-ineffective
Feasibility	Feasible in intended settings	Unfeasible or feasibility varies in intended settings
Equity	Increased equity	Decreased equity or effect on equity is variable

The certainty of the body of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach *(5)*, based on considerations of risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose–response and opposing confounding. Based on these criteria, the overall certainty of evidence was defined as follows:

- high (we are very confident that the true effect lies close to that of the estimate of the effect);
- moderate (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 (we have limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect);
- very low (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect).

The evidence about benefits and harms was summarized in the GRADE summary of findings tables and Evidence Profiles that contained the estimates of the effect (in relative and absolute terms), and the assessments of the certainty of evidence (see **Web Annexes A–F** for the evidence to decision tables).

Review of evidence and drafting of recommendations

The GDG met virtually to review the evidence. Because of the complexity of developing the

recommendations, several subgroup virtual meetings were held with the topic leaders to further review the evidence before or after GDG meetings and draft judgements (with explanations) for each EtD factor, as well as recommendations (with justifications). The GDG assessed the EtDs, judged on different considerations and voted on their agreement or disagreement with the draft recommendations using GRADEpro Panelvoice (www.gradepro.org/panelvoice). Judgements about benefits and harms were based on the direction and size of the estimated effects and the uncertainty in those effects (GRADE-level evidence), not on whether the effect was statistically significant (i.e. avoiding the misinterpretation that "not statistically significant" means "no effect" *[6]*).

Making of recommendations

During the GDG meetings, judgements for each of the criteria of the EtD made during voting were discussed and the GDG recommendation drafts were confirmed or revised. A methodologist facilitated the process during the GDG meetings, and the Chair and co-Chair led the discussions. 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 …". These were arrived at after consideration of the various domains of the EtD framework. Strong and conditional recommendations have differing implications, as shown in **Table 2.2**.

Table 2.2. Implications of differing 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.

When addressing patients' values (for which there was no research evidence available), judgements about the most important outcomes and the likelihood of variability across people were made by the GDG. It was agreed that, across the recommendation questions, the most important

outcome for people was live birth. It was also agreed that there was probably no important variability across people on how they trade off outcomes. The value placed on these outcomes were considered for all recommendations.

All decisions on recommendations were reached by discussion and consensus in virtual meetings, informed by the voting about agreement or disagreement using the GRADEPro online software, including the strength of the recommendations, and where appropriate, the remarks for each recommendation. Before the process, the group decided that any recommendation with less than 80% agreement would undergo discussion and revisions, whereas recommendations with more than 80% agreement would be presented to the GDG for confirmation and a plan for addressing minor comments to improve the clarity of the EtD frameworks. In cases where there was disagreement, additional evidence and data were requested and reviewed, additional discussions were held with topic leaders, and recommendations were redrafted and posted for virtual voting, with the goal of reaching a consensus. In all cases, the percentage of panel members in disagreement and their reasons or comments were summarized and shared with the topic leaders. Additional guidance to facilitate the implementation of the guideline recommendations in different settings was also written according to discussions and comments made by the GDG. The full guideline document was circulated to the GDG, reviewed and approved.

Good practice statements

Good practice statements were made in topics where 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. Good practice statements were rooted in the fact that answers were deemed obvious by the GDG. The methodologist guided the development of good practice statements based on existing GRADE guidance *(7)*.

Implementation considerations and research gaps

Implementation considerations highlighting critical elements that facilitate the appropriate application of recommendations *(8)* were drafted and presented to the GDG for their input, comments or agreements. Research gaps summarized important questions that needed to be addressed in each topic.

Management of conflicts of interest

Management of conflicts of interest (COIs) was a priority throughout the guideline development process. Before assuming their roles, all external contributors to the guideline, including members of the GDG, completed a WHO declaration of interests (DOI) form in accordance with WHO policy for experts. A brief biography of each GDG member was published on the WHO website for 14 days before the first meeting of the GDG. No public comments or objections were received.

The DOI forms were reviewed by the WHO Secretariat; statements therein were summarized and a management plan was developed and documented. At the beginning of guideline development, three invited members of the GDG were identified as having COIs. The Secretariat consulted with the Department of Compliance and Risk Management and Ethics and jointly determined that one member could participate fully, a second could participate as temporary adviser and a third was excluded from the GDG. During the development of the guideline, DOIs were updated by each GDG member every 2 years. After analysing the updated DOI, the WHO Secretariat concluded that four GDG members had a COI. These GDG members were not excluded from participating but their votes were not counted on specific PICOs where they had a COI. None of the members of the ERG were determined to have COIs that required exclusion from reviewing the guideline; however, consideration of comments from several ERG members was restricted on several topics based on their declared interests (see **Annexes 4** and **5** for the summary of declared interests from members of the GDG and ERG, respectively).

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Chapter 3 Approach to evaluation and management of infertility

This chapter provides information on the objective and key steps involved in the clinical assessment and management of infertility.

Relevant resources

Annex 6. Components of female medical history and physical examination

Annex 7. Components of male medical history and physical examination

Web Annex A. Evidence to decision tables for approach to the evaluation and management of infertility

3.1 Objective

The objective of a comprehensive evaluation is to facilitate prompt diagnosis and treatment of infertility, while mitigating predisposing risk factors in order to enhance the chances of achieving a pregnancy.

3.2 Indication

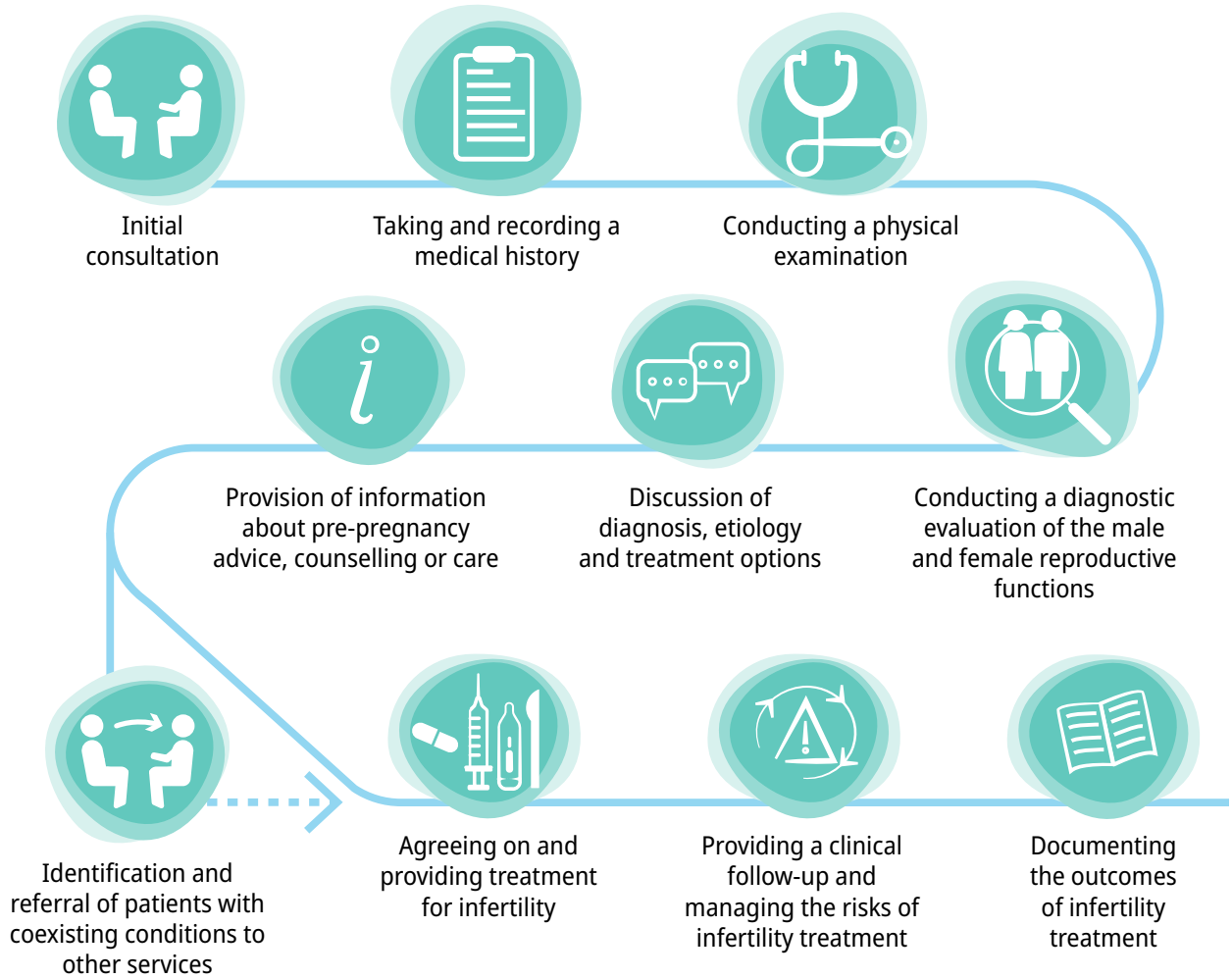
Evaluation of both the female and male partners is initiated simultaneously to provide prompt diagnosis of infertility before commencing treatment. A diagnosis of infertility is arrived at if there is failure to achieve a pregnancy after 12 months of unprotected intercourse *(1)*.

WHO defines infertility as failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.

3.3 Elements of evaluation and management

Fig. 3.1. Elements of evaluation and management

The basic evaluation and management of infertility includes the following components:



Initial consultation

The first contact with a health provider is often initiated by patients, especially females, with concerns about a delay or failure to achieve pregnancy. The disproportionate blame for infertility placed on females can result in them seeking care unaccompanied by their male partners. In other cases, infertility may come up in the context of other health issues. Specific complaints and symptoms are identified during the initial consultation. In all cases, it is essential that there is a conducive and private environment to enable individuals and couples to freely discuss their complaints or concerns with the health care provider.

It is important for health care providers to anticipate and manage privacy, which can affect (or cause discomfort with) the disclosure of sensitive information among couples with infertility. Interactions with people with infertility may involve some loss of privacy *(2–4)*. Although it is helpful to interview the couple together for history-taking, creating opportunities for interviewing each partner separately can be more gender-sensitive because it can avail additional or sensitive information; some questions are better asked when either partner is alone, for example, history of previous sexual partners, pregnancies, STIs and intimate partner violence, among others. These questions can be asked conveniently at the same time as the physical examination is performed *(5, 6)*.

Taking and recording medical history

A comprehensive history is important in establishing the likelihood of infertility and potential risk factors that could be contributing to it. Some readily apparent causes of infertility can be identified through a comprehensive medical history and examination. It is important for health care providers to be non-judgemental in their approach to history-taking.

For females, key aspects of medical history include obstetric history, pregnancy history, duration of attempting to get pregnant, menstrual history, past medical and surgical history, gynaecological history (including previous investigations or treatment for infertility), history of STIs, sexual history (including frequency and timing of sex, and sexual dysfunction), childhood and developmental history, family history, occupational history (including history of potential gonadotoxic exposure) and a review of systems, current health status, lifestyle (including tobacco smoking, alcohol and substance use) and medications (see **Annex 6. Components of female medical history and physical examination**).

For males, history typically covers past medical history, reproductive history, sexual history (including STIs, erectile dysfunction, ejaculatory dysfunction and injuries to reproductive organs), duration of attempting to achieve pregnancy, past medical and surgical history (including previous investigations or treatment for infertility), childhood and developmental history, family history, occupational history (including history of potential gonadotoxic exposure) and a review of systems, current health status, lifestyle (including tobacco smoking, alcohol and substance use) and medications (see **Annex 7. Components of male medical history and physical examination**.)

Conducting a physical examination

A focused physical examination is essential. The scope and procedures for the physical examination of couples are outlined in the *WHO manual for the standardized investigation and diagnosis of the infertile couple (6)*. For females, a targeted physical examination may include vital signs, BMI, breast examination, thyroid examination, examination of the external genitalia, speculum/vaginal examination and a bimanual pelvic examination, which includes an examination of the vaginal, cervical, uterine and pelvic anatomy (see **Annex 6. Components of female medical history and physical examination**).

For males, a focused physical examination includes assessment of vital signs and BMI, examination of the body characteristics (such as poor virilization, gynaecomastia or obesity), inguinal and genital areas (for scars), external genitalia including the penis (for hypospadias, epispadias, phimosis or curvature), testes (for location, size, texture, consistency, pain, nodules or tenderness), vas deferens and epididymis (if present, absent, inflamed or obstructed), and the spermatic cord and scrotum (for varicocele, hydrocele or cysts) (see **Annex 7. Components of male medical history and physical examination**).

Health care providers should inform patients what the examination will entail, obtain consent and conduct the examination in privacy, under hygienic conditions and in the presence of a chaperone if required. If presence of a chaperone is not feasible (e.g. because of staff shortage), health care providers should obtain consent from the patients to be examined without a chaperone. All findings should be recorded.

Conducting a diagnostic evaluation of the male and female reproductive functions

The basic diagnostic evaluation includes the following:

- Semen analysis. The procedures for the evaluation and interpretation of a semen analysis are included in the *WHO laboratory manual for the examination and processing of human semen (7)*, which is updated regularly (see **Chapter 5.4** for recommendations on semen analysis);
- Assessment of ovulation and ovulatory function (see **Chapter 5.1** for recommendations on confirmation of ovulation, assessment of reproductive hormones and assessment of ovarian reserve);
- Assessment of the fallopian tubes (see **Chapter 5.2** for recommendations related to the diagnostic evaluation of fallopian tubes);
- Assessment of the uterus (see **Chapter 5.3** for recommendations on diagnostic evaluation of the uterine cavity).

Good practice statement

For males and females being evaluated and managed for infertility, it is good practice to select diagnostic tests based on the clinical findings from the medical history and physical examination to ensure that evaluation is systematic and cost-effective.

Discussion of diagnosis, etiology and treatment options

The purpose of the initial and any additional diagnostic tests is to identify the cause(s) of infertility, which could be due to female factors, male factors, a combination of these or unexplained factors, which can then be treated to improve fertility outcomes. There may be specific underlying causes of infertility, such as fibroids, endometriosis, ovarian damage caused by prior ovarian surgery, infection, obstruction, varicocele, chemotherapy and radiation therapy, among others. An important consideration is age-related fertility decline, particularly in females. As the number of oocytes in the ovaries decreases progressively through atresia *(8, 9)*, fecundity decreases with increasing age *(10)*. Information about the causes of infertility, including age, comorbidities, previous STIs, reproductive tract and other pelvic infections, lifestyle and behavioural factors (including exercise, BMI, diet and the use of alcohol and tobacco products), and environmental and occupational factors, will be helpful to patients (see **Chapter 4.2** on information provision for couples with infertility and **Chapter 4.3** on risk reduction from use of tobacco).

Informing patients about the diagnostic and treatment options is important. When discussing treatment options, it is important to inform patients about the inter-pregnancy interval, the fertility window (as appropriate) and the likelihood of pregnancy and live birth in the context of parental goals and desired family size. Patients seeking fertility care are often anxious or worried about their diagnosis of infertility *(11–13)* but the ability of health care providers to identify the psychological and emotional support needs of patients is often suboptimal *(14)*. Patients may require supportive psychosocial services on-site or via referrals.

Good practice statement

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

Provision of pre-pregnancy advice, counselling or care

The goal of providing pre-pregnancy advice, counselling or care for individuals with pregnancy intentions is to reduce the risk of adverse reproductive and obstetric outcomes by improving or optimizing health, addressing modifiable risk factors during the pre-pregnancy or peri-conception period. Providing information on factors that can increase the risk of infertility is an important part of pre-pregnancy advice, counselling and care. It provides an opportunity to assess lifestyle, improve health status and modify behaviours and other individual, behavioural and environmental factors that could contribute to poor pregnancy outcomes around the time of conception *(15)*. It also provides an opportunity to review medications, immunization status, nutritional status and carrier and other genetic conditions, such as neural tube defects *(15)*. Nutrition is important during pre-pregnancy or the peri-conception period for a couple, and a balanced diet provides many vitamins and trace elements that are essential for good health *(16)*.

Identification and referral of patients with coexisting conditions to other services

Multiple health conditions may affect the ability to achieve pregnancy and subsequent pregnancy outcomes. Such comorbidities may coexist alongside

infertility or may contribute to infertility itself. Comorbidities may include communicable (such as STIs) or noncommunicable (such as cancer, cardiovascular disease, diabetes, and poor mental health) conditions. Depending on the capacity of the health care system, patients may need to be referred to other specialities or centres for appropriate management of the identified comorbidities. Some patients with coexisting conditions may be identified and managed easily on-site, while others may require referral to a specialist for a thorough workup and management, to ensure that no comorbidities are missed.

Agreeing on and providing treatment for infertility

Based on the identified causes of infertility, it is essential to provide appropriate treatment without unnecessary delay. Treatment is provided after agreeing with patients about the treatment approach and obtaining informed consent, based on collaborative decision-making and transparent information from health care providers about treatment expectations and what is involved. Treatment should be evidence-based and should adhere to the non-maleficence principle (first do no harm); great care must be taken not to induce any pathology in the mother or the offspring *(5)*. The diagnostic pathway, referral and management plan for either partner ought to be informed by the results of the tests of the other partner, and be progressively adjusted to optimize efficiency. For example, in some couples presenting initially with an isolated pathology in one partner, a relevant complementary pathology may thereafter be identified in the other partner during investigations, which may alter the overall management plan *(5)*. See the following chapters for recommendations related to treatment of infertility because of ovulatory dysfunction (**Chapter 6**), tubal disease (**Chapter 7**), uterine cavity disorders (**Chapter 8**), male factors (**Chapter 9**) and unexplained factors (**Chapter 10**).

Good practice statements

For males and females being evaluated and managed for infertility, it is good practice to base treatment decisions on benefits and harms, patient values and preferences, feasibility, costs and availability of resources.

For males and females being evaluated and managed for infertility, it is good practice to consider the cost-effectiveness of treatment (e.g. least expensive but effective treatments should be provided initially).

Providing a clinical follow-up and managing the risks of infertility treatment

While IVF and other fertility treatments are generally safe, a variety of risks can be encountered, which may range from minor side-effects to serious complications, such as multiple pregnancy, ovarian hyperstimulation syndrome (OHSS), infections and iatrogenic adverse effects. Infertility patients may also be exposed to a variety of risks due to cross-border reproduction, disease epidemics or natural disasters. Patients with infertility often travel long distances to access fertility care; depending on the health care system context, they may occasionally come under interim care of health care providers who have less knowledge of infertility treatments, for example, in geographically underserved areas. In some countries, the health system may require transfer of patients to other health care providers for ongoing care after infertility treatment has been provided. Although information about the plan for clinical follow-up and management of potential risks that could occur during treatment of infertility and how to mitigate risks is desired by patients *(17, 18)*, health care providers do not always provide it *(19)*. It is important for health care providers to discuss clinical care plans and how potential risks can be managed with their patients, as part of a wider safety and risk management strategy for fertility care services.

Good practice statement

For males and females being evaluated and managed for infertility, it is good practice to discuss the plan for clinical follow-up and management of potential risks that may occur during infertility treatment.

Documenting the outcomes of infertility treatment

Many individuals and couples seeking pregnancy are generally highly motivated; however, treatment dropout rates can be high for several reasons *(20–22)*, and among patients who complete their treatment journey, outcomes may vary. Antenatal guideline recommendations are provided by WHO to facilitate a positive pregnancy experience while enhancing continuity and quality of care throughout pregnancy and ensure good outcomes *(23)*. However, reporting of the outcomes of infertility treatment, including of resulting pregnancies, by health care providers is often suboptimal. Improved documentation of outcomes is required to verify the effects of infertility treatment and facilitate monitoring, surveillance and quality improvement of fertility care. Depending on the health care system context and capacity, the following may be required: referrals; integrated reporting or better data connectivity in health information systems, which enables linking ART and other medically assisted reproduction registries; birth and neonatal registries; and other electronic health records.

Good practice statement

For males and females being evaluated and managed for infertility, it is good practice to document the outcomes of pregnancies resulting from infertility treatment.

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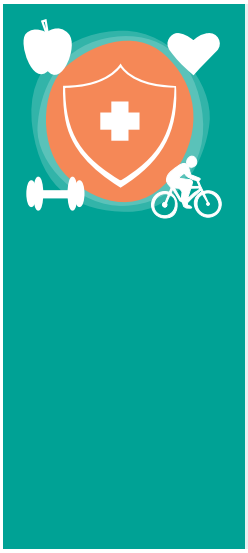
Chapter 4 Prevention of infertility

This chapter presents several recommendations related to the prevention of infertility.

Relevant resources

Web Annex B. Evidence to decision tables for prevention of infertility

4.1 Information provision on fertility and infertility for the general population



Recommendation

For the general population of reproductive age, WHO suggests providing information about fertility and infertility using low-cost strategies or whenever there is opportunity. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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.

Background and rationale

Education about fertility and infertility can be provided at various stages of the reproductive lifespan, for example, to the general population who may consider conceiving in the future, individuals who are trying to achieve a pregnancy, people who are at high risk of infertility or those who are already experiencing infertility.

Information on fertility and infertility can be provided at different time points in relation to risk factors that limit fertility: (i) before the risk factor is present; (ii) when the risk factor is present but not yet fertility-limiting (population is at risk); or (iii) when the disease is present (population has infertility). The present recommendation applies to the general population not at risk of infertility.

For the general population, fertility education can include information on fertility potential, risk factors for infertility and how to reduce risk factors or improve healthy lifestyle factors in general. The aim of information provision in this (presumed fertile) population is to improve fertility awareness and future pregnancy planning. Fertility awareness is defined as the "understanding of reproduction, fecundity, fecundability, and related individual risk factors (e.g. advanced age, sexual health factors such as sexually transmitted infections (STIs), and lifestyle factors such as smoking, obesity) and non-individual risk factors (e.g. environmental and workplace factors); including the awareness of societal and cultural factors affecting options to meet reproductive family planning, as well as family building needs" *(1)*.

Fertility education can be provided through a variety of methods, including information pamphlets, brochures, counselling and online platforms, such as websites, videos or animations, mobile applications or other information tools aimed at increasing public awareness about fertility and infertility. It can be provided individually or in group settings. Other preventive interventions can also be provided to the general population to reduce risk factors that go beyond simply education, such as nutrition and fitness and wellness programmes. Recommendations for these types of interventions are not addressed in this guideline but will be in the future.

For this recommendation, the GDG addressed the question: should information on fertility and infertility be provided to the general population or people who are not at risk or not?

Fig. 4.1. Information on fertility and infertility

Providing information on fertility and infertility to people of reproductive age **helps reduce risk factors and promotes timely care-seeking.** It also enables reproductive planning.

Schools / educational institutions
Integrate into health education

Primary care
During routine health visits and checkups

Sexual health
Family planning and reproductive clinics

Understanding infertility
What infertility is, common causes, when to seek help and available support options for individuals and couples

Healthy lifestyle
Risk factors include:
- smoking,
- excessive alcohol use,
- obesity,
- being underweight,
- others (see **Chapters 1** and **4** of this guideline).

Age-related fertility decline
Understanding fertility potential changes with age especially among females

Sexual health
Untreated sexually transmitted infections can cause infertility

Balancing harms and benefits

A systematic review was conducted and identified nine trials (10 publications) that reported on the effects of specific information provision interventions on a group of participants. Two trials recruited women presenting at primary care clinics *(2)* or to donate oocytes *(3)*. Two trials recruited women visiting midwives for contraceptive counselling *(4, 5)*. Four trials recruited adolescents and young adults *(6–10)* and one trial involved women of reproductive age *(11)*. One study included men *(8)*. All studies compared an education intervention to a control or no intervention. Specific education interventions addressed in these trials included:

- fertility-related brochures *(3, 6, 8, 9, 11)*;
- fertility-related slide presentations *(10)*;
- reproductive life plan counselling *(2–5)*;
- informative fertility awareness videos *(7)*;
- fertility education chatbot *(11)*.

When considering the effects of all information provision interventions compared to a control or no intervention, evidence indicated that there may be small benefits. Knowledge is likely increased with education, but intentions to improve pre-pregnancy behaviours or optimally plan for

pregnancy (e.g. advanced intended timing of childbirth or the age of the first or last child) are likely minimally changed or inconsistently affected. The GDG was uncertain about the effects of education on live births (54 more [from 11 fewer to 226 more] per 1000; relative risk [RR]: 2.12; 95% confidence interval [CI]: 0.78–5.71 after 1 year of follow-up; 42 more [from 31 fewer to 146 more] per 1000; RR: 1.22; 95% CI: 0.84–1.76 after 2 years of follow-up) and there were no data on pregnancy. The GDG was also uncertain about whether education may accelerate the timing of childbirth: in one study *(8)*, where the sample mean age was 30–31 years, there was a fivefold increase in new births at 12 months among partnered individuals in the intervention group compared to the control group; however, both groups had similar numbers of new births at 24 months.

In terms of undesirable effects, the GDG judged that information provision probably results in a trivial increase in anxiety levels compared to no information provision (mean difference: 1.94 higher with education; 95% CI: 1.18–2.7 higher on the State subscale of the State-Trait Anxiety Inventory score; score range: 20–80) *(12)*.

Overall, the GDG agreed that there may be greater benefit than harm with fertility information provision, but the certainty of evidence was very low because of few participants or events, high heterogeneity and potential risk of bias because of poor randomization and incomplete data. Given that outcomes such as live births and pregnancy are probably the most important to most individuals trying to achieve pregnancy, the GDG agreed that providing education is probably favoured.

Other considerations

Provision of information requires resources and results in additional costs when applied population-wide. The GDG judged that the resources required for fertility education vary depending on context and the methods used to disseminate information. Some modalities, such as brochures or pamphlets, cost less when compared to other interventions, such as counselling. Therefore, when costs are low, small and uncertain benefits could outweigh the costs but the downsides of high-cost interventions would outweigh potential benefits.

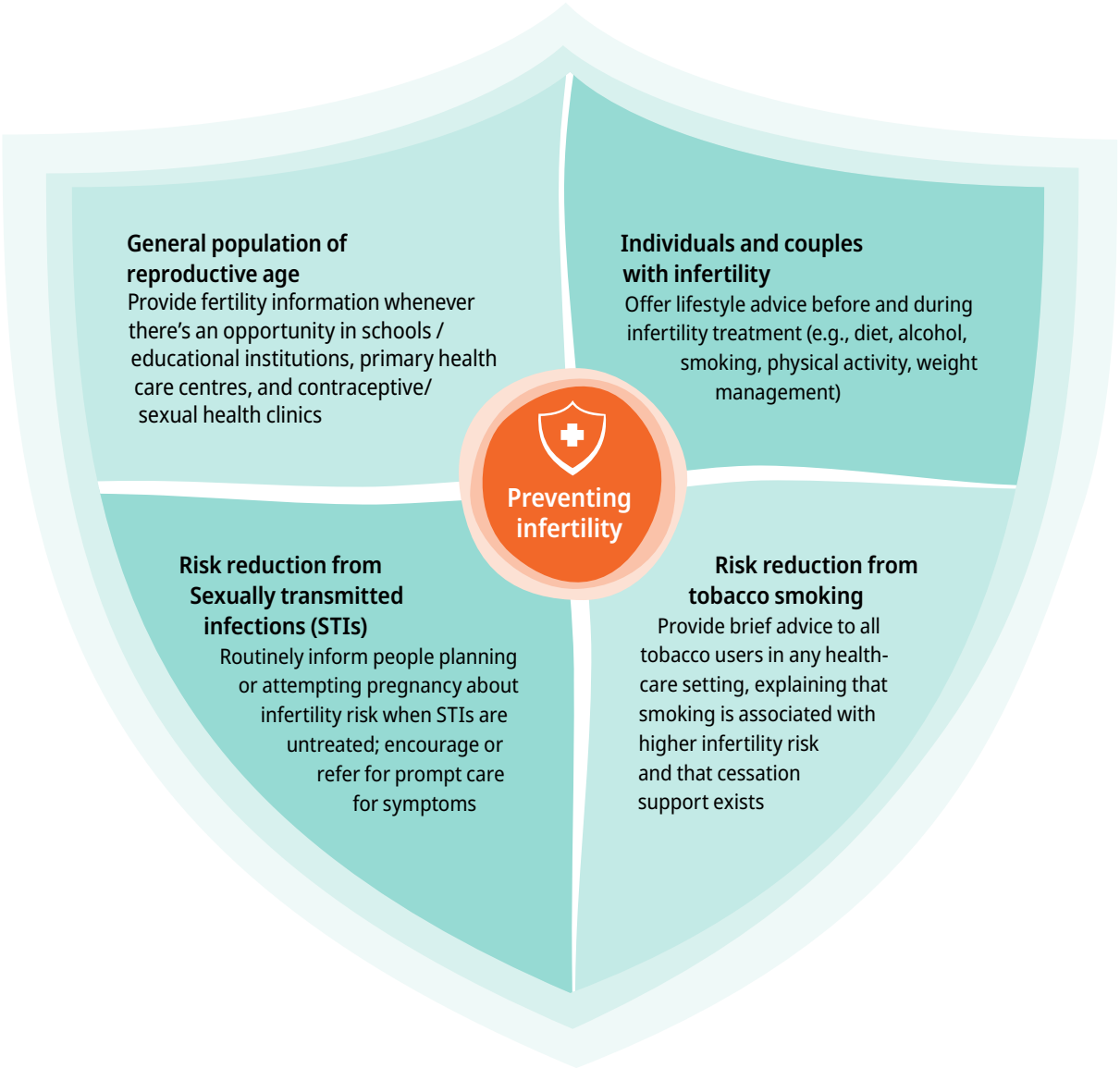
Regarding equity, the GDG agreed that providing education could be applied across different populations and settings and may not have a differential impact on equity because the whole population would be reached with the intervention. However, differences could emerge if the method of providing education was more resource-intensive (e.g. providing in-person counselling for some populations and information leaflets for other populations).

Several studies provided evidence on the acceptability of fertility-related brochures *(6, 13)*, reproductive life plan counselling *(2, 4, 5, 14)*, chatbot education *(11)* and a culturally adapted fertility status awareness tool (FertiSTAT) *(15)*. Based on data from these studies, the GDG judged that both the general population and health care providers would probably find education interventions acceptable. In addition, the GDG judged that providing information to the general population would be feasible in schools, clinics and primary care settings where other health information is being provided and noted that information and education should be adapted and tailored to local contexts, the audience, risk factors and methods of dissemination.

Summary justification

Overall, there is very-low-certainty evidence for small benefits, such as increased knowledge and improved behaviours, and for trivial harms, such as anxiety, when providing fertility information. Evidence is very uncertain on the effect of information on live births, and no data are available on pregnancies. Providing information may incur varying costs depending on the format or channel used; therefore, when cheaper dissemination methods, such as pamphlets and posters, are used, benefits may likely outweigh the costs in the general population not at risk (i.e. the presumed fertile general population). However, when costly strategies are used, such as counselling, the benefits are unlikely to outweigh the costs. Provision of information adapted and tailored to local contexts and audiences is probably acceptable and probably feasible.

Fig. 4.2. Recommendations for preventing infertility included in the guideline



Implementation considerations

Education messages need to be adapted and tailored to local contexts, risk factors, the audience (e.g. age and sex among others) and available methods of dissemination. For example, educational resources can be co-designed with the participation of the intended target audience, in their contexts. In all contexts providing specific information on age-related fertility decline/potential, and the long-term impact of lifestyle factors will be important. It is important for individuals and couples to obtain accurate information on fertility and infertility from trusted sources to minimize the risk of misinformation (e.g. via social media *[16]* or online marketing *[17]*); health care providers have a role in providing educational information that can inform reproductive planning. In implementing this recommendation, health care providers should note that this guideline contains several recommendations for preventing infertility for different population groups and risk factors (See **Fig. 4.1** and **Fig. 4.2**).

Research gaps and future guideline update

Given the variability in the evidence on the impact of information provision on fertility outcomes, future evaluation of what information works for whom, in which setting and why, will be needed to ascertain the value of providing information to the public according to the context. Future research is required to ascertain whether subpopulations of people (e.g. partnered individuals, single women of advanced age, among others) may respond differently to fertility information. Fertility education should include men because men also benefit from fertility education; therefore, future studies should include more men as they were underrepresented in the studies evaluated.

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4.2 Information provision for individuals and couples with infertility

Recommendation

For individuals and couples with infertility, WHO suggests providing low-cost lifestyle advice before and during infertility treatment. *(Conditional recommendation, low certainty of evidence)*

Remarks:

- Lifestyle advice may include advice to change diet, alcohol intake, smoking, physical activity and/or weight management.

Background and rationale

Lifestyle advice can be provided at various stages of the reproductive lifespan, for example, to the general population who may consider having a child in the future, individuals who are currently trying to achieve pregnancy, people who are at high risk of infertility or those who are already diagnosed with infertility. The present recommendation refers to individuals with infertility.

Modifiable lifestyle behaviours such as diet, physical activity, alcohol intake and smoking may affect fertility *(1)*. Although the extent of the impact varies *(2)*, these factors may negatively affect the ability of people with infertility to achieve a pregnancy resulting in a live birth. Providing lifestyle advice regarding these factors to people with infertility is intended to optimize the pre-pregnancy health of women and men with infertility and improve their fertility outcomes, such as achieving a pregnancy or live birth. Lifestyle advice includes provision of information, education or counselling about modifiable lifestyle behaviours.

For people with infertility, lifestyle advice could be provided before beginning infertility treatments such as ovulation induction, intrauterine insemination (IUI) or IVF or when receiving these treatments. Lifestyle advice can be provided individually or in group counselling sessions, through web-based or mobile-based applications, telephone calls, pamphlets, booklets or by a combination of these and other delivery channels.

For this recommendation, the GDG addressed the question: should lifestyle advice be provided to people with infertility or not?

Balancing harms and benefits

A published systematic review provided data for this assessment *(3)*. Seven randomized controlled trials (RCTs) published up to January 2021 were included in this review. Most couples and women with infertility in the studies received information before and/or while receiving fertility treatment, specifically: before fertility treatment in the intervention group *(4, 5)*; before ovulation induction *(6)*; while receiving IVF, IUI or none *(7)*; before any type of fertility treatment in the intervention group *(8)*; while undergoing IVF treatment *(9)*; while having investigations or receiving treatment *(10)*; or before or while undergoing IVF with or without intracytoplasmic sperm injection (ICSI) *(11)*. Of these, one study included men and women *(11)*.

The types of lifestyle advice included a smartphone coaching programme, individual and group counselling (motivational interviewing) and workouts, or information and behavioural modification. Lifestyle advice was provided for 6–24 months.

In terms of desirable effects, the GDG agreed that there are likely small effects on important outcomes, such as live births and clinical pregnancies (RR: 0.90; 95% CI: 0.77–1.06 and

RR: 1.17; 95% CI: 0.90–1.53, respectively). There is likely no difference to behavioural changes, although diet-related behaviours (such as fruit intake and lower alcohol intake) may be slightly improved. Evidence suggests no difference to quality of life.

In terms of undesirable effects, evidence suggested trivial increases in miscarriages (RR: 1.49; 95% CI: 0.96–2.32, meaning 46 more [from four fewer to 124 more] per 1000 couples) and hypertension during pregnancy (RR: 1.07; 95% CI: 0.66–1.75, meaning 11 more [from 55 fewer to 121 more] per 1000 couples). The overall certainty of evidence was low because of lack of blinding, unclear randomization in some studies and few participants or events. Notably, most of the control groups in the studies also received some form of lifestyle advice. As such, comparisons were more about the effects of more intensive or detailed forms of providing advice than no advice per se. The GDG agreed that couples value pregnancy and live births and that there is probably no important variability in how people value these outcomes. Overall, the GDG judged that the balance of effects probably favours information provision over no provision of information on lifestyle.

Other considerations

Provision of lifestyle advice involves resources; however, the GDG judged that the costs vary: some lifestyle advice interventions may be costly (such as individual one-to-one counselling), while others may incur lower costs (e.g. information brochures). The GDG also considered evidence from two studies *(12, 13)* showing that providing lifestyle advice could be cost-effective. When considering the small increase in pregnancy rates, a low-cost lifestyle advice intervention may be favoured.

In relation to equity, the GDG noted that while not all forms and intensities of information delivery would be available everywhere, individuals with infertility could be reached with lifestyle advice through delivery methods available locally. However, differences in equity could emerge if the method of providing lifestyle advice was more resource-intensive (e.g. providing in-person counselling for some populations and settings, and information leaflets for other populations and settings).

The GDG considered evidence from two studies *(6, 11)* and agreed that providing lifestyle advice may be acceptable to most couples; however, increased efforts to maintain participation may be needed. The GDG noted that the evidence is from couples before or during treatment, who were also receiving different fertility treatments; therefore, lifestyle advice is likely applicable and acceptable to couples at different treatment stages or receiving a variety of fertility treatments. None of the studies examined the effects in people with infertility who chose not to undergo treatment. Feasibility may be dependent on the intensity and timing of the lifestyle advice; intense or multi-component lifestyle advice may be more challenging to provide and use.

Summary justification

Overall, there is low-certainty evidence that the small improvements in live births and pregnancy and health behaviours may outweigh the trivial harms. Although costs may be greater for some types of lifestyle advice, the benefits may outweigh costs when low-cost lifestyle advice is provided. Providing lifestyle advice is probably acceptable to most people, and feasible.

Implementation considerations

When implementing this guideline, health care providers should try to maintain contact and engagement with patients. Sustained engagement for some populations (e.g. patients who need to manage their weight *[14]*) and some forms of lifestyle advice (e.g. more intensive forms of lifestyle face-to-face advice) may be difficult to maintain unless specific efforts are put in place. The goal should be to respectfully explain lifestyle-related risk factors and provide advice, while remaining sensitive to patient experiences and avoiding placing blame on them.

Health care providers should monitor and support compliance and should regularly assess prevalent lifestyle risks (e.g. during clinic visits) to continually tailor lifestyle advice. Health care providers should select contextually appropriate lifestyle advice and delivery channels according to prevalent lifestyle risks and audience preferences in different settings.

Research gaps and future guideline update

Future research and guidance will be needed on the optimal components of lifestyle advice, their timing and intensity. In addition, future studies should include a diverse group of patients, including men, the male and female partners of patients, and men and women of advanced age, among others. Most of the available evidence is about couples who are receiving ART; future studies should include couples with infertility who are not and people not seeking any medical treatment. Future guidance will be required for specific subgroups, such as those with a high BMI and impaired glucose tolerance, among others. Future research is needed on which lifestyle modification techniques are optimal for achieving the desired effects.

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4.3 Risk reduction from the use of tobacco

Recommendation

WHO recommends that brief advice (between 30 seconds and 3 minutes per encounter) be consistently provided by health care providers as a routine practice to all tobacco users accessing any health care settings. *(Strong recommendation, moderate certainty of evidence)*

Remarks:

- 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 a current or previous history of smoking.
- Assessment of lifestyle, including the use of tobacco, is part of medical history-taking 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 5As: *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.

Background and rationale

Tobacco use is highly prevalent among populations of reproductive age *(1, 2)* and is a leading cause of morbidity and mortality globally *(2–5)*. Nicotine is the pharmacologically active compound that occurs naturally in the tobacco plant and is typically consumed via inhalation or ingestion. It is highly addictive; a significant number of people who use tobacco regularly do so because they are addicted to it *(6, 7)*.

Tobacco has negative effects on health *(5)*. Cigarette smoke contains several chemicals that may act in isolation or cumulatively *(8)* to negatively affect cellular apoptosis, autophagy, DNA damage, meiosis and signalling *(8, 9)*. These effects of cigarette smoke may be mediated by individual vulnerability, timing and type of exposure *(8)*. For this recommendation, the GDG addressed the question: should brief advice about tobacco be provided to couples who are planning a pregnancy, attempting to achieve a pregnancy or with infertility when they access health care settings or not?

Balancing harms and benefits

A recommendation concerning brief advice to tobacco users was published in 2024 in the *WHO clinical treatment guideline for tobacco cessation*

in adults (10). It built on existing WHO guidance, including the actions recommended by the guidelines for implementation of Article 14 of the WHO Framework Convention on Tobacco Control to help tobacco users quit as part of a tobacco control approach *(11)*. The GDG adopted this recommendation by considering the evidence used to make the original recommendation.

Evidence of the harms and benefits used to make the original recommendation

A systematic review of 13 RCTs comparing the provision of brief advice to no advice to tobacco users provided information about the benefits of brief advice *(10)*. The review found that brief advice slightly increases short-term abstinence from smoking and likely increases it over the long term. However, brief advice probably has little to no effect on quitting attempts. No harms were reported in the systematic review. Subgroup analyses found that the effects were similar across multiple populations. The GDG noted that the evidence reviewed for the original recommendation was not specific to populations planning a pregnancy or attempting to achieve a pregnancy.

Applicability of evidence to men and women planning a pregnancy or attempting to achieve a pregnancy

To determine whether the evidence from the original systematic review of brief advice would also be beneficial to people planning a pregnancy, or attempting to achieve a pregnancy, we conducted an overview of reviews published since 2015 and tracked references to other systematic reviews. Four reviews were found that covered smoking and the risk of infertility in men or women.

Several reviews published before 2015 reported a positive association between smoking and infertility in women. A 1998 review reported that the odds of infertility among female smokers was 1.6 times (95% CI: 1.3–1.9) the odds in non-smokers *(12)*. In 2011, a comprehensive review of clinical and experimental studies evaluated the effects of exposure to cigarette smoke across different stages of reproduction from folliculogenesis to implantation. The review suggested that cigarette smoking impairs, alters, adversely affects or interferes with normal reproductive functions *(8)*. More recently, a review of three non-randomized studies reported that the odds of infertility in female smokers was 1.85 times (95% CI: 1.08–2.14) the odds in non-smokers *(13)*.

Evidence on infertility and smoking in men was reviewed in a 2016 study, which assessed the association between smoking and semen quality using the 2010 *WHO laboratory manual for the examination and processing of human semen*. Twenty studies with 5865 men contributed to the analyses *(14)*. It reported that smoking may be associated with a reduction in some semen parameters: semen volume; sperm count; sperm motility; and sperm morphology. A subgroup analysis of a smaller set of studies reported that reductions in semen parameters may be greater in moderate and heavy smokers. Although some results were statistically significant, it is not clear whether the magnitude of the reductions in semen parameters is clinically relevant and whether the observed reductions affect fertility, given that semen parameters per se are not a reliable indicator of male fertility status *(15, 16)*.

Other considerations

No research evidence was identified specifically from fertility contexts regarding the feasibility, acceptability, equity, cost or cost-effectiveness of brief advice. In keeping with the recommendation and evidence published in the original recommendation in the *WHO clinical treatment guideline for tobacco cessation in adults* in 2024 *(10)*, the GDG agreed that brief advice was also supported by its likely feasibility and acceptability, negligible costs, cost-effectiveness and low impact on equity.

Summary justification

The GDG adopted the strong recommendation for brief advice for all tobacco smokers from the *WHO clinical treatment guideline for tobacco cessation in adults* published in 2024 *(10)*. There was moderate certainty of evidence in the general population for the benefits of providing brief advice. Given that there is likely an association of smoking with infertility in women and there may be an association of smoking with reduced semen parameters in men, the GDG decided that this evidence would apply directly to couples who are planning a pregnancy or attempting to achieve a pregnancy. The GDG also agreed with the judgements in the original recommendation that providing brief advice is probably low-cost, feasible, acceptable and would probably have no impact on equity.

Implementation considerations

Assessment of lifestyle, including the use of tobacco, is part of the medical history-taking (see **Chapter 3** and accompanying algorithms in this guideline). This guideline suggests providing information about fertility and infertility using low-cost strategies, or whenever there is an opportunity, including how to reduce risk factors for infertility (see **Chapter 4**). Despite the need, information on the risks of tobacco smoking, and referral to tobacco cessation services, are not consistently provided by health care providers during the pre-pregnancy period *(17)* at primary health care centres *(18, 19)*, when referring for fertility care *(20)*, or when providing infertility evaluation and treatment *(17, 21)*.

Development of specific job aids or tools (such as scripts) for brief advice may be necessary to ensure that messages provided by health care providers are consistent. Brief advice should be tailored or personalized based on individual circumstances and may need to be adapted to local contexts and audiences. Depending on the context, advice may be tailored to the audience to pinpoint the biological functions that are affected by smoking. For more information on the 5As (referred to in the remarks section), see the existing WHO guidance related to disease interventions at the primary health care level *(22)*.

Health care providers should note that not all smokers may be willing to quit; however, those willing to quit may be more receptive to being provided information, and offered or referred to appropriate services aimed at aiding cessation. Providing access to and encouraging the use of effective cessation interventions increases the likelihood of successfully quitting tobacco; however, health care providers should respect individual choice. Repeated brief advice during appointments can allow progressive tailoring of information and dialogue to the specific circumstances and readiness to quit of an individual *(20)*; however, health care providers should note that acceptability of persistent information can differ among smokers because it can evoke guilt, self-blame or frustration *(23)*. The goal should be to respectfully provide brief advice, while remaining sensitive to patient experiences and avoiding putting the blame on patients.

People who are willing to quit may prefer using some or multiple tobacco cessation interventions. To identify the range of interventions that couples can be informed about, provided with or referred to, health care providers should refer to the *WHO clinical treatment guideline for tobacco cessation in adults (10)* and other existing WHO guidelines for preventing tobacco use uptake, promoting tobacco cessation or diagnosing and treating tobacco dependence *(11, 22, 24)*. Given that tobacco cessation can be influenced by social interactions, including with partners *(25, 26)*, health

care providers should aim to reach both partners in a couple with brief advice, based on individual circumstances.

Tobacco use may adversely affect maternal or neonatal outcomes after pregnancy. The WHO guideline on antenatal care provides recommendations regarding the need for health care providers to ask all pregnant women about their tobacco use (past and present) and exposure to second-hand smoke as early as possible in the pregnancy and at every antenatal care visit *(27)*.

Research gaps and future guideline update

Cigarette smoking can have negative effects on a range of reproductive parameters or functions in women *(8, 9, 28, 29)* or men *(14, 30)*. However, more research is needed in assessing and quantifying the risk of infertility in men who smoke or use tobacco.

Additionally, the GDG is aware of studies exploring the effects of cessation of tobacco smoking on fecundability in women *(31–33)* and on sperm parameters in men *(34–36)*, which suggests that smoking cessation could have a role in reversing infertility. More research addressing this question would be beneficial for future guideline updates. Future guidance will be required regarding information that should be provided by health care providers regarding tobacco use during assisted reproduction, which is not within the scope of this PICO question because it relates to a slightly different population (i.e. people already diagnosed with infertility, who are accessing ART). Future guidance will also be required in relation to exposure to secondary smoke, use of vapes and e-cigarettes, non-smoked/smokeless tobacco products, as well as other smoked substances, such as cannabis (see **section 12.2**).

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4.4 Risk reduction from sexually transmitted infections

Good practice statement

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.

Remark:

- If symptoms of an STI are present, or if infection is confirmed, WHO guideline recommendations on the management of STIs are available.

Background

Variable proportions of infertility are attributable to untreated infections that ascend along the reproductive tract, capable of causing inflammation, abscess, damage, adhesions or permanent scarring to reproductive organs (see **Annex 1. Distribution of the causes of infertility**). Several pathogenic mechanisms have been proposed in females *(1–3)* and males *(4, 5)* for some organisms. However, the speed and extent to which such infections induce these pathogenic processes and progressively alter the anatomy or physiology of reproductive organs differs between organisms and individuals *(6)*: not all reproductive tract infections have been clearly demonstrated to contribute to the pathogenesis of infertility in females *(7)* or males *(8)*. Notably, reproductive tract infections that are associated with infertility may be sexually or non-sexually transmitted (e.g. genital schistosomiasis or tuberculosis) with varying virulence.

WHO has quantified the burden of selected curable STIs *(9–11)* and issued recommendations related to the screening, diagnosis and management of STIs *(12)*. Recommendations for the testing and treatment of people with symptoms, such as vaginal discharge (in females), abdominal pain (in females), urethral discharge (in males) or genital ulcers, including anorectal ulcers (in both males and females), are available from WHO *(13)*.

Necessity of the message

Given some potential uncertainty and variability about the timing, sequence and magnitude of the effects of STIs on the reproductive tract and subsequent infertility *(15–18)*, clinicians may not always communicate with patients about these infections. A lack of information about STIs and the consequences of infertility exists, which is often linked to stigma, embarrassment, privacy, lack of centres for sexual health, or lack of communication and counselling from health care providers on sexual issues *(19–21)*. Although health care providers are an important and often preferred source of information on sexually transmitted infections *(21, 22)*, missed opportunities for communicating about STIs and sexual health have been identified in clinical settings *(22)*.

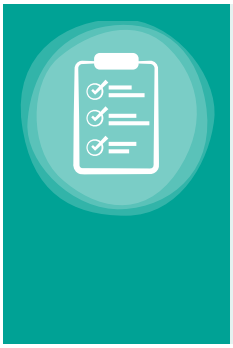
Consequences

The GDG agreed that there would be net positive consequences of communicating about STIs and the risk of infertility, given the risk of infertility in people with a history of STIs. A systematic review of over 147 studies in populations with infertility found that the prevalence of *Neisseria gonorrhoeae* was higher in those populations than in the general population globally (2.2% versus 0.8%). Populations with tubal factor infertility, a variety of different types of infertility, unexplained infertility and secondary infertility had the highest prevalence compared to other conditions; prevalence was also

higher in women than in men *(14)*. In addition, a systematic review of studies including women with current or a history of infection with *N. gonorrhoeae* found a greater but small risk of tubal infertility in women compared to women without an STI infection, and a greater risk in women with overt pelvic inflammatory disease (PID) *(15)*.

A systematic review of case–control studies also found approximately 2.2 greater odds of infertility in males or females with *Chlamydia trachomatis (16)*. Another systematic review found that the prevalence of *Trichomonas vaginalis* in women attending infertility clinics in the Middle East and North Africa was higher than in a general population of women *(17)*. Untreated *N. gonorrhoeae* and *C. trachomatis* infection can lead to PID. A longitudinal follow-up of women in the PEACH trial, which included approximately 800 women, found that the odds of infertility may be approximately two times greater in women with recurrent PID versus women with no recurrent PID *(18)*.

The GDG agreed that given the higher prevalence of STIs in women and men with infertility, and the likelihood of temporal precedence (rather than infertility leading to greater STI incidence), routinely informing couples about STIs, including the risk of infertility when untreated, or encouraging that they seek care if they have symptoms of STIs, would result in benefits and little to no harm. The GDG noted that the burden of STIs varies across countries, but awareness about STIs can contribute towards prevention. The GDG also agreed that informing couples would be acceptable and feasible to both clinicians and couples, and there would be negligible costs or resources required. In addition, it would probably have limited impact on equity.



Rationale

Overall, the GDG agreed that informing people of the risk of infertility caused by STIs would increase awareness and potentially reduce infertility as evidence found greater prevalence of some types of STIs in people with infertility. Informing couples is acceptable, feasible and requires negligible resources and costs, and probably has no impact on equity. The opportunity cost of collecting and summarizing evidence is large.

Implementation considerations

In implementing this good practice statement, health care providers should note that providing information on factors that can increase the risk of infertility is an important part of pre-pregnancy advice, counselling and care (see **Chapter 3**). In addition, assessment of previous lifestyle history, including history and management of sexually transmitted, non-sexually transmitted and other reproductive tract infections, is important when evaluating couples for infertility (see **Chapter 3**). Implementation of this good practice complements other avenues for providing information about fertility and infertility, adapted to local contexts and audiences, when opportunities occur in schools, at primary health care centres or reproductive health (contraceptive, sexual health) clinics (see **Chapter 4.1** for the recommendation on information provision on infertility and fertility for the general population).

It is important for health care providers to be aware and to communicate to couples and individuals that some reproductive tract infections are not acquired sexually but could also be associated with infertility; therefore, health care providers should also assess for these in the medical history and physical examination. Health care providers should inform couples and individuals that some STIs may be asymptomatic

and that diagnostic screening could be indicated. If the symptoms of an STI are present or infection is confirmed, WHO guidelines for the diagnosis and management of STIs are available *(12, 13, 19, 20)*.

Given that a person with an STI will have contracted it from a sexual partner who also had the infection, health care providers should aim to inform all sexual partners. Awareness and preventive actions can be hindered by a low perception of an STI risk with trusted partners *(21)*, a lack of knowledge of a partner's prior risky sexual behaviours *(22)*, or low awareness or use of STI prevention interventions *(12)*.

Following pregnancy, STIs can have a negative impact on maternal and neonatal outcomes. The WHO antenatal guideline provides recommendations regarding the identification and management of STIs during pregnancy *(23)* to reduce the risk of adverse reproductive, obstetric and neonatal outcomes.

Research gaps and future guideline update

Better quantification of the risks of infertility from some sexually transmitted and non-sexually transmitted infections of the reproductive tract is needed. Efforts to improve the quality of the data (e.g. using standardized criteria instead of relying on self-reporting) are also needed. Studies (including modelling) to explore infertility risk reversal after treatment of STIs and other reproductive tract infections are needed. Specific guidance will be required in future regarding screening for STIs as part of pre-pregnancy care, which is not within the scope of this guideline.

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Chapter 5 Diagnosis of infertility

This chapter provides guidance related to diagnosis of infertility. These are grouped into three main categories:

- **Female factors** – such as ovulation, fallopian tubes, and the uterus
- **Male factors** – issues that may affect sperm health and function
- **Unexplained factors** – when no clear cause is found

Female-factor diagnosis

5.1 Diagnosis of infertility due to ovulatory dysfunction

5.2 Confirmation of ovulation

5.3 Assessment of reproductive hormones

5.4 Assessment of ovarian reserve

5.5 Diagnosis of infertility due to tubal disease

5.6 Diagnosis of infertility due to uterine cavity disorder

Male-factor diagnosis

5.7 Diagnosis of infertility due to male factors

Unexplained infertility

5.8 Diagnosis of unexplained infertility

Relevant resources

Figures: diagnostic algorithms

5.1 Female-factor infertility and unexplained infertility

5.2 Assessment of the uterine cavity

5.3 Male-factor infertility

Annex 6. Components of female medical history and physical examination

Annex 7. Components of male medical history and physical examination

Web Annex C. Evidence to decision tables for diagnosis of infertility

5.1 Diagnosis of infertility due to ovulatory dysfunction

This and subsequent sections contain recommendations related to the diagnosis of infertility due to female-factor (**sections 5.1–5.6**), male-factor (**section 5.7**) and unexplained-factor (**section 5.8**). Recommendations on infertility due to female factors are related to ovulation (**sections 5.2–5.4**), tubal disease (**section 5.5**) or uterine cavity disorder (**section 5.6**). **Figure 5.1** below shows how recommendations on female factors and unexplained factors relate to each other, illustrated in a diagnostic algorithm. A diagnostic algorithm related to male factors is presented later in **section 5.7**.

5.2 Confirmation of ovulation

Recommendation

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 women 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. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- Mid-luteal serum progesterone levels are assessed approximately 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

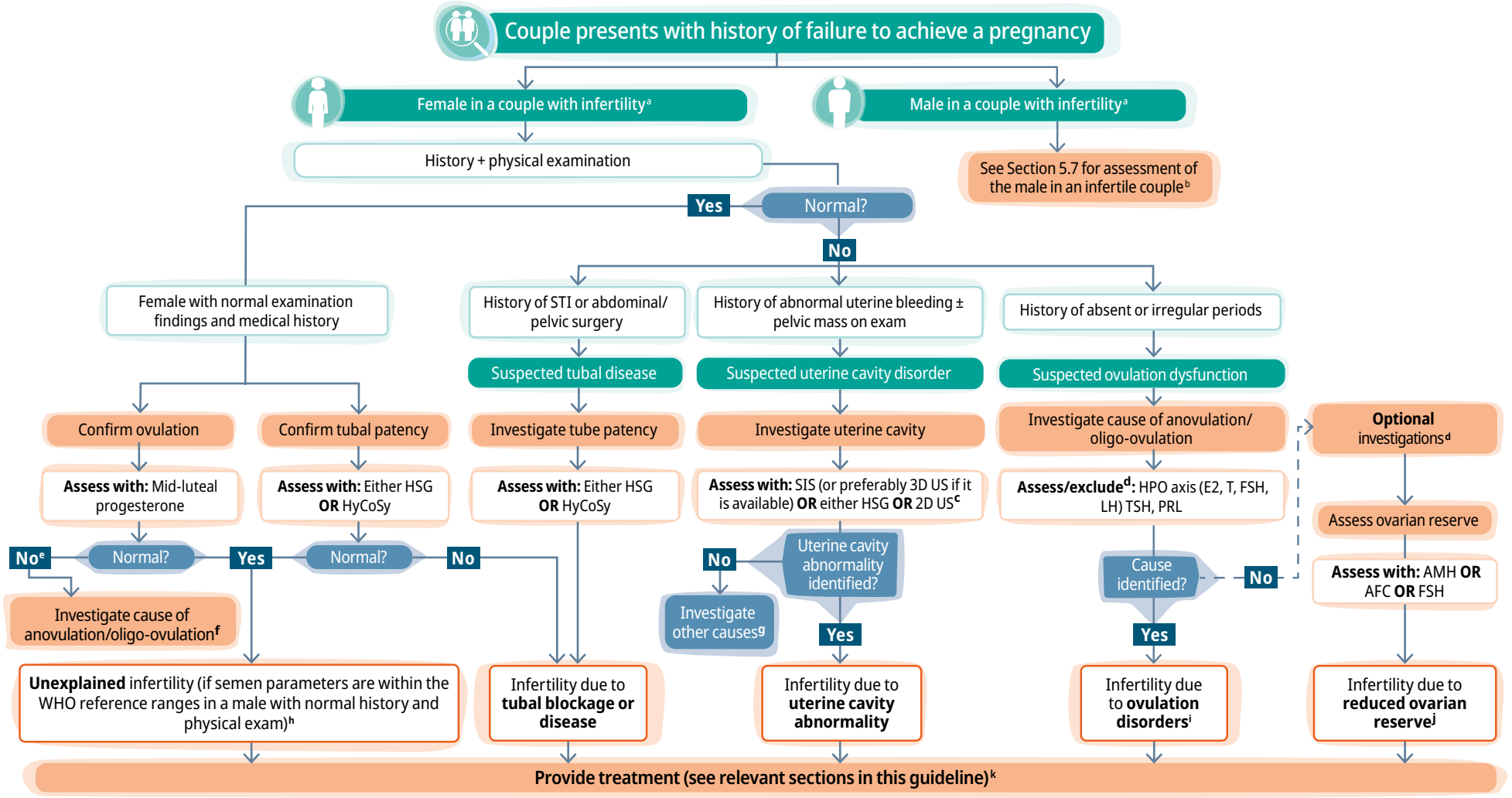
Background and rationale

Disorders of ovulation can cause infertility *(1, 2)*. In a multi-country study involving 8500 patients in 25 countries, anovulatory and ovulatory disorders accounted for 26.1% of identifiable causes of female infertility *(3)*; therefore, a key aspect of management of infertility includes the assessment of ovulation.

When a couple presents with a history of failure to achieve a pregnancy, history-taking and a physical examination are conducted in the female. If these are normal[2] (including a history of regular menstrual cycles), ovulation is assessed (see **Fig. 5.1** Diagnostic algorithm for female-factor infertility and unexplained infertility). Although a history of regular menstrual cycles may be clinically suggestive of ovulation in most cases, further assessment of ovulation with diagnostic tests may be needed given the small potential for anovulatory menstrual cycles in eumenorrheic women, as reported in studies *(4–6)*.

[2] That is, nothing abnormal is detected.

Fig. 5.1. 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** and **Fig. 5.3** for diagnosis of infertility due to male factors.
[c] See detailed diagnostic algorithm for uterine factors in **Fig. 5.2.**
[d] Based on clinical findings; see **Good Practice Statements in Chapter 3**.
[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**.
[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.**
[j] For example, due to advanced age, ovarian surgery, POI.
[k] See **Chapters 6–10** for treatment recommendations.

2D US, two-dimensional ultrasound; 3D US, three-dimensional ultrasound; AFC, antral follicle count; AMH, anti-Müllerian hormone; E2, estradiol; FSH, follicle-stimulating hormone; HPO, hypothalamic–pituitary–ovarian; HSG, hysterosalpingogram; HyCoSy, hysterosalpingo contrast sonography; LH, luteinizing hormone; PRL, prolactin; SIS, saline infusion sonohysterography; STI, sexually transmitted infection; T, testosterone; TSH, thyroid-stimulating hormone.

Historically, several tests have been used to either predict or detect ovulation *(7–10)*. Tests that predict impending ovulation (e.g. urine ovulation predictor kits that measure urinary luteinizing hormone [LH] surge levels) could be useful for proper timing of intercourse during the fertile period *(11)*, and are increasingly available over the counter *(12, 13)*. Tests that are intended to confirm ovulation are important for diagnostic purposes in the context of evaluation of the female. The latter application (related to the confirmation of ovulation) was prioritized by the GDG, given the uncertainty regarding anovulatory menstrual cycles in regularly menstruating women *(4, 5)*.

The GDG agreed that a key decision when investigating women with infertility and suspected ovarian pathology is whether to perform ultrasound scan or measure mid-luteal serum progesterone level to presumptively confirm ovulation. The GDG noted that existing tests only provide **presumptive** or **indirect** evidence of ovulation. For this recommendation, the GDG addressed the question: should mid-luteal progesterone versus ultrasound be used to confirm ovulation in women with infertility but normal exam findings and history, or not?

Ultrasound imaging (sonography) involves the generation and transmission of ultrasonic (high-frequency sound) waves from a transducer and processing of a returning echo to generate an image. It is based on non-ionizing energy *(14)*. Ovulation is *indirectly* established using ultrasound follicle tracking through a series of ultrasound scans that are performed between mid-follicular phase (day 8/9) to mid-luteal phase *(15)*. The development, growth and morphological changes of follicles are monitored *(15, 16)*. The collapse of the dominant follicle indicates ovulation *(16–18)*. Although US examination may be conducted using several approaches *(19–21)*, the transvaginal approach is most commonly used for assessing ovulation *(22)*.

Progesterone is a steroidal female sex hormone essential for endometrial receptivity, embryogenesis and the successful establishment of pregnancy. It is produced by ovarian granulosa-theca and corpus luteum cells and, during pregnancy, by placental tissue *(23)*. Assessment of the serum progesterone *indirectly* establishes ovulation by measuring whether the peak (mid-luteal) levels of progesterone are above a specified threshold *(24–26)*. Progesterone levels are measured several days (typically seven) before the expected menses. Levels greater than certain arbitrary thresholds,[3] provide presumptive evidence of ovulation *(25, 27)*.

Balancing harms and benefits

Literature searches were conducted to identify diagnostic accuracy studies addressing mid-luteal progesterone and ultrasound follicle tracking from 1990 up to September 2019. The accuracy studies could have compared the tests to a presumed gold standard or compared two or more tests to predict the presence or absence of ovulation. An updated search was later conducted in PubMed up to October 2023.

No studies comparing both tests to endometrial biopsy were identified. One study compared the accuracy of mid-luteal progesterone to the "gold standard" of ultrasound in women with infertility who also had regular menstrual cycles *(28)*. In this study, which involved 101 women (97 menstrual cycles with ovulation), mid-luteal serum progesterone threshold level of at least 6 ng/ml was compared to transvaginal US. The sensitivity and specificity are presented in **Table 5.1**. These results imply that of 100 women, of whom 96 ovulate, 19 would be incorrectly classified as not ovulating (false negative); in addition, one woman would be incorrectly classified as having ovulated (false positive) if mid-luteal progesterone is used to determine ovulation (see **Table 5.1**).

[3] These thresholds are dependent on the assay used by laboratories and may range from 9.6 to 38 nmol/L *(24–26)*.

Table 5.1. Test performance of a single mid-luteal progesterone test

	Single mid-luteal progesterone test
Sensitivity (95% CI)	80% (72–88%)
Specificity (95% CI)	71% (not reported)

CI, confidence interval.

In assessing benefits, the GDG noted that there were fewer true positives and true negatives with mid-luteal progesterone compared to ultrasound (as ultrasound had higher sensitivity and specificity); however, the number of true positives or true negatives could be increased if a repeat mid-luteal progesterone test is performed in women whose initial test results indicate anovulation, as illustrated in **Table 5.2**.

Table 5.2. Absolute effects on 100 women when different combinations of mid-luteal progesterone test with or without ultrasound are provided

	Progesterone only	Progesterone + repeat progesterone for women whose results show that they are anovulatory on the initial progesterone test	Progesterone followed by US for women whose results show that they are anovulatory on the initial progesterone test
True positives	77	81	81
True negatives	3	13	18
False positives	1	6	1
False negatives	19	1	0
Sensitivity	80	80 (first test), 80 (repeat test)	80 (progesterone), 100 (US)
Specificity	71	71 (first test), 71 (repeat test)	80 (progesterone), 100 (US)

US, ultrasound.

Based on these data, the GDG concluded that the benefits of mid-luteal progesterone compared to ultrasound may be trivial when the mid-luteal progesterone measurement is repeated in women whose initial test results indicate anovulation. In reaching this conclusion, the GDG considered that ultrasound is not a gold standard per se; it provides presumptive evidence of ovulation, and false positives are possible, given that ultrasonic evidence of luteinization has been documented in unruptured preovulatory follicles *(15, 29, 30)*.

Regarding harms, the GDG agreed that with the use of a single mid-luteal progesterone measurement approach, the harms of one out of 100 false positives may be trivial; however, 19 out of 100 false negatives may mean that these women (who are ovulating) would undergo unnecessary tests.

However, if a mid-luteal progesterone measurement were to be repeated in women who were negative (i.e. 22% of women), the number of women who would be incorrectly classified as anovulatory (i.e. false positives) may increase slightly (from 1 to 6 women out of 100), but the women who would have unnecessary investigations for anovulation or oligo-ovulation may be greatly reduced (from 19 to 1 out of 100). Therefore, the GDG concluded that the difference in harms may be trivial when using this testing approach.

Considering these benefits and harms, the GDG agreed that the balance of effects of repeating mid-luteal progesterone in women with an initial negative mid-luteal progesterone test result may be similar to the balance of effects when performing ultrasound as a single test. The GDG noted that, when mid-luteal progesterone measurement is repeated, 94 out of 100 women will be accurately diagnosed and that 100 women may be accurately diagnosed with ultrasound (assuming that ultrasound has 100% specificity and sensitivity).

Although no studies on patient values were available, the GDG reached a consensus that women would value tests capable of correctly assessing ovulation, and they would also value tests with few harms, such as unnecessary tests, frequent travel (e.g. for serial tests) and costs. The GDG judged that there are probably no important uncertainties or variabilities in how much people value these outcomes.

The overall certainty of evidence was rated as very low because of the limited number of available studies and the absence of a reference standard. The GDG agreed that both ultrasound and mid-luteal progesterone measurement provide indirect and presumptive confirmation of ovulation.

Other considerations

Two studies from the United Kingdom showed that the cost differences between mid-luteal progesterone measurement and ultrasound are negligible *(31, 32)*. However, the GDG agreed that in LMICs, the cost differences may be greater, with serum progesterone measurements possibly costing moderately less and resulting in savings. In addition, the GDG judged that the cost difference would not change significantly even when the progesterone measurement is repeated in women whose results indicate anovulation on the initial progesterone measurement result.

No data on cost-effectiveness were available. However, the guideline panel agreed that, given that there are similar benefits and harms between ultrasound and a strategy that involves repeat progesterone measurement in women whose results indicate anovulation on the initial progesterone test, and the cost of ultrasound is greater than serum progesterone, then cost-effectiveness probably favours the mid-luteal progesterone measurement. The GDG judged that cost-effectiveness would likely not change significantly when the progesterone test is repeated in women whose initial progesterone measurement results indicate anovulation.

Although there was no direct evidence on the impact of either test on equity, the GDG agreed that a mid-luteal progesterone measurement could probably increase equity because it requires fewer resources and is more widely available than ultrasound. The GDG judged that equity would likely not change significantly even when the progesterone measurement is repeated in women whose initial progesterone measurement results indicate anovulation.

In terms of acceptability, one study reported that serial ultrasound is time-consuming, which may lead to frustration in patients and overcrowded waiting rooms *(33)*. No studies assessing the acceptability of a mid-luteal progesterone measurement were found. In the absence of comparative data, the GDG agreed that although some women would require a repeat measurement, a mid-luteal serum progesterone test is likely more acceptable than transvaginal ultrasound for most patients.

No comparative studies were identified on the feasibility of mid-luteal progesterone measurement and US. In the absence of direct evidence, the GDG judged that measuring the level of mid-luteal progesterone is probably feasible to perform; it could also be more feasible than US considering that it requires fewer resources than ultrasound, and ultrasound requires training.

Summary justification

There is very low certainty evidence indicating that a small number of women may be incorrectly informed that they have not ovulated when using mid-luteal serum progesterone measurement. For women whose results show no ovulation from the initial mid-luteal serum progesterone level, providing an additional mid-luteal serum progesterone measurement would likely reduce the number of women referred for additional investigations for anovulation or oligo-ovulation. Measuring the level of mid-luteal progesterone costs less, is more feasible and probably more acceptable compared to performing an US scan.

Implementation considerations

While regular menstrual cycles are predictive of ovulation in most women *(4–6)*, it is important to confirm ovulation for the purpose of arriving at a diagnosis that can be communicated to patients, most of whom have expressed a desire to be informed about the cause of their infertility *(34)*.

Health care providers should note that similar to ultrasound, serum progesterone level only provides "indirect" or "presumptive" evidence of ovulation. Measurement of serum progesterone indicates the formation of a corpus luteum, but does not provide definitive proof that a mature, fertilizable oocyte has been released from the ovary *(35)*. Additionally, suboptimal timing of sample collection (vis-à-vis menstrual cycle day), pulsatile secretion, circadian effect, assay error, luteinized unruptured follicles and inherent biological heterogeneity all contribute to variability and potential false negative results *(36-40)*; hence, the need to repeat it if the initial measurement result indicates no ovulation in women with normal findings on history and physical examination.

Considering the normal variation of secreted progesterone in ovulatory menstrual cycles *(41, 42)*, and given that the follicular and luteal phases differ in their contribution to this variability *(37, 41)*, health care providers should note that obtaining mid-luteal serum progesterone levels approximately 7 days before the expected onset of the next menses is more informative than obtaining it on a specified cycle day. While mid-luteal serum progesterone levels should be assessed approximately 7 days before the expected onset of the next menses, the specific cycle day can vary based on the length of the cycle, for example, day 21 of a 28-day cycle or day 28 of a 35-day cycle.

Research gaps and future guideline update

There were limited data on the acceptability of mid-luteal progesterone measurement or its impact on equity. Implementation research is required to assess the downstream impact of implementing the suggested test for ovulation (mid-luteal progesterone) for women with normal findings on history (including regular menstrual cycles) and physical examination, including regularly menstruating non-hirsute women; such data can inform future considerations. Guidance regarding the role or potential use of LH assessments for the confirmation of ovulation will be required in the future. This recommendation relates to the application of ovulation tests in health care settings and does not relate to direct-to-consumer products, such as fertility tracking wearables and applications, which will require future guidance.

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5.3 Assessment of reproductive hormones

Good practice statement

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 follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and in some clinical presentations, estradiol (E2), testosterone [T]). Additional testing (e.g. thyroid-stimulating hormone [TSH], prolactin [PRL]) may also be considered 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.

Background and rationale

The clinical pattern of ovulation is influenced by several physiological factors *(1, 2)*. When a couple presents with a history of failure to achieve a pregnancy, history-taking and a physical examination are conducted in the female. If these are normal,[4] including a history of regular menstrual cycles, ovulation is assessed (see **section 5.2**). Diagnostic assessment of the female and male should take place concurrently (see **sections 3**, **5.5** and **5.7**).

If the history identifies women who do not have a regular menstrual pattern (menstrual bleeding at intervals of 28 ± 7 days) further hormonal evaluation is indicated to identify potential causes of anovulation and oligo-ovulation. These women may include those with primary amenorrhea (patients aged over 18 years[5] who have never experienced spontaneous vaginal bleeding), secondary amenorrhea (absence of spontaneous vaginal bleeding for 6 months or more in a patient who had previously experienced it) or oligomenorrhea (infrequent or scanty menstruation characterized by spontaneous vaginal bleeding at intervals from 36 days to 6 months) *(1)*. Age of menarche varies *(3, 4)*.

WHO classifies ovulation disorders into three groups *(2)* as follows:

- **Group I:** women with amenorrhea and little or no evidence of endogenous estrogen activity, including patients with (i) hypogonadotropic ovarian failure, (ii) complete or partial hypopituitarism or (iii) pituitary-hypothalamic dysfunction. Group I is characterized by low or unmeasurable serum and urinary gonadotrophins, and low estrogen levels. Plasma progesterone levels are typically less than 1.0 ng/ml and plasma hydroxyprogesterone are typically less than 0.2 ng/ml. Patients in WHO Group I may have primary or secondary amenorrhoea.
- **Group II:** women with a variety of menstrual cycle disturbances (including amenorrhoea) who exhibit distinct endogenous estrogen activity (urinary estrogens usually less than 10 µg/24 h), whose urinary and serum gonadotrophins are in the normal range and fluctuating, and who may have fairly regular spontaneous menstrual bleeding (i.e. less than 35 days apart), but without ovulation. Patients with galactorrhoea associated with amenorrhoea may be classified under WHO Group II or, rarely, WHO Group

[4] That is, nothing abnormal is detected.

[5] An earlier age may be considered, for example, because of international variation in ages at menarche *(2, 3)* or based on clinical presentation.

I based on laboratory and indirect clinical findings.
- **Group III:** women with primary ovarian failure associated with low endogenous estrogen activity and pathologically elevated serum and urinary gonadotrophins.

This WHO diagnostic classification aims to inform clinical management of infertility and does not aim to provide a comprehensive classification *(1)*. Other more comprehensive classifications exist *(5, 6)*. For this recommendation, the GDG addressed the question: should reproductive hormones versus none be performed for the initial evaluation of women with infertility and suspected anovulation and oligo-ovulation.

Considering existing guidance on good practice statements *(7)*, the GDG agreed that it is good practice to evaluate reproductive hormones during the initial evaluation of anovulation and oligo-ovulation, specifically those related to the HPO axis (such as FSH and LH, and in some clinical presentations, E2, T). The GDG agreed that additional testing (e.g. TSH, PRL) may also be considered based on the clinical presentation. The GDG agreed that the choice of diagnostic tests should be based on clinical findings from a comprehensive medical history and physical examination, and should ensure that evaluation is systematic and cost-effective.

Necessity of the message

Given the importance of hormonal and endocrine causes of female infertility *(1, 8)*, the GDG agreed that it is important for health care providers to have clear guidance on whether reproductive hormones should be assessed or not in women with infertility and suspected anovulation or oligo-ovulation.

Consequences

The GDG agreed that normal menstrual function involves the coordinated function of several physiological and structural components: the hypothalamus, the anterior pituitary gland, the ovary and the genital outflow tract composed of the uterus/endometrium, cervix and vagina. The physiological balance between gonadotrophic hormones and ovarian sex steroids is necessary for an orderly ovulatory sequence; failure to ovulate may be the result of a dysfunction at any level of this system. This system involves hormonal functions in higher centres in the brain, the HPO axis and the steroid feedback mechanism. In this context, the GDG agreed that measuring the following hormones will identify dysfunction in the ovulatory sequence and inform diagnosis, prognosis and management of anovulation and oligo-ovulation leading to large net positive consequences.

FSH and LH

The gonadotrophin-releasing hormone (GnRH) stimulates the synthesis and secretion of pituitary gonadotrophin hormones, FSH and LH. FSH and LH stimulate and sustain follicular growth and maturation (differentiation and luteinization) *(9, 10)*. In the absence of the FSH and LH hormones, the development of ovarian follicles is impaired at early antral or preovulatory stages, respectively *(9, 10)*, although follicular proliferation may not be entirely inhibited *(10, 11)*. Gonadotropins also have a part in sustaining follicular steroidogenesis *(10)* by mediating aromatization of androgens to estrogens *(12)*. Gonadotropin deficiency can result either from a pituitary abnormality *(13, 14)* or a deficiency of GnRH *(14)*. FSH and LH levels are low or unmeasurable in WHO Group I, normal in WHO Group II and high in WHO Group III.

Estradiol

Estrogens have an important role in the development of ovarian follicles by regulating gonadotrophin secretion for ovulation *(15)*. Ovarian granulosa cells are the key source of serum estrogens in premenopausal women; smaller amounts are produced in peripheral adipose tissue *(15, 16)*. Estrogen regulates FSH secretion through a negative feedback loop on the HPO axis *(17)*: it stimulates the production of GnRH, which in turn stimulates FSH; when FSH levels are high, E2 secretion is inhibited. Estrogens occur

in various isoforms including estrone (E1), 17β-estradiol (E2), estriol (E3) and estetrol (E4) *(18)*. E2 is the main circulating and most potent naturally occurring estrogen in premenopausal women; it is predominantly produced in the ovaries *(17)*. E2 levels are low in WHO Group I, normal in WHO Group II and low in WHO Group III.

Testosterone

Several androgens, including testosterone, are produced in the ovary and the adrenal glands in women *(15, 19)*. Ovarian androgens are generated in thecal cells and mediated by gonadotrophins, particularly LH *(12, 20, 21)*. Androgens are also produced in peripheral tissues through local conversion of prohormones *(15, 22)*. Ovarian hyperandrogenism, typically featuring high levels of testosterone, is characterized by oligomenorrhoea, hirsutism or acne *(23)*.

Progesterone

Progesterone is required for the maintenance of pregnancy *(24, 25)* and is initially produced by the corpus luteum after ovulation *(24)* and later by the fetoplacental unit after implantation *(25)*. Measurement of progesterone is suggested for the assessment of ovulation in this guideline (see **section 5.2** on the use of progesterone for presumptive confirmation of ovulation).

PRL

Hyperprolactinaemia is present in 6.6% of those with infertility *(26, 27)*, while hypoprolactinaemia is rare *(28)*. PRL secretion is regulated by multiple factors, including thyroid-releasing hormone (TRH) *(29)* and dopamine *(30)*. Clinical features of hyperprolactinaemia include oligomenorrhoea, amenorrhoea, infertility and galactorrhoea *(31)*. Symptoms of pituitary mass effect, such as headaches and visual disturbances, may also be present *(31)*.

TSH

When thyroid antibodies are present, both hypothyroidism and hyperthyroidism are more frequent in women with infertility *(32)*. Both hyperthyroidism and hypothyroidism can lead to menstrual disturbances *(32, 33)* and may result in changes in sex hormone binding globulin (SHBG) and sex steroids *(32)*. Hyperthyroidism arises when the thyroid gland produces excessive amounts of the thyroid hormones T_4 and/or T_3. Hyperthyroidism may present with either too scanty (hypomenorrhoea) or too frequent (polymenorrhoea) uterine bleeding, alongside other clinical features ranging from subclinical hyperthyroidism, overt hyperthyroidism, Graves' disease, toxic multinodular goitre and toxic adenoma *(32)*. Hypothyroidism results from an underactive thyroid gland *(34)* and may present with oligomenorrhoea alongside wide-ranging features, from subclinical hypothyroidism, overt hypothyroidism, or with symptoms secondary to pituitary disease *(13, 32)*. Hypothyroidism results in excessive hypothalamic secretion of TRH, which increases TSH *(29, 32)* and can affect PRL secretion *(29, 35, 36)*.

International reference standards

WHO international reference biological standards for bioassay and immunoassay are available for FSH, LH *(37, 38)*, PRL *(38, 39)* and TSH *(38, 40)*. In addition, an international reference biological standard for SHBG, which has clinical utility in interpreting the result of E2 and T, is also available *(38)*. In addition, FSH, LH, E2, PRL and TSH are already included in the WHO model list of essential in vitro diagnostics *(41)*. However, future efforts will be needed to include T in the WHO model list of essential in vitro diagnostics.

Rationale

The GDG agreed that measuring these hormones will assist to identify ovulation dysfunction and in selecting appropriate management of infertility. Assessment of these hormones will result in large net positive consequences and the opportunity cost of collecting and summarizing evidence is large. The GDG agreed that the choice of diagnostic tests should be based on clinical findings from a comprehensive medical history and physical examination, and ensure that evaluation is systematic and cost-effective.

Implementation considerations

The GDG agreed that multiple endocrinopathies may coexist in the same patient, which may require concomitant identification; therefore, the utility of each test may depend on the clinical profile. Indiscriminate ordering of tests should be avoided. Interactions between metabolic and reproductive systems may occur in patients *(42)*, including those with anovulation and oligo-ovulation, for example, in polycystic ovary syndrome (PCOS) *(43)*. Anovulation and oligo-ovulation may occur in a small proportion of eumenorrhoeic women (such as those with hirsutism and/or obesity) *(44, 45)*, whose differential diagnosis can be informed by history-taking and a physical examination. Consequently, selection of diagnostic tests based on clinical findings from medical history-taking and a physical examination is needed to ensure that evaluation is systematic and cost-effective (see **Chapter 3. Approach to the evaluation and management of infertility**).

Laboratory technical parameters can affect test results, and training and rigorous quality safeguards are necessary to minimize errors. Invalid results may result from cross-reactivity, interference, inter-assay or inter-laboratory variability, sample integrity, stability, storage and handling, and lack of standardization, among other factors. Whenever possible, laboratories should be encouraged to use low-cost matched reagents or international standards, engage in regular reagent and kit renewal, and perform internal and external quality assurance. Health care providers should note that hormones have infradian, circadian and ultradian rhythms *(46–48)* that may affect the results or optimal timing of blood draws *(1)*. To maintain a high-quality service, laboratories should be accredited to a suitable national or international body, such as the International Organization for Standardization (ISO), with a goal to comply with relevant standards, such as the international standard ISO 15189 *(49)*.

It is good practice to evaluate reproductive hormones during the initial evaluation of anovulation and oligo-ovulation, but these may not always ascertain a final diagnosis from a list of differential diagnoses. Further clinical or diagnostic evaluation may be required to fulfil the criteria for specific diagnosis. For example, further assessment of specific hormones is required to fulfil the diagnostic criteria for PCOS *(50)*, while further clinical evaluation is required to ensure that no anatomical or organic cause of amenorrhoea exists before making a diagnosis of functional hypothalamic amenorrhoea. In addition, measurement of E2 is essential in interpreting FSH levels, while measurement of SHBG is required to correctly interpret the serum levels of E2 and T. Similarly, when TSH is elevated, measurement of other thyroid parameters, such as serum free T_4 may be needed to make the final diagnosis. Depending on the clinical presentation, other hormonal assessments such as 17-α-hydroxyprogesterone or dehydroepiandrosterone sulfate, among others, may be needed to diagnose a range of endocrine conditions associated with anovulation and oligo-ovulation. Health care providers should carefully consider a potential differential diagnosis

based on clinical profile while ordering tests (see **Fig. 5.1. Diagnostic algorithm for female-factor infertility and unexplained infertility**). In all cases of amenorrhoea, health care providers should exclude pregnancy as part of infertility investigation.

Research gaps and future guideline update

Future updating of WHO classification of ovulation disorders is required through the revision procedures of the International Classification of Diseases.

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5.4 Assessment of ovarian reserve

Recommendation

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 follicle-stimulating hormone (FSH).
(Conditional recommendation, very low certainty of evidence)

Remarks:

- 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.

Background

Disorders of ovulation can cause infertility. In a multi-country study involving 8500 patients in 25 countries, anovulation and oligo-ovulatory disorders accounted for 26.1% of identifiable causes of female infertility *(1, 2)*; therefore, a key aspect of management of infertility includes the assessment of ovulation.

Ovarian reserve refers to the quantity of oocytes remaining in a woman's ovaries that have the potential to yield a pregnancy. The need to quantify the amount of remaining oocytes is based on the fact that the number of oocytes in the ovaries decreases progressively through atresia *(3, 4)*, resulting in declining fecundity over time *(5)*. Age is the most important determinant of reproductive potential; however, women of the same chronological age may have varying quantity and quality of oocytes *(6, 7)*, and there is a lack of a reliable metric for assessing oocyte quality.

When a couple presents with history of infertility and ovulatory dysfunction is suspected as a cause, several investigations may be undertaken to assess the HPO axis and endocrine hormones, as suggested in **Section 5.3**. In this PICO question, the GDG was interested in evaluating the role of ovarian reserve testing in the evaluation of anovulation or oligo-ovulation as a cause of infertility.

Conceptually, counting the number of oocytes would provide the definitive indicator of ovarian reserve; however, it can only be directly assessed through the histological examination of entire ovaries. Consequently, there are two overlapping interpretations and application of ovarian reserve testing, that is, (i) as an indirect indicator of biological reserve and (ii) as an indication of clinical response to stimulation *(8, 9)*. The first is related to the true number of primordial follicles. The second is a functional assessment of ovarian response to stimulation, that is, the quantity of follicles that are at late stages of development and capable of responding to stimulation *(8)*, that is, the potential number of oocytes that could potentially be available for retrieval during IVF *(9)*. Patients whose biological reserve is low are likely to exhibit a "poor"

response to ovarian stimulation (OS) *(10)*; however, there is a lack of consensus on the threshold that constitutes a decreased ovarian reserve.

Several tests are used for ovarian reserve testing, including AFC measured sonographically, E2, FSH, and inhibin B, and AMH *(11)*. For this PICO, the GDG was interested in the first application. The GDG agreed that an important decision that health care providers face is whether to use AFC, AMH or FSH.

AFC is an ultrasonographic test of ovarian reserve that quantifies the total number of follicles in both ovaries (typically 2–10 mm in diameter) observed during a transvaginal ultrasound scan *(12)*, typically during the early follicular phase. The number of antral follicles is interpreted as being an *indirect* indicator of the magnitude of the remaining follicular pool based on demonstrated correlations between AFC with histologically determined primordial follicle numbers *(11)*.

AMH is a glycoprotein produced by the granulosa cells of ovarian follicles *(13, 14)*. AMH declines as the number of ovarian follicles declines with age *(15, 16)*, and its levels correlate with the primordial follicular pool *(11)*.

FSH is a glycoprotein secreted in the anterior pituitary gland in response to the production of inhibin B by preantral follicles via a negative feedback loop that involves a complex interaction of several factors, including sex steroid hormones (mainly estrogens) and GnRH *(17, 18)*. With advancing age, secretion of early follicular phase inhibin B declines, which partly contributes to increased pituitary FSH secretion, and higher late luteal and early follicular FSH concentrations *(19–21)*. Measuring FSH levels (typically around cycle day 3) provides an indirect measure of pool of ovarian follicles *(7, 8)*.

For this recommendation, the GDG addressed the question: should AFC versus FSH or AMH be used for the assessment of ovarian reserve in women with infertility in whom other causes of anovulation or oligo-ovulation have been ruled out?

Balancing harms and benefits

We first searched for systematic reviews published since 2000 and found three reviews published in the early 2000s *(22–24)*. These reviews assessed FSH, AMH and AFC to predict poor response to ovarian stimulation which can provide indirect evidence for ovarian reserve. More recently, a systematic review and meta-analysis of individual patient data was conducted to assess the effect of adding ovarian reserve tests to age to predict poor response to ovarian stimulation *(25)*. This review reported that age was a good predictor of poor response and the addition of tests such as AFC and AMH only marginally improved this prediction.

Searches were also previously conducted from 1990 to July 2019 for test accuracy studies and studies measuring health outcomes that directly compared AFC versus FSH versus AMH in the same women. We found a systematic review published in 2023 by Liu et al. *(26)* with a search date up to May 2022 *(26)*, comparing AMH and AFC, and one study by Jaiswar et al. *(27)* comparing all three tests.

The study by Jaiswar et al. *(27)* was a low risk of bias study that included 100 women with infertility aged < 40 years old in India who received clomiphene citrate stimulation and poor response was defined as < 3 oocytes retrieved. In this study, FSH was measured once per participant, and paired E2 levels were not assessed. Sensitivity and specificity were calculated from this study (with 95% lower and upper confidence intervals [CIs]) as shown in **Tables 5.3** and **5.4**.

Table 5.3. Sensitivity and specificity for AFC, AMH and FSH

	AFC	AMH	FSH
Sensitivity (95% CI)	78% (64–88%)	80% (67–90%)	63% (48–76%)
Specificity (95% CI)	65% (51–76%)	74% (61–84%)	69% (55–79%)

AFC, antral follicle count; AMH, anti-Müllerian hormone; CI, confidence interval; FSH, follicle-stimulating hormone.

Source: Jaiswar et al., 2015 *(27)*.

Table 5.4. Absolute effects on 100 women when AFC, AMH and FSH are provided

	AFC	AMH	FSH
True positives	36	37	29
True negatives	35	40	37
False positives	19	14	17
False negatives	10	9	17

AFC, antral follicle count; AMH, anti-Müllerian hormone; CI, confidence interval; FSH, follicle-stimulating hormone.

Source: Jaiswar et al., 2015 *(27)*.

The systematic review by Liu et al. *(26)* included 42 studies and did not conduct a paired analysis of studies; it pooled studies together that assessed the accuracy of one test and then compared those pooled results to the pooled analysis of the studies that assessed the accuracy of the other test. Studies were conducted in women with infertility to predict poor or high response to IVF treatment. The results for poor response are presented in **Table 5.5** (a range of cut-offs were used).

Table 5.5. Results for poor response from a systematic review

	AMH	AFC
Sensitivity (95% CI)	80% (74–85%)	73% (62–83%)
Specificity (95% CI)	81% (75–85%)	85% (78–90%)

AFC, antral follicle count; AMH, anti-Müllerian hormone; CI, confidence interval.

Source: Liu et al., 2023 *(26)*.

This review *(26)* showed that per 100 patients tested, and compared to AMH, the use of AFC resulted in two fewer true positives, two more false negatives, three more true negatives and three fewer false positives.

In considering desirable effects, the GDG noted that the study comparing all tests and the systematic review comparing AFC to AMH reported differences in false positives and false negatives of about 2–5 women out of 100. The GDG agreed that the benefits of AFC compared to AMH or FSH are trivial. In addition, the GDG considered the systematic reviews of poor response showing that when compared to age, AMH may moderately predict a poor response, AFC could be a good predictor at very low levels and FSH may not be a better predictor, and agreed that the benefits of these tests were trivial. The GDG agreed that when added to age, the benefits of these tests were trivial.

In terms of harms, the GDG noted that the comparative study comparing all tests and the systematic review comparing AFC to AMH found differences in false positives and false negatives of about 2–5 women out of 100. The GDG agreed that the harms of AFC compared to AMH or FSH are trivial.

The certainty of the evidence in the comparative accuracy of the tests was low and was further rated to very low because of indirectness by the GDG. The studies did not quantify the numbers of oocytes remaining in a woman's ovaries; instead, they measured ovarian response to stimulation, which is then taken as an indirect measure of the numbers of oocytes remaining in a woman's ovaries with the potential to yield a pregnancy.

No studies were identified on patient values; however, the GDG agreed that women would value tests that can identify the diagnosis correctly and would seek to minimize the harms of unnecessary tests, frequent travel (e.g. for serial tests) and costs. The GDG agreed that probably no important uncertainty or variability existed in how much people value these outcomes. Based on these data, the GDG agreed that the balance of effects does not favour any of the tests compared to one another.

Other considerations

There was no direct research evidence for resources required; however, the GDG agreed that in LMICs the cost differences vary among AFC, AMH and FSH. There was no direct evidence on cost-effectiveness; however, the GDG agreed that given that there are similar benefits and harms with all tests, and the cost differences vary, then cost-effectiveness would vary. No studies reported on health inequities related to any of the three tests; however, the GDG agreed that in some settings certain tests may be more available. Therefore, the impact on equity varies.

The GDG considered several studies that assessed the acceptability of these tests to patients *(8)* and providers *(28–33)* and judged that acceptability varies. The GDG agreed that the feasibility and availability of the different tests varies in different settings and countries.

Summary justification

Evidence found that there may be little to no difference in the test accuracy of AFC or AMH or day 3 FSH, but this evidence is of very low certainty. The costs, resources, feasibility and acceptability of FSH, AMH and AFC likely vary across different settings and countries; therefore, the preferred test will be dependent on those factors.

Implementation considerations

Health care providers should note that ovarian reserve tests are suggested in this guideline as an optional test for diagnostic purposes, during the evaluation of anovulation or oligo-ovulation, where other causes of anovulation or oligo-ovulation have been excluded or have not been identified (e.g. by assessing the HPO axis [E2,

T, FSH, LH], as well as TSH and PRL), and whose explanation of failure to achieve pregnancy could potentially be related to reduced numbers (or quality) of oocytes.

Health care providers should note that the primordial follicles count is the definitive indicator of ovarian reserve; however, it can only be measured directly using histological examination of entire ovaries. For this reason, surrogate markers, such as AFC, AMH and FSH, which may correlate with the primordial follicle count, provide an indirect indication of biological reserve. Health care providers should note that each of these tests have advantages and disadvantages, whose relative importance varies in different settings and countries; therefore, it is important to consult with the patients when selecting the test, through a process of collaborative decision-making. The application of these tests during IVF treatment, including to predict outcomes, is not within the scope of this diagnostic PICO.

Selection of optional test to assess ovarian reserve should be based on relative acceptability, availability and resources in local contexts. In selecting these tests, health care providers should also consider several technical parameters, such as those related to inter-laboratory or inter-observer variability *(8, 34)*, turnaround times for these tests and availability of WHO international assay standards *(35–37)*. Technical parameters can affect test results, and training and rigorous quality safeguards are necessary to minimize errors.

Correct interpretation of the results of hormonal tests, such as FSH, may require concomitant evaluation of other test results (e.g. E2 *[38]*) and may be influenced by cycle-to-cycle variations, particularly AMH and AFC *(8, 35)*. In the studies reviewed for this recommendation, AFC was assessed in the first half of the menstrual cycle, AMH was cycle-independent and **FSH in combination with E2** was assessed on either cycle days 2–3 or cycle days 2–4.

Health care providers should consider how these tests fit in with other planned investigations. Selection of diagnostic tests should be based on clinical findings from comprehensive medical history and physical examination to ensure that evaluation is systematic and cost-effective (see **Chapter 3**). For example, the ability of age to predict ovarian reserve may be limited in some clinical scenarios such as cases of premature ovarian insufficiency.

Research gaps and future guideline update

Data were insufficient to determine if there are subgroups of patients that may benefit more from any of the tests, for example, patients with ovarian endometriomas or other ovarian masses. Future comparative studies among different subgroups are needed to respond to this gap. Given the very low certainty of evidence, future comparative studies assessing ovarian reserve should be better designed and implemented. Future guidance will be required on the role of ovarian reserve testing during IVF, including to predict outcomes and the likelihood of success, as this was not within the scope of this diagnostic PICO. This recommendation relates to application of these tests in health care settings and does not relate to direct-to-consumer tests, for example, AMH tests *(39)*, which will require future guidance.

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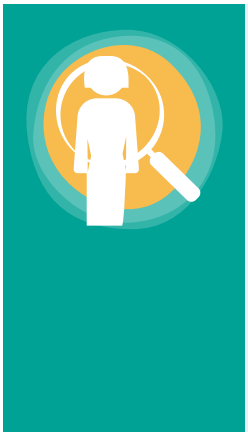
5.5 Diagnosis of infertility due to tubal disease



Recommendation

For females with infertility and suspected tubal disease, WHO suggests using either hysterosalpingogram (HSG) or hysterosalpingo contrast sonography (HyCoSy) to assess tubal patency. *(Conditional recommendation, low certainty of evidence)*

Remark:

- 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.

Background and rationale

Evaluation of tubal patency is an essential part of investigating the cause of infertility. In a large WHO multi-country study involving 8500 couples in 25 countries, bilateral tubal blockage contributed to 17.7% of identifiable causes of female infertility *(1)*. The diagnosis of tubal occlusion is generally established by a combination of clinical suspicion based on patient history and confirmatory diagnostic tests. Diagnostic laparoscopy with chromopertubation is considered the reference gold standard for confirming suspected tubal disease because it allows visualization of the fallopian tubes and adjacent pelvic tissue. However, it is invasive and costly, and requires general anaesthesia, making it unsuitable for routine diagnostic assessment of tubal pathology. Alternative options include HSG and HyCoSy. HSG and HyCoSy are typically performed during the follicular phase of the menstrual cycle between cycle days 6 and 10, before the lining gets too thick, which may obscure any pathology, and to avoid interrupting an undiagnosed very early pregnancy.

During HSG, iodinated contrast medium is slowly flushed through the uterine cavity and fallopian tubes using a catheter or cannula, resulting in their distension and visualization under fluoroscopic guidance. Still radiographs are performed. HSG uses either oil- or water-soluble contrast medium *(2)*. Opacification of the fallopian tubes with subsequent free intraperitoneal spill is considered a sign of tubal patency. Although HSG is less invasive than laparoscopy, it may result in adverse effects, such as pain, infection, allergic reaction to iodine, as well as exposure to ionizing radiation *(3)*.

During HyCoSy, echogenic distending medium is slowly injected distending the uterine cavity, uterus and fallopian tubes using a catheter or cannula, allowing visualization of the fallopian tubes with the aid of transvaginal or rarely, transabdominal ultrasonography. HyCoSy can be performed with either air-saline or microbubble distending medium. High-contrast echoes in the fallopian tube indicate tubal patency. Although HyCoSy circumvents the risk of iodine allergy and radiation, it may also be complicated by adverse effects, such as pain, infection, or allergy to the distending medium used *(3)*. The GDG agreed that a key decision when investigating women with infertility and suspected tubal disease is whether to use HSG or HyCoSy. For this recommendation, the GDG addressed the question: should HyCoSy versus HSG be used to evaluate women with infertility and suspected tubal disease? Assessment of the uterine cavity is presented in **section 5.6** and is not included in this recommendation question.

Balancing harms and benefits

Diagnostic test accuracy

We updated a prior systematic review by Maheux-Lacroix et al. *(3)* on data about the test accuracy of HyCoSy up to July 2019. Eight non-randomized studies *(4–11)* were included, in which participants received both tests and the results were compared to a gold standard reference (typically laparoscopy). Based on the comparable sensitivity and specificity of the tests (including the respective 95% CIs, as shown in **Table 5.6**), we calculated the absolute effects on true and false positives, and true and false negatives. The results showed that there is likely little difference in the absolute effects of the two tests. Compared with HSG, HyCoSy likely results in three more true positives, three fewer false negatives, eight fewer true negatives and eight more false positives per 1000.

Table 5.6. Sensitivity and specificity of HyCoSy and HSG

	HyCoSy	HSG
Sensitivity (95% CI)	0.93 (0.79–0.98)	0.92 (0.74–0.98)
Specificity (95% CI)	0.89 (0.79–0.94)	0.90 (0.86–0.93)

CI, confidence interval; HyCoSy, hysterosalpingo contrast sonography; HSG, hysterosalpingogram.

Effects on health outcomes

To assess whether the use of HyCoSy versus HSG could lead to better management and improved outcomes, a systematic review was conducted from 1990 to July 2019, and 12 studies were identified. Very few studies measured benefits; therefore, the evidence is uncertain for the effect on pregnancy or live birth. One study *(12)* evaluated clinical pregnancies during a 6-month follow-up period. From that study, there may be 53 fewer clinical pregnancies (from 81 to 14 fewer) per 1000 participants (odds ratio [OR]: 0.61; 95% CI 0.42–0.89) with HyCoSy compared to HSG. A second study *(13)* with a follow-up period of 3 years showed that HyCoSy may result in 24 fewer clinical pregnancies per 1000 (from 74 fewer to 29 more) (OR: 0.90; 95% CI 0.72–1.13) compared to HSG. Only one study *(14)* assessed live births and it showed that there may be 16 more (from 35 fewer to 95 more) per 1000 (RR: 1.13; 95% CI 0.71–1.79) with HyCoSy compared to HSG.

Adverse effects

To assess whether the use of HyCoSy versus HSG could lead to better management and fewer side-effects, a systematic search was conducted and 11 comparative non-randomized studies were included *(8, 12, 14–22)*. There is very-low-certainty evidence for most harms. Compared to HSG, the effects of HyCoSy were uncertain on severe pain (four studies) (74 fewer, [from 239 fewer to 251 more], per 1000, RR: 0.82; 95% CI 0.42–1.61), miscarriages (one study) (20 fewer, [from 39 fewer to 18 more], per 1000, OR: 0.64; 95% CI 0.3–1.35), other adverse effects such as vasovagal reactions, nausea or vomiting, vaginal bleeding and bloating (39 fewer, [from 93 fewer to 70 more], per 1000, five studies; RR: 0.72; 95% CI 0.34–1.5), ectopic pregnancies and anxiety. Although there is radiation exposure with HSG, the GDG did not consider the potential harms to be of great concern but noted the need for future evaluation of its effects on maternal and neonatal outcomes.

The certainty of evidence was moderate for differences in the accuracy of the tests and low to very low for the downstream health outcomes. Thus, the overall certainty of the evidence is low. There were no studies on patient values; however, the GDG agreed that women would value better

pregnancy and birth outcomes and would seek to minimize harms. Given that the net desirable and undesirable effects between HyCoSy and HSG are trivial, neither test is favoured over the other.

Other considerations

No data were identified related to costs or cost-effectiveness between HSG and HyCoSy. Although HSG may require a radiographic unit, the GDG considered that HyCoSy is highly operator-dependent *(23)*, but both HSG and HyCoSy require training of health care providers. Thus, the GDG agreed that both tests likely involve similar costs and resources, and there is likely no difference in cost-effectiveness between the two. Given that the costs are similar between HSG and HyCoSy, the GDG agreed that providing one test rather than another would probably have no impact on equity.

A systematic search was conducted of other factors related to the acceptability of HSG and HyCoSy. The GDG considered evidence from several studies *(21, 24–26)* and agreed that both tests are probably acceptable to patients and providers. The GDG agreed that both tests are similarly feasible and require resources and expertise to conduct or interpret, based on the evidence from two studies *(23, 27)*.

Summary justification

Overall, there was low-certainty evidence for trivial differences in desirable and undesirable effects between the use of HSG or HyCoSy in women who have infertility and suspected tubal disease. The costs, resources, feasibility and acceptability are probably similar, and choosing either test would probably have no impact on equity.

Implementation considerations

When selecting a diagnostic method, health care providers should also consider the potential for allergy and the need to evaluate the uterus, ovaries and myometrium in the context of infertility. Health care providers should monitor patients for adverse effects and consider analgesics as appropriate *(28)*. Health care providers should be aware of and monitor patients for potential thyroid dysfunction associated with iodine-based contrast media and should adhere to contraindications of specific products to prevent such harms, especially among patients with thyroid disease *(29)*.

To ensure safety, training of health care providers on how to perform HSG or HyCoSy procedures is required. Given equipoise between HSG and HyCoSy, health care providers should seek patients' preferences in keeping with the principles of shared decision-making. Future studies comparing HSG and HyCoSy should report patient preferences and whether the use of either test improves management and, consequently, the effects on live births to better inform future recommendations.

Research gaps and future guideline update

Additional data are required on the costs and cost-effectiveness of HSG and HyCoSy, given the lack of evidence on these aspects. Further guidance is required to identify populations that would benefit from the use of oil-based contrast compared with water-based contrast during HSG. Further guidance is required on the use of either air-saline or microbubble commercial contrast media, probe type (vaginal versus abdominal) and Doppler sonography versus conventional two-dimensional (2D) or three-dimensional (3D) US during HyCoSy. Future guidance is required on the effect of location of tubal pathology (distal versus proximal) on the test performance of both HSG and HyCoSy. Although radiation exposure with HSG is

considered low, there is a need for the evaluation of the potential effects of peri-conceptional radiation exposure on maternal thyroid function and offspring neurodevelopment. Further guidance will be needed on whether prophylactic antibiotics should be used during HyCoSy or HSG.

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5.6 Diagnosis of infertility due to uterine cavity disorder

This section contains several recommendations related to the diagnostic assessment of the uterine cavity. Figure 5.2. shows how these recommendations relate to each other, illustrated in a diagnostic algorithm. Specific recommendations are presented in the sections that follow, based on head-to-head comparisons of different diagnostics methods.

Hierarchy of uterine investigations

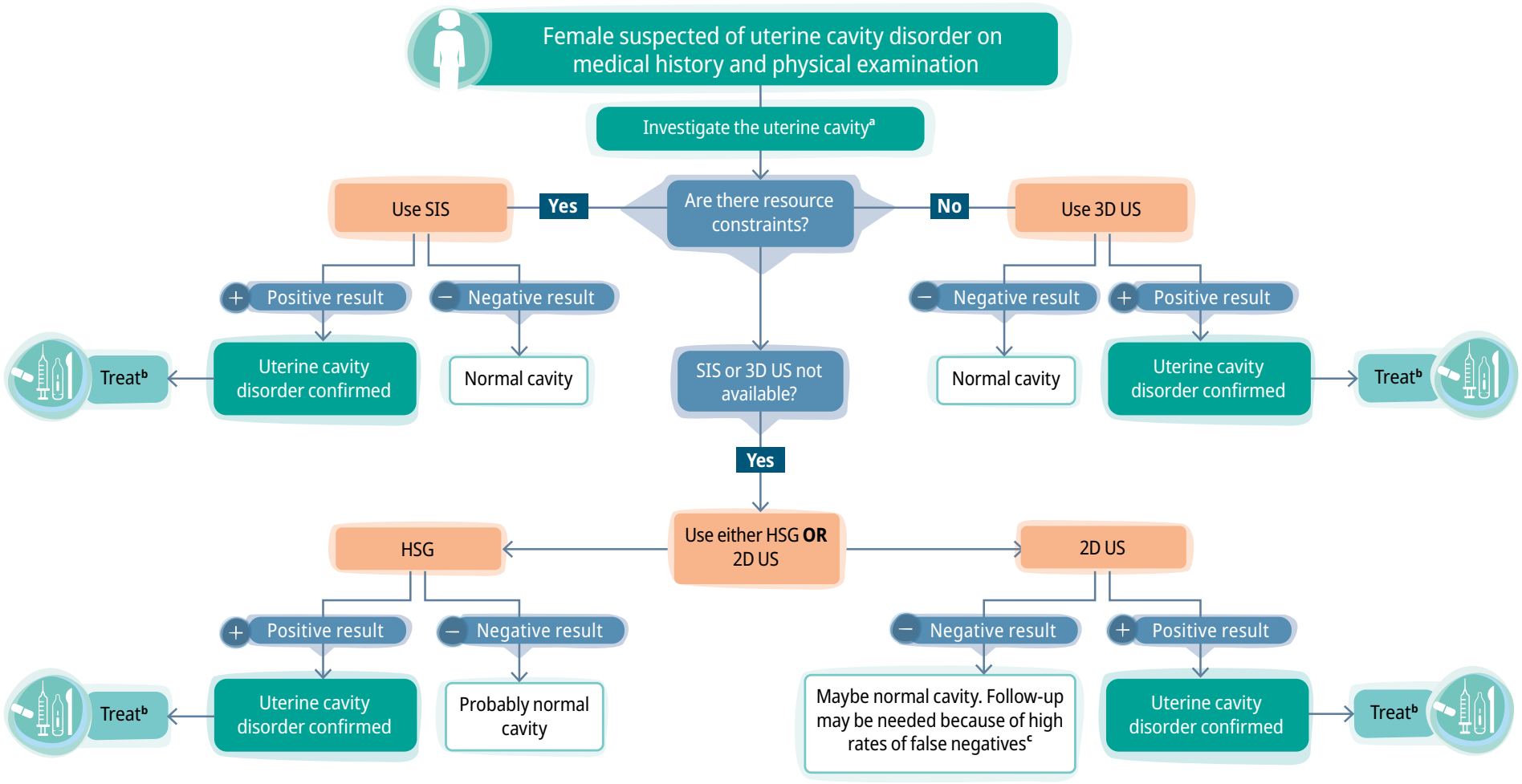
Hysteroscopy (± laparoscopy) is the gold standard in the assessment of the uterine cavity; however, it is an invasive procedure that may require anaesthesia or sedation, making it unsuitable for routine diagnostic assessment of the uterine cavity. As illustrated in **Fig. 5.2**, this guideline suggests that saline infusion sonohysterography (SIS) should be ordinarily used because of cost considerations, unless 3D US is readily available within existing resources. Where SIS or 3D US are not available, either HSG or 2D US may be used. **Table 5.7** shows the comparison of test performance between 3D US, SIS, 2D US and HSG with hysteroscopy for the diagnosis of uterine cavity disorders.

Table 5.7. Comparison of 3D US, SIS, 2D US and HSG with hysteroscopy for the diagnosis of uterine cavity disorders

	3D US	SIS	2D US (paired data with 3D US)	HSG (paired data with SIS)	Hysteroscopy
Sensitivity (95% CI)	96% (59–100)	89% (72–95)	68% (59–75)	72% (56–84)	100%
Specificity (95% CI)	94% (77–99)	100% (27–100)	93% (64–99)	93% (66–99)	100%
True positives	14	13	10	11	15
False negatives	1	2	5	4	0
False positives	5	0	6	6	0
True negatives	80	85	79	79	85

2D, two-dimensional ultrasound; 3D, three-dimensional; CI, confidence interval; HSG, hysterosalpingogram; SIS, saline infusion sonohysterography; US, ultrasound.

Fig. 5.2. Diagnostic algorithm for the assessment of the uterine cavity



[a] See **Fig. 5.1** for the overall diagnostic algorithm for female-factor infertility.
[b] See recommendations for the treatment of uterine-factor infertility in **Chapter 8**.
[c] See the **Table 5.7** for the comparison of 3D US, SIS, 2D US and HSG with hysteroscopy for the diagnosis of uterine cavity disorders.
2D, two-dimensional; 3D, three-dimensional; HSG, hysterosalpingogram; SIS, saline infusion sonohysterography; US, ultrasound.

Recommendation

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 three-dimensional ultrasound (3D US).
(Conditional recommendation, low certainty of evidence)

Remark:

- In settings where 3D US is already available within the existing resources, 3D US may be the preferred option.

Background and rationale

Infertility can be affected by uterine cavity abnormalities. The incidence of intrauterine abnormalities, such as polyps, fibroids, adhesions and congenital malformations, is higher in women with infertility than in the general population *(1, 2)*. Therefore, accurate detection of uterine cavity abnormalities is important in the identification of the cause and subsequent management of infertility.

Hysteroscopy is considered the reference gold standard for the assessment of uterine abnormalities because it allows direct visualization of the endometrial cavity, as well as the ability to obtain tissue for histological diagnosis. The procedure involves inserting a flexible, semi-flexible or rigid telescope into the endometrial cavity. To optimize visualization, uterine distension with carbon dioxide or normal saline is typically performed. However, it is an invasive procedure that may require anaesthesia or sedation, making it unsuitable for routine diagnostic assessment of the uterine cavity.

SIS is a diagnostic procedure that involves the manual installation of saline into the uterine cavity transcervically to act as a negative contrast agent and facilitate enhanced endometrial visualization during transvaginal assessment of the endometrial cavity using ultrasound *(3, 4)*. The infusion of sterile isotonic fluid during transvaginal sonography into the uterine cavity facilitates uterine distension and enhanced visual contrast during real-time ultrasonographic examination *(4, 5)*.

Ultrasonography (US imaging) involves the generation and transmission of ultrasonic (high-frequency sound) waves from a transducer and processing of a returning echo to generate an image. It is based on non-ionizing energy *(6)*. Although ultrasound examination of the myometrium may be performed using a transabdominal transvaginal or more rarely transrectal approach *(7, 8)*, the transvaginal approach is most commonly used for assessing uterine abnormalities *(7–9)*. 3D US is an enhancement of ultrasonography, which formats the sound wave data into 3D images and enables their offline examination and manipulation *(9, 10)*.

The GDG agreed that a key decision when investigating women with infertility and suspected uterine pathology is whether to use SIS or 3D US. For this recommendation, the GDG addressed the question: should SIS versus 3D US be used to evaluate women with infertility and suspected uterine cavity abnormality?

Balancing harms and benefits

De novo searches were conducted to identify diagnostic test accuracy (DTA) studies on SIS and 3D US and to identify studies on health outcomes up to November 2019. We found one study in which women received both SIS and 3D transvaginal ultrasound, and results were compared to the reference standard of hysteroscopy. It determined the sensitivity and specificity of each test to identify fibroids, endometrial polyps, intrauterine synechiae and Müllerian anomalies, as well as arcuate, unicornuate, bicornuate and subseptate uteri *(11)*, as shown in **Table 5.8**.

Table 5.8. Sensitivity and specificity for 3D US and SIS with 95% CIs from one paired study *(11)*

	3D US	SIS
Sensitivity (95% CI)	74% (60–85%)	88% (76–96%)
Specificity (95% CI)	100% (87–100%)	100 (87–100%)

3D, three-dimensional; CI, confidence interval; SIS, saline infusion sonohysterography; US, ultrasound.

The search also found comparative studies that included different tests, one of which was either SIS or 3D US. Therefore, one arm of those studies was used to pool the sensitivity and specificity of the two tests. Because of lack of large studies on each uterine anomaly, the synthesized evidence in this recommendation question pooled data related to many uterine abnormalities. Each of the identified studies diagnosed the uterine cavity disorders shown in **Table 5.9**.

Table 5.9. Studies comparing 3D US and SIS, and the conditions identified

Test modality	Study	Condition identified
3D	Abdelmagied et al. *(12)*	Cavitary lesions (e.g. polyps in 47%)
	Aboulghar et al. *(11)*	Fibroids; endometrial polyps; intrauterine synechiae; Müllerian anomalies; arcuate, unicornuate, bicornuate and subseptate uteri (few)
	Niknejadi et al. *(13)*	Septate uterus (arcuate, subseptate, septate)
SIS	Alatas et al. *(14)*	Endometrial polyp, uterine anomaly, submucous myoma
	Ayida et al. *(15)*	Submucosal fibroid, endometrioma, structural abnormality, adhesions. Atrophic endometrium, fibrosis, echogenic endometrium
	Bartkowiak et al. *(16)*	Submucous myomas, endometrial polyp, septate uteri, intrauterine synechiae
	Fadl et al. *(17)*	Endometrial polyps
	Guven et al. *(18)*	Endometrial polyps, submucosal myomas
	Ragni et al. *(19)*	Intrauterine pathology (polyp, myoma, malformation, synechiae, thick endometrial mucosa)
	Soares et al. *(20)*	Polypoid lesions, uterine malformations, intrauterine adhesions and endometrial hyperplasia
	Sitimani et al. *(21)*	Endometrial polyp, submucous myoma, intrauterine synechiae or any other (thin endometrium, endometrial hyperplasia)

Test modality	Study	Condition identified
	Alborzi et al. *(22)*	Total tubal and uterine pathologies: tubal obstruction. Intracavitary pathologies: Asherman syndrome, endometrial polyps, myomatous uterus. Structural uterine anomalies: septate uterus and other structural uterine anomalies
	De Felice et al. *(23)*	Abnormalities of the uterine cavity
	Aboulghar et al. *(11)*	Fibroids; endometrial polyps; intrauterine synechiae; Müllerian anomalies; arcuate, unicornuate, bicornuate and subseptate uteri (few)

3D, three-dimensional; SIS, saline infusion sonohysterography; US, ultrasound.

Calculations of sensitivity and specificity were conducted based on unpaired studies, as shown in **Table 5.10**.

Table 5.10. Sensitivity and specificity of 3D US and SIS with 95% CIs from unpaired studies

	3D US	SIS
Sensitivity (95% CI)	96% (59–100%)	88% (72–95%)
Specificity (95% CI)	94 (77–99%)	100 (27–100%)

3D, three-dimensional; CI, confidence interval; SIS, saline infusion sonohysterography; US, ultrasound.

Calculations of absolute effects on true and false negatives and positives were based 15% prevalence of uterine cavity disorders in women with infertility. The results showed that there may be one less true positive per 100 with SIS than with 3D US, one more false negative per 100 with SIS than 3D US, five more true negatives per 100 with SIS compared with 3D US and five fewer false positives per 100 with SIS compared with 3D US. The GDG agreed that in a population where the prevalence of uterine cavity disorder was 15%, five fewer false positives is a trivial difference in the number of women correctly identified with SIS compared to 3D US; likewise, one more missed woman with uterine cavity disorder (false negative) with SIS is considered trivial. The GDG noted that the synthesized evidence combined the analysis of many uterine abnormalities, and that sensitivity and specificity may differ between anomalies.

Additional data for health outcomes, such as adverse events, were obtained from studies *(11, 19, 20, 24–28)*. Based on these data, the GDG judged that the undesirable effects with SIS may be trivial compared to 3D US although the evidence is uncertain. Given the trivial differences in benefits and harms between SIS and 3D US, the GDG judged that the balance of effects probably does not favour one over the other. There were no studies on patient values; however, the GDG agreed that women would likely value tests that can identify the diagnosis correctly and would seek to minimize harms, and that there was probably no important uncertainty or variability in how women value these outcomes. The overall certainty of evidence was low.

Other considerations

Although comparative data about costs were not available, the GDG agreed that 3D US is likely more expensive than SIS and SIS would probably lead to moderate savings. There were no data on cost-effectiveness; however, the GDG agreed that given the trivial differences in benefits and harms but moderate savings with SIS, that SIS is probably

favoured. In addition, the GDG judged that SIS could probably increase equity because it is more widely available than 3D US. Although no data were available, the GDG agreed that SIS and 3D US are likely both acceptable. One study *(29)* provided an analysis of feasibility of 3D US and SIS. The GDG considered that although both require training of health care providers, SIS is probably more feasible than 3D US because 3D US is not as widely available.

Summary justification

There is low-certainty evidence that there are trivial differences in benefits and harms with SIS compared to 3D US. Although both are acceptable, 3D US likely costs more than SIS and is less available; therefore SIS is suggested. In settings where it is already available within the existing resources, 3D US may be the preferred option.

Implementation considerations

Training of health care providers is required to ensure the correct assessment, documentation and reporting of uterine cavity assessment *(9, 30)*.

Research gaps and future guideline update

Because of the lack of large studies on each uterine anomaly, the synthesized evidence in this PICO is based on pooled data related to many uterine abnormalities. Future large studies are required to provide sufficient discriminatory power. Future guidance is required to compare the role of colour, power and spectral Doppler, as well as four-dimensional (4D) ultrasonography in evaluating uterine cavity disorders, including different types of Müllerian anomaly disorders *(31)*.

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Recommendation

For females with infertility who are suspected to have a uterine cavity disorder, WHO suggests assessing the uterine cavity with three-dimensional ultrasound (3D US) rather than two-dimensional ultrasound (2D US) where resources are available. *(Conditional recommendation, low certainty of evidence)*

Background and rationale

Ultrasound imaging (sonography) involves the generation and transmission of ultrasonic (high-frequency sound) waves from a transducer and processing of a returning echo to generate an image. It is based on non-ionizing energy *(1)*. The image is subsequently displayed on a monitor, from which a hard copy may be captured, for example, using thermal printing paper *(1)*. Although US examination of the myometrium may be performed using a transabdominal transvaginal or more rarely transrectal approach *(2, 3)*, a transvaginal approach is more commonly used for assessing uterine abnormalities *(2–4)*. 3D US is an enhancement of ultrasonography, which formats the sound wave data into 3D images and enables their examination offline *(4, 5)*.

The GDG agreed that a key decision when investigating women with infertility and suspected uterine pathology is whether to use 3D or 2D US. For this recommendation, the GDG addressed the question: should 3D versus 2D US be used for women with infertility and suspected uterine cavity abnormality? Although advancements in technology have allowed further enhancements of sonography, including colour, power and spectral Doppler, which allow assessments of endometrial vascularity and blood flow, as well as 4D US, this PICO focuses on 3D US compared to 2D US.

Balancing harms and benefits

A de novo search was conducted to identify DTA studies on 3D and 2D US up to November 2019. Studies included women who received 3D or 2D US and compared results to the reference standard of hysteroscopy. Because of the lack of large studies on each uterine anomaly, the synthesized evidence in this recommendation question pooled data related to many uterine abnormalities. The identified studies assessed the sensitivity and specificity of uterine cavity disorders as shown in **Table 5.11**.

Table 5.11. Included studies comparing 3D and 2D US, and the conditions identified

Study	Condition identified
Abdelmagied et al. *(6)*	Cavitary lesions (e.g. polyps in 47%)
Aboulghar et al. *(7)*	Fibroids; endometrial polyps; intrauterine synechiae; Müllerian anomalies; arcuate, unicornuate, bicornuate and subseptate uteri (few)
Niknejadi et al. *(8)*	Septate uterus (arcuate, subseptate, septate)

2D, two-dimensional; 3D, three-dimensional; CI, confidence interval; US, ultrasound.

Pooled sensitivity and specificity were calculated across the studies with paired analysis (with 95% lower and upper CIs) as shown in **Table 5.12**.

Table 5.12. Pooled sensitivity and specificity for 3D and 2D US with 95% CIs

	3D US	2D US
Sensitivity (95% CI)	96% (59–100%)	68% (59–75%)
Specificity (95% CI)	94% (77–99%)	93% (64–99%)

2D, two-dimensional; 3D, three-dimensional; CI, confidence interval; US, ultrasound.

The GDG noted that 3D US had greater sensitivity and specificity compared to 2D US, although there was overlap in CIs. The GDG noted that the synthesized evidence combined the analysis of many uterine abnormalities, but sensitivity and specificity may differ between anomalies; however, available data are insufficient to provide discriminatory power.

Calculations for the absolute effects on true and false negatives and positives were conducted, assuming a 15% prevalence of uterine cavity disorders among women with infertility. Based on this prevalence, results showed that there may be four more true positives with 3D US compared to 2D US, four fewer false negatives with 3D US compared to 2D US, one more true negative with 3D US compared to 2D US and one fewer false positive with 3D US compared to 2D US. The GDG judged that in a population where 15 out of 100 people have a uterine cavity disorder, four more true positives and four more true negatives was a small number of women correctly identified with and without uterine cavity abnormality, and that even fewer women were missed (false negatives).

Data for health outcomes such as adverse events and complications were available from Soares et al. *(9)* and Aboulghar et al. *(7)*. In terms of harms, data from two RCTs showed that no complications were reported from participants who underwent both procedures. The GDG agreed that adverse events (pain and complications) may be similar between 3D and 2D US, but the evidence is uncertain. There were no data for pregnancy or quality of life outcomes.

There were no studies on patient values; however, the GDG agreed that women would value tests that can identify the diagnosis correctly and would seek to minimize harms, and there was probably no important uncertainty or variability in these outcomes. Given the small benefits and trivial harms, the balance of effects probably favoured 3D over 2D US. The GDG judged that the certainty of evidence was low.

Other considerations

Although comparative data for costs were not available, the GDG judged that 3D US is relatively more expensive than 2D US. In regard to cost-effectiveness, and in the absence of data, the GDG judged that given the small benefits and moderate costs of 3D US, neither 3D nor 2D US is favoured. There were no data on acceptability; however, the GDG judged that 3D US and 2D US are both acceptable. The GDG agreed that 3D US could probably reduce equity because it is less widely available than 2D US. One study *(10)* reported an analysis of feasibility of 3D and 2D US. The GDG agreed that 3D US is probably feasible, but it requires appropriate probes, software and software maintenance and training of health care providers.

Summary justification

There is low-certainty evidence that there are small benefits (correct identification of women with uterine cavity disorders) and trivial differences in harms (pain and complications) with 3D US compared to 2D US. In addition, acceptability is likely similar. The additional costs and resources required for 3D US are outweighed by the benefits, and 3D US is suggested where resources permit.

Implementation considerations

Training is required to ensure that health care providers have the skills to assess safely and correctly document and report findings while evaluating the uterus *(2, 4, 11, 12)*.

Research gaps and future guideline update

Because of the lack of large studies on each uterine anomaly, the synthesized evidence combined the analysis of many uterine abnormalities. Future large studies are required to provide sufficient discriminatory power. Future guidance is required to compare the role of colour, power and spectral Doppler, as well as 4D ultrasonography.

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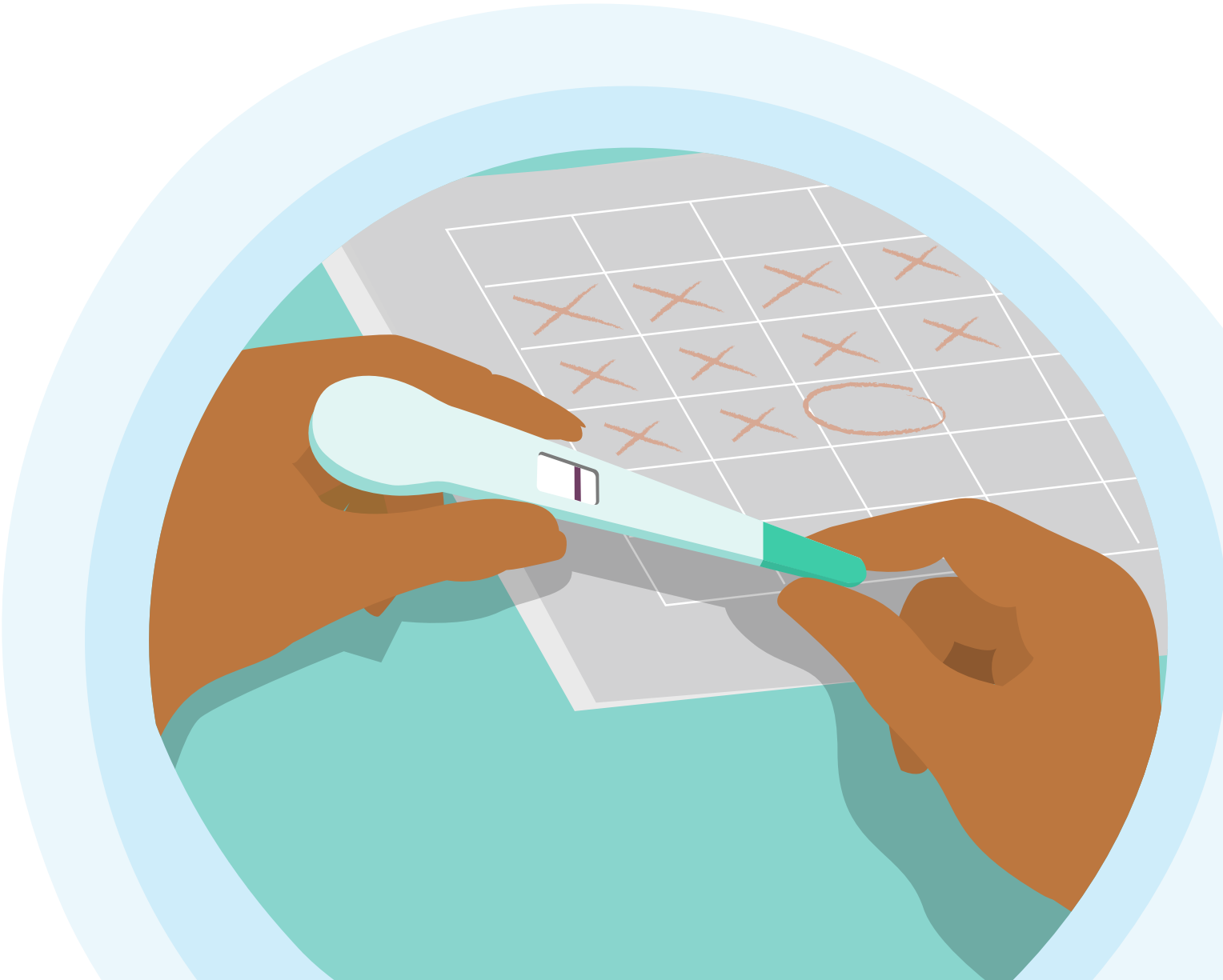

Recommendation

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 two-dimensional ultrasound (2D US).
(Conditional recommendation, low certainty of evidence)

Background and rationale

SIS is a diagnostic procedure that involves the manual installation of saline into the uterine cavity transcervically to act as a negative contrast agent and facilitate enhanced endometrial visualization during transvaginal assessment of the endometrial cavity using ultrasound *(1, 2)*. The infusion of sterile isotonic fluid during transvaginal sonography into the uterine cavity facilitates uterine distension and enhanced visual contrast during real-time ultrasonographic examination *(2, 3)*. SIS is also referred to as SHG.

Ultrasound imaging (sonography) involves the generation and transmission of ultrasonic (high-frequency sound) waves from a transducer and processing of a returning echo to generate an image. It is based on non-ionizing energy *(4)*. The image is subsequently displayed on a monitor, from which a hard copy may be captured, for example, using thermal printing paper *(4)*. Although US examination of the myometrium may be performed using a transabdominal transvaginal or more rarely transrectal approach *(5, 6)*, the transvaginal approach is more commonly used for assessing uterine abnormalities *(5–7)*. 2D US is the use of ultrasonic data to display the acquired information in two dimensions, B-scan *(4)*.

For this recommendation, the GDG addressed the question: should SIS (i.e. SHG) versus 3D US be used for women with suspected uterine cavity disorder infertility? The GDG agreed that a key decision when investigating women with infertility and suspected uterine pathology is whether to use SIS or 2D US.

Balancing harms and benefits

We conducted de novo searches to identify DTA studies on SIS and 2D US up to November 2019. Studies included women who received SIS or 2D transvaginal ultrasound and compared the results to the reference standard of hysteroscopy. Because of the lack of large studies on each uterine anomaly, the synthesized evidence in this recommendation question pooled data related to many uterine abnormalities. Each identified study assessed sensitivity and specificity to diagnose the uterine cavity disorders shown in **Table 5.13**.

Table 5.13. Included studies comparing SIS and 2D US, and conditions identified

Study	Conditions identified
Alatas et al. ***(8)***	Endometrial polyp, uterine anomaly, submucous myoma
Ayida et al. ***(9)***	Submucosal fibroid, endometrioma, structural abnormality, adhesions, atrophic endometrium, fibrosis, echogenic endometrium
Bartkowiak et al. ***(10)***	Submucous myomas, endometrial polyp, septate uteri, intrauterine synechiae
Fadl et al. ***(11)***	Endometrial polyps
Guven et al. ***(12)***	Endometrial polyps, submucosal myomas
Ragni et al. ***(13)***	Intrauterine pathology (polyp, myoma, malformation synechiae, thick endometrial mucosa)
Soares et al. ***(14)***	Polypoid lesions, uterine malformations, intrauterine adhesions and endometrial hyperplasia
Sitimani et al. ***(15)***	Endometrial polyp, submucous myoma, intrauterine synechiae or any other (thin endometrium, endometrial hyperplasia)

We calculated the sensitivity and specificity based on paired studies as shown in **Table 5.14**.

Table 5.14. Pooled sensitivity and specificity for SIS and 2D US with 95% CIs

	SIS	2D US
Sensitivity (95% CI)	88% (72–95%)	56% (34–77%)
Specificity (95% CI)	100% (27–100%)	100% (43–100%)

2D, two-dimensional; CI, confidence interval; US, ultrasound.

Data for health outcomes such as adverse events were available from Soares et al. *(14)*, Hassa et al. *(16)*, Ragni et al. *(13)* and Aboulghar et al. *(17)*. Calculations for absolute effects on true and false negatives and positives were based on an assumption of 15% prevalence of uterine cavity disorders in women with infertility.

Compared to 2D US, SIS likely results in five more women of 15 out of 100 being correctly identified with a uterine cavity disorder (true positives) and five fewer women of 85 out of 100 being incorrectly identified with uterine cavity disorder (false negatives). There is also likely no difference in true negatives or true positives. In a population where 15 out of 100 people have a uterine cavity disorder, the GDG agreed that five fewer false negatives with SIS (i.e. five more true positives) is a small number of women correctly identified compared to 2D US for uterine cavity pathologies.

In terms of adverse effects, evidence from three RCTs *(13, 14, 16)* in which participants underwent both tests (n = 734), there were two complications

with SIS and none with 2D US. In another RCT *(17)* (*n* = 77), participants did not report any discomfort or pain after undergoing both procedures. Based on these data, the GDG concluded that adverse events (pain and complications) may be similar between SIS and 2D US. The overall certainty of evidence was rated low because of risk of bias, and few events and low total numbers of participants across all the studies. There were no studies on patient values; however, the GDG agreed that women would value tests that can identify the diagnosis correctly and would seek to minimize harms.

Given the small benefits and trivial harms of SIS compared to 2D US, SIS is probably favoured. The GDG noted that the synthesized evidence combined the analysis of many uterine abnormalities, but sensitivity and specificity may differ between anomalies; however, available data are insufficient to provide discriminatory power.

Other considerations

No data were available on resource requirements; however, the guideline panel agreed that the additional resources required for SIS are negligible. The GDG agreed that given the small benefits, but negligible additional costs of SIS compared to 2D US, that SIS is likely more cost-effective. The GDG agreed that there is probably no impact on equity. Although no data were available on acceptability, the GDG agreed that SIS is likely acceptable. One study *(18)* provided an analysis of feasibility of 2D US but none was available for SIS. The GDG agreed that SIS is probably feasible and requires training of health care providers.

Summary justification

There is low certainty evidence that there are small benefits and trivial differences in harms with SIS compared to 2D US. The balance of effects favours SIS. In addition, SIS is acceptable and feasible, and has negligible additional resource requirements and impact on equity when compared to 2D US.

Implementation considerations

Training is required to ensure that health care providers have the skills to safely and correctly assess, document and report diagnostic findings while evaluating the uterus *(5, 7, 19, 20)*.

Research gaps and future guideline update

Because of the lack of large studies on each uterine anomaly, synthesized evidence combined the analysis of many uterine abnormalities. Future large studies are required to provide sufficient discriminatory power. Future guidance is required to compare the role of colour, power and spectral Doppler, as well as 4D ultrasonography.

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Recommendation

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)*

Background and rationale

HSG and SIS could be potential alternatives in the investigation of the uterine cavity; the GDG agreed that a key decision when investigating women with infertility and suspected uterine pathology is whether to use SIS or HSG.

HSG involves the flushing of iodinated contrast medium through the uterine cavity using a catheter or cannula, resulting in the distension of the uterine cavity, and allowing it to be visualized under fluoroscopic guidance using an X-ray. Still radiographs are performed. HSG uses either oil- or water-soluble contrast medium *(1)*.

SIS is a diagnostic procedure that involves the manual installation of saline into the uterine cavity transcervically to act as a negative contrast agent and facilitate enhanced endometrial visualization during transvaginal assessment of the endometrial cavity using ultrasound *(2, 3)*. The infusion of sterile isotonic fluid during transvaginal sonography into the uterine cavity facilitates uterine distension and enhanced visual contrast during real-time ultrasonographic examination *(3, 4)*. SIS is also referred to as SHG.

HSG and SIS are typically performed during the follicular phase of the menstrual cycle before the lining becomes too thick, which may obscure any pathology, and to avoid an undiagnosed very early pregnancy. For this recommendation, the GDG addressed the question: should HSG versus SIS be used for women with infertility and suspected uterine cavity disorder? Although HSG and SIS could be used for assessment of the fallopian tubes, this recommendation focuses on their use for assessing the uterine cavity. The assessment of fallopian tubes is presented in **Section 5.5**.

Balancing harms and benefits

Evidence from a 2015 systematic review by Seshadri et al. *(5)* was used. The search was then updated to search for new studies from 2014 to November 2019 and no further studies were identified. Studies included at least 80% of women who had infertility; women were not specifically suspected of uterine cavity disorders. The studies directly compared women who were assessed with HSG and SIS, and the diagnostic accuracy of both tests reported. The reference standard was hysteroscopy with or without laparoscopy *(6)*. Several studies *(6–10)* assessed sensitivity and specificity in identifying uterine cavity disorders as shown in the **Table 5.15**. Comparative data for health outcomes, such as adverse events *(10)* and pain *(11–14)* were also obtained.

Table 5.15. Included studies comparing HSG and SIS, and conditions identified

Study	Sample size, *n*	Conditions identified
Acholonu et al. *(7)*	149	Polyps, cavitary fibroids, adhesions and septae
Alatas et al. *(8)*	66	Endometrial polyp, uterine anomaly, submucous myoma
Alborzi et al. *(9)*	186	Total tubal and uterine pathologies: tubal obstruction. Intracavitary pathologies: Asherman syndrome, endometrial polyps, myomatous uterus. Structural uterine anomalies: septated uterus and other structural uterine anomalies
De Felice et al. *(6)*	104	Abnormalities of the uterine cavity
Soares et al. *(10)*	65	Polypoid lesions, uterine malformations, intrauterine adhesions and endometrial hyperplasia

Pooled sensitivity and specificity estimates with 95% lower and upper CIs were calculated across the studies from the raw data extracted from the studies. Details of the extracted data are shown in the relevant EtD tables in the **Web Annexes A–F**. Calculations of pooled estimates used a 15% baseline risk of uterine cavity disorder in women with infertility.

Table 5.16. Pooled sensitivity and specificity for HSG and SIS with 95% CIs

	HSG	SIS
Sensitivity (95% CI)	0.717 (0.555–0.837)	0.894 (0.819–0.940)
Specificity (95% CI)	0.931 (0.661–0.989)	1 (0.587–1)

CI, confidence interval; HSG, hysterosalpingogram; SIS, sonohysterography.

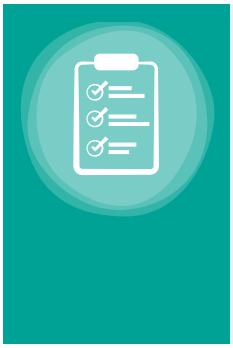
In terms of beneficial effects, the results showed that there are likely two fewer true positives per 100 with HSG than SIS, two more false negatives per 100 with HSG than SIS, six fewer true negatives per 100 with HSG than SIS and six more false positives per 100 with HSG than SIS. Based on these data, the GDG agreed that compared to SIS, the desirable benefits of HSG compared to SIS are likely trivial given that the increase in true negatives were trivial with HSG compared to SIS. The GDG noted that the synthesized evidence combined the analysis of many uterine abnormalities, but sensitivity and specificity may differ between anomalies; however, available data are sufficient to provide discriminatory power.

In terms of harms, one complication (pelvic pain) was reported with SIS and none with HSG in an RCT *(10)*. In another RCT, mean pain scores were lower with SIS compared with HSG when assessed on a scale of 0–10 (mean scores of 2.7 versus 5.8; P <0.0001), where higher scores reflected more pain) *(13)*. Among participants who underwent both procedures, 45 participants reported pain with SIS and 154 reported pain with HSG *(11, 12)*. The GDG agreed that compared to SIS, the harms of HSG may be small because of slightly greater false negatives, more false positives and greater pain. There were no studies on patient values; however, the GDG agreed that women would value tests that can identify the diagnosis correctly and would

seek to minimize harms, and that there is probably no important uncertainty or variability in how much people value these outcomes. Overall, the certainty of evidence was rated very low because of low evidence from diagnostic accuracy data, which also included women who were not recruited into studies on the basis of suspected uterine pathology and very low certainty with harms (such as pain). The GDG agreed that the balance of effects probably favours SIS because HSG may have slightly greater harms (greater false negatives and false positives and pain).

Other considerations

The GDG judged that although HSG is probably feasible, it involves moderately more resources and costs compared to SIS (e.g. fluoroscopy equipment, radiology facility), whereas SIS adds minimal additional resources and time to conventional ultrasonography. Given that the equipment required for SIS is more widely available, the GDG agreed that HSG could probably reduce equity, although there were no direct data on this factor. Similarly, no evidence on cost-effectiveness was identified. Nevertheless, the GDG considered that given the moderate costs of HSG, and slightly greater harms, HSG is unlikely to be as cost-effective as SIS. In terms of acceptability, the GDG considered that SIS does not use radiation and does not use iodine contrast. Based on further evidence from two studies *(14, 15)*, the panel concluded that SIS is probably more acceptable and better tolerated by patients compared to HSG.



Summary justification

There was very low certainty evidence that the balance of desirable and undesirable effects probably favours SIS over HSG in women who have infertility and suspected uterine cavity disorder. Although HSG is probably feasible, it requires moderate resources related to the need for a radiological unit. SIS is cheaper and probably more acceptable to patients compared to HSG. Given the cost and resource requirements, HSG may probably reduce equity.

Implementation considerations

Health care providers require training to ensure they have the skills and experience to safely evaluate the uterine cavity using SIS. Health care providers should monitor patients for pain, discomfort and other adverse effects and consider analgesics as appropriate. Health care providers should be aware and observe general contraindications for this procedure (e.g. women who are pregnant or who could be pregnant).

Research gaps and future guideline updates

Current evidence is insufficient to provide sufficient data to separately assess diagnostic accuracy for separate subgroups of uterine cavity pathology, such as polyps, fibroids, adhesions and congenital uterine malformations. Future larger studies are required to circumvent the current lack of statistical power, which limits recommendations to specific subgroups. Further guidance will be needed on whether prophylactic antibiotics should be used during SIS procedures.

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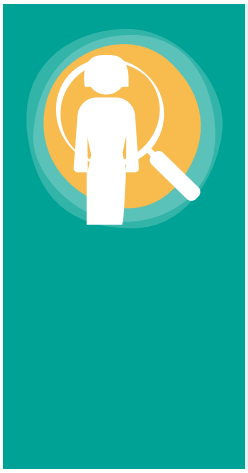

Recommendation

For females with infertility who are suspected to have a uterine cavity disorder, WHO suggests assessing the uterine cavity with either two-dimensional ultrasound (2D US) or hysterosalpingogram (HSG). *(Conditional recommendation, very low certainty of evidence)*

Remark:

- 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.

Background and rationale

Ultrasound imaging (sonography) involves the generation and transmission of ultrasonic (high-frequency sound) waves from a transducer and processing of a returning echo to generate an image. It is based on non-ionizing energy *(1)*. The image is subsequently displayed on a monitor, from which a hard copy may be captured, for example, using thermal printing paper *(1)*. Although ultrasound examination of the myometrium may be performed using a transabdominal, transvaginal or more rarely transrectal approach, the transvaginal approach *(2, 3)* is more commonly used for assessing uterine abnormalities *(2–4)*. 2D US is the use of ultrasonic data to display the acquired information in two dimensions, B-scan *(1)*.

HSG involves the flushing of iodinated contrast medium through the uterine cavity (and fallopian tubes) using a transcervical catheter or cannula, resulting in the distension of the uterine cavity, and allowing it to be visualized under fluoroscopic guidance using an X-ray. Still radiographs are performed. HSG uses either oil- or water-soluble contrast medium *(5)*.

The GDG agreed that guidance on whether to use 2D US or HSG is needed, particularly in settings where 3D US or SIS are not available. Therefore, in this recommendation, the GDG addressed the question: should 2D US versus HSG be used for women with infertility and suspected uterine cavity abnormality?

Balancing harms and benefits

A de novo search was conducted to identify DTA studies on 2D US and HSG up to November 2019. Studies included at least 80% of women who had infertility (women were not specifically suspected to have uterine cavity disorders). Women received both 2D US and HSG and their results were compared to the reference standard of hysteroscopy.

We found two comparative studies *(6, 7)* with useful data that could be pooled, and another study *(8)* from which data could not be pooled because of how the data were reported. The first two of these studies assessed sensitivity and specificity to diagnose the uterine cavity disorders shown in **Table 5.17**.

Table 5.17. Included studies comparing 2D US and HSG, and conditions identified

Study	Condition identified
Alatas et al. ***(6)***	Endometrial polyp, uterine anomaly, submucous myoma
Soares et al. ***(7)***	Polypoid lesions, uterine malformations, intrauterine adhesions and endometrial hyperplasia

We calculated sensitivity and specificity based on paired studies as shown in **Table 5.18**.

Table 5.18. Pooled sensitivity and specificity for 2D US and HSG, with 95% CIs from paired studies

	2D US	HSG
Sensitivity (95% CI)	40% (21–62%)	60% (38–79%)
Specificity (95% CI)	100% (0–100%)	98% (93–100%)

2D, two-dimensional; CI, confidence interval; HSG, hysterosalpingogram; US, ultrasound.

Calculations for the absolute effects on true and false negatives and positives were based on a 15% prevalence of uterine cavity disorders in women with infertility. Results showed that there may be three fewer true positives with 2D US, three more false negatives with 2D US, two more true negatives with 2D US and two fewer false positives with 2D US. Based on these data, the GDG agreed that the benefits of 2D US are trivial in correctly identifying uterine cavity pathologies; there were two fewer false positives with 2D US (incorrect diagnosis of uterine cavity disorder). The GDG agreed that there may be more harm (three more false negatives) with 2D US but that this difference was trivial.

Data on adverse effects were not reported in the studies included. The GDG noted that the synthesized evidence combined the analysis of many uterine abnormalities, but sensitivity and specificity may differ between anomalies; however, available data are insufficient to provide discriminatory power. There were no studies on patient values; however, the GDG agreed that women would value tests that can identify the diagnosis correctly and would seek to minimize harms, and that there was probably no uncertainty or variability on how people value these outcomes. The GDG agreed that the balance of effects does not favour either 2D US or HSG. Certainty of evidence was judged as very low because there was a lack of evidence for adverse events.

Other considerations

Although comparative data about costs were not available, the guideline panel agreed that 2D US is less costly than HSG and could lead to moderate savings. There was no direct evidence on cost-effectiveness; however, given that HSG has increased costs, the GDG agreed that cost-effectiveness probably favours 2D US. In addition, the GDG agreed that 2D US could probably increase equity as it requires fewer resources and is more widely available compared to HSG. Although no data were available, the GDG judged that 2D US is probably acceptable. The GDG considered the available analysis on feasibility from one study *(9)* and agreed that 2D US is probably feasible to perform. HSG requires a radiography unit and training, but it is widely available and it is also feasible.

Summary justification

There is very low certainty in the evidence that the balance of effects does not favour either HSG or 2D US. However, there are slightly more false negatives with 2D US that may necessitate following up. Both 2D US and HSG are probably feasible and acceptable, but 2D US likely requires fewer resources, and may be the preferred option in low-resource settings.

Implementation considerations

Training is required to ensure that health care providers have the skills to safely and correctly assess, document and report US and HSG findings while evaluating the uterus *(4, 10–12)*.

Research gaps and future guideline updates

Because of the lack of large studies on each uterine anomaly, the synthesized evidence combined the analysis of data related to many uterine abnormalities. Future large studies are required to provide sufficient discriminatory power. Future guidance is required to compare the role of colour, power and spectral Doppler, as well as 4D ultrasonography.

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5.7 Diagnosis of infertility due to male factors

This section contains recommendations related to the diagnosis of infertility due to male factors, and referral pathways for further evaluation. Figure 5.3 illustrates this in a diagnostic algorithm.

Recommendation

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. *(Conditional recommendation, very low certainty of evidence)*

Remark:

- 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.

Background and rationale

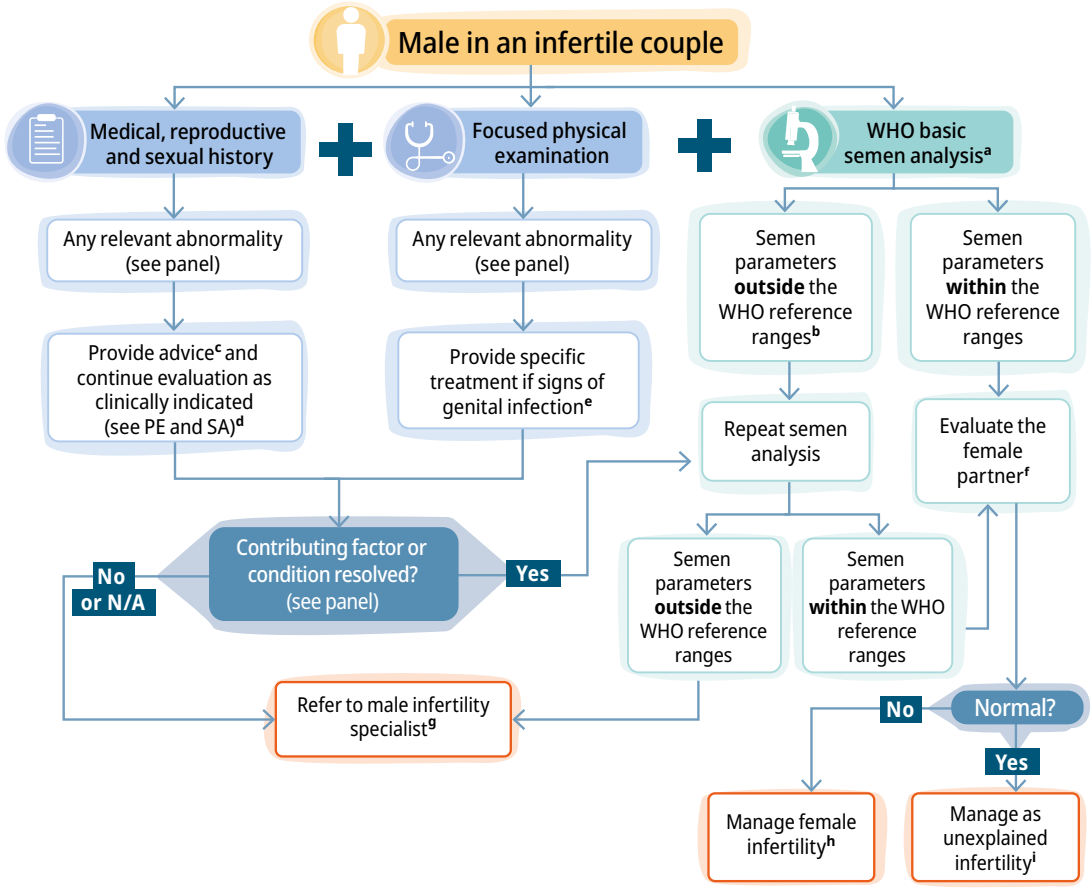
According to the largest multi-country study to date, involving 8500 couples in 25 countries, male factors contribute wholly or in part to 45.1% of infertility cases *(1)* (see **Annex 1. Distribution of the causes of infertility**). Therefore, investigation of the male partner is essential in the diagnosis and treatment of infertility (see **Fig. 5.3 Diagnostic algorithm for male-factor infertility**).

A semen analysis, as outlined in the *WHO laboratory manual for the examination and processing of human semen* is recommended for assessing male fertility *(2)*. Notably, semen parameters per se are not a reliable diagnostic indicator of fertility status as shown by several studies *(3–5)*. However, when combined with a thorough history and physical examination *(6)*, a basic semen analysis provides valuable information about the male reproductive function. Semen parameters may fall within or outside the reference ranges provided in the *WHO laboratory manual for the examination and processing of human semen (2)*.

Spermatogenesis is a biological process *(7)*, which displays intraindividual variability of semen parameters in healthy *(8, 9)* and infertile men *(10)*. Given this intraindividual variability, the *WHO laboratory manual for the examination and processing of human semen (2)* indicates that "to define an exact baseline of an individual, it may be necessary to examine two or three ejaculates", citing several studies *(9, 11–14)*.

Concerns with conducting one test or repeating a test are related to one of two risks: (i) unnecessarily referring men who do not need to be referred for further investigation; or (ii) failing to identify men with infertility who need to be investigated further, leading to underdiagnosis of male factors and delay in treatment.

Fig. 5.3. Diagnostic algorithm for male-factor infertility



[a] See the *WHO laboratory manual for the examination and processing of human semen* (sixth 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 or latest edition).
[c] See **Chapter 4** of this guideline, for details on information provision.
[d] Evaluation should include PE and SA regardless of history findings; see **Chapter 3**.
[e] See **Chapter 4**, and the WHO guidelines for the management of sexually transmitted infections.
[f] Female evaluation is essential and should proceed regardless of semen analysis outcome; **see Chapter 5** for the evaluation of the female.
[g] Health care provider with appropriate qualifications, for example, urologist, clinical andrologist or reproductive medicine specialist with relevant qualifications.
[h] See **Chapters 6**, **7** and **8**.
[i] See **Section 5.8** and **Chapter 10**.
N/A, not applicable; PE, physical examination; SA, semen analysis; WHO, World Health Organization.

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, body mass index (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

In this context, the GDG agreed that there was a need to provide guidance regarding whether two consecutive samples are necessary for all males who are being investigated for infertility by the initial evaluating health care provider. For this recommendation, the GDG addressed the question: should the initial semen analysis be repeated in a male in a couple with infertility?

Balancing harms and benefits

Within-individual variability of semen analysis

A review of the literature published in the *WHO laboratory manual for the examination and processing of human semen* and in other guidelines published over the last five years up to September 2023 was conducted. The search found three studies that evaluated the within-individual variability of semen analysis: Blickenstorfer et al. *(15)*, Boeri et al. *(16)* and Chiu et al. *(17)*. These studies included men who had a repeat analysis within 3 months or later.

The studies reported that in men who had:

- normozoospermia on the first semen analysis, 27% had pathological results on the second semen analysis *(15)*;
- normozoospermia on the first semen analysis, 60% had pathological results on the second semen analysis *(16)*;
- normozoospermia on the first semen analysis, 51% had pathological results on the second analysis *(17)*;
- pathological results on the first semen analysis, 23% had normozoospermia on the second semen analysis *(15)*;
- pathological results on the first semen analysis, 8.5% had normozoospermia on the second semen analysis *(17)*.

The 2010 *WHO laboratory manual for the examination and processing of human semen* reported that it may be necessary to test two or three ejaculates based on four studies reporting variability in results *(9, 11–14)*. The sixth edition of the *WHO laboratory manual for the examination and processing of human semen*, published in 2021 *(2)*, states that it may be necessary to examine two or three ejaculates to establish a true baseline for an individual.

Variation in semen parameters

The sixth edition of the *WHO laboratory manual for the examination and processing of human semen* also reported that semen analysis results can be affected by ejaculate characteristics that depend on the following: (i) whether a complete sample is collected; (ii) activity of the accessory sex glands; (iii) time between ejaculates or abstinence or abstention time; (iv) testicle size; (v) endocrine status; (vi) medications (e.g. antihypertensives, antidepressants); (vii) supplements and nonprescribed medications; and (viii) recent (particularly febrile) illness.

Timing of semen analysis

Spermatogenesis is a complex process involving distinct phases, such as proliferation, meiosis and spermiogenesis, and each phase has its specific duration *(18, 19)*. Spermatogenesis was initially thought to take 64 days *(7)*. However, further empirical evidence showed that it takes approximately 74 days, which is equivalent to four and a half cycles of the seminiferous epithelium *(20)*, with some likely variability of up to 74 ± 2 days (4.6 cycles) *(21)*. There are still ongoing uncertainties, as suggested by some studies *(22, 23)*. For instance, in an in vivo study (n = 11) that used stable isotope labelling of sperm DNA followed by gas chromatography and mass spectrometry analyses, Misell et al. *(23)* reported that the duration of spermatogenesis, that is, the duration it took to detect labelled sperm, was an average ± standard deviation (SD) of 64 ± 8 days (range: 42–76 days).

Other outcomes

Other outcomes, such as quality of life, including fear, worry or other psychosocial and psychological impacts, and accuracy and downstream consequences of diagnosis were not reported in studies.

Based on this summary of evidence, the GDG agreed that the results of semen analysis may not always be consistent between a first and second (repeat) test. The GDG also agreed that semen parameters outside the WHO reference ranges could be a reflection of the true baseline of an individual or could be due to transient factors not related to infertility (e.g. incomplete sample taken, a febrile illness or intraindividual biological variability).

In terms of the benefits of repeating a semen analysis, the GDG agreed that when the first semen analysis results are outside the WHO reference ranges, the benefits of a repeat analysis may be moderate by ruling out a "diagnosis" of male infertility (in cases where the second test results are within the reference ranges) as it would avoid unnecessary fear or the psychological impact associated with an "abnormal" semen analysis result, and also reduce the risk of an unnecessary referral to infertility specialists. The GDG agreed that when the results of the first semen analysis are within the WHO reference range, the benefits of a repeat analysis may be trivial. This is because diagnosis is based not only on semen analysis but also on complete history-taking and a physical examination. The GDG agreed that the maximum benefit of a repeat test is after a minimum of 11 weeks, aligning with the duration for spermatogenesis.

In terms of the harms of repeating a semen analysis, the GDG agreed that when the first analysis is outside the reference ranges, there are no adverse events that would arise from a repeat semen analysis. The GDG agreed that when the results of the first semen analysis are within the WHO reference range, small harms may occur if the second test is outside the reference ranges, which may be due to factors not related to infertility and occurs in many individuals, and may result in unnecessary and high referral rates; it may also cause unnecessary fear or have a psychological impact (false positive). Although some cases may be missed by not doing a repeat test (false negative), the risk of not identifying men with infertility is likely low as the diagnosis is based not only on the semen analysis but also on comprehensive medical history and physical examination. Additionally, if after investigation of the female partner a couple is infertile (e.g. because of unexplained infertility), additional assessment of sperm will most likely be conducted during the course of treatment.

The GDG considered the values of patients; in the absence of specific studies on these, the GDG agreed that men would value confirmation of results that are outside the WHO reference ranges before referral to an infertility specialist. The GDG placed a greater weight on reducing false positives in this PICO because of the downstream consequences, including referrals to specialists and associated costs.

Considering all of the judgements, the GDG concluded that the balance of effects favours a repeat test when the first analysis is outside the WHO reference ranges, and that the balance of effects favours NO repeat test when the first analysis is within the WHO reference ranges. Overall, the certainty of evidence was very low because of a lack of evidence for important patient outcomes.

Other considerations

The GDG considered resource requirements and judged that although there are costs with performing any test, the costs of a semen analysis are negligible. The cost of performing one additional repeat test is also negligible. The GDG agreed that for men whose semen parameters are outside the WHO reference ranges, repeating the test would result in negligible costs and moderate benefits because referral rates are reduced, meaning it is cost-effective; therefore, repeating the test is favoured. However, for men whose parameters are within the WHO reference ranges, even though the costs of testing are negligible, sending men to an infertility specialist based on an abnormal repeat test may result in moderate harms, meaning that repeating the test in this scenario is not cost-effective; therefore, not repeating the test is probably favoured.

The GDG agreed that although there are no direct data on equity, there is potential for inequity in men's access to and use of infertility testing. However, semen tests are widely available; therefore, requiring a repeat test may not have an impact on equity.

There was no evidence identified on acceptability of repeat semen analysis among health providers or patients. However, the GDG agreed that the initial evaluating health care provider would find it acceptable to perform a repeat test in men with results outside the WHO reference ranges before referral, and not to repeat it in men with results within the WHO reference ranges. Both physicians and men would likely find it acceptable to avoid referrals and unnecessary additional testing.

Similarly, there were no identified studies on the feasibility of repeat semen analysis. However, the GDG agreed that performing repeat tests is feasible. The GDG also considered that male infertility specialists (e.g. urologist or clinical andrologist) are often not widely available, and agreed that increasing referral to male infertility specialists may not be feasible in many countries.

Summary justification

There was very-low-certainty evidence for the benefits and harms of repeating or not repeating semen analysis. Evidence suggests that when a semen analysis test is conducted twice, the semen parameter results may not always be consistent between the first and second test.

Evidence also suggests that semen parameters outside the WHO reference ranges could be a reflection of the true baseline of an individual or could be due to transient factors not related to infertility (e.g. incomplete sample taken, a febrile illness or intraindividual biological variability).

The GDG agreed that when a first test reports semen parameters outside the WHO reference ranges and a repeat test is not conducted and the man is sent for investigation, there is a concern that too many men will be sent for further investigation who did not need to because the results were likely due to transient factors unrelated to infertility (e.g. incomplete sample taken, a febrile illness or intraindividual biological variability). A repeat test would minimize the effect of transient factors unrelated to infertility and confirm that parameters are outside the WHO references ranges and are likely related to infertility; therefore, men with two tests reporting parameters that are outside the WHO references ranges would be appropriately sent for further investigation by male infertility specialists.

When the first test (performed in accordance with the standardized procedures outlined in the *WHO laboratory manual for the examination and processing of human semen*) reports semen parameters outside the WHO reference ranges and the repeat test shows parameters within the WHO reference ranges, a possible explanation is that the first test was likely outside the WHO reference ranges because of transient factors unrelated to infertility, and the man would not need further investigation or referral to a male infertility specialist. If these men are not investigated or referred to a male infertility specialist, the risk of not identifying men with infertility due to male factors is likely low because the diagnosis is based not only on semen analysis but also on comprehensive medical history and physical examination. If after investigation of the female partner a couple is infertile (e.g. because of unexplained factors), additional assessment of sperm will most likely be conducted during treatment; therefore, these men will likely be retested and will not be missed. Therefore, the GDG agreed that a repeat test may be conducted if one or more parameters are outside the WHO reference ranges because repeating the semen analysis could reduce unnecessary referral rates and could reduce the negative psychological impact and fear in men and couples associated with a test outside the WHO ranges; the test is low-cost and probably acceptable and feasible. The GDG also agreed that given that the minimum duration of spermatogenesis is approximately 11 weeks, repeating the test should align with this time period.

If all semen parameters are within the WHO reference ranges and a repeat test is not performed, the risk of not identifying men with infertility is likely low because if after investigation of the female partner a couple is infertile (e.g. because of unexplained infertility), additional assessment of sperm will most likely be conducted during treatment. In addition, if a repeat test is conducted and the parameters are outside the WHO reference ranges, then some men would have been sent for further testing without need as the parameters could be outside the reference ranges because of transient factors unrelated to infertility. Therefore, the GDG agreed to not repeating the test when a first test is within the WHO reference ranges to reduce unnecessary referral and associated costs and burden, and also agreed that not performing a repeat test is probably acceptable.

Implementation considerations

Health care providers should note that semen analysis provides partial information related to fertility potential, and that reference range thresholds do not entirely distinguish between fertile and infertile males. This and other limitations may contribute to the shifting of the burden of infertility investigation and management to the female partner *(24)*, despite male factors contributing wholly or in part to 45.1% of infertility cases *(1, 25)*. In addition, although the odds of a man being infertile increase when more parameters are outside the WHO reference ranges *(5)*, the abnormalities themselves (either one or all) are not reliable indicators of fertility status *(4, 5)*. Therefore, semen analysis should be performed in conjunction with comprehensive (medical, reproductive and sexual) history-taking, and physical examination.

Spermatogenesis is a complex process involving distinct phases, such as proliferation, meiosis and spermiogenesis, each

with its specific duration *(18, 19)*. Repeating a semen analysis after 11 weeks aligns with the estimated time for spermatogenesis to occur. In addition, time is needed for the effect of any modifiable factors on semen parameters to wane (e.g. febrile illnesses, medications, among others). To ensure that the results are valid and provide useful information, the latest edition of the *WHO laboratory manual for the examination and processing of human semen* outlines standardized procedures for semen collection and analysis. It provides guidance on: (i) semen examination; (ii) sperm preparation and cryopreservation; and (iii) quality assessment and quality control.

The evaluation and management of male infertility is a stepwise process involving comprehensive assessment and consultation to determine appropriate treatment options (see **Fig. 5.3** for the diagnostic algorithm for male-factor infertility). Referral of the male to a specialist and further evaluation may identify comorbidities requiring management beyond fertility *(26, 27)*. Health care providers should be aware of this and, whenever possible, mitigate contextual issues that may affect the implementation of this recommendation related to the health system (e.g. personnel training and quality control of laboratories), economics (e.g. cost of tests and repeat appointment) and social (e.g. stigma, masculine norms or other cultural) barriers to male testing.

In addition, female evaluation is essential and it should proceed regardless of the outcome of semen analysis. Evaluation and management should be conducted in parallel for both male and female partners, and the investigation of a female partner should not be delayed by repeated semen analyses. At the same time, the diagnostic pathway, referral and management plan for the male partner should be informed by, and be progressively adjusted, based on the results of the tests of the female partner to optimize efficiency (see **Chapter 3. Approach to the evaluation and management of patients with infertility**).

Research gaps and future guideline update

Future studies should assess relevant outcomes, including values, preferences, costs and cost-effectiveness of repeat semen testing. Given that semen analysis per se does not entirely rule out the presence of a male-factor cause of infertility, further research is required to determine the downstream outcomes of males with semen samples within and outside the WHO reference ranges, as well as those with borderline semen parameters, to determine if any subsets of these populations could benefit from further advanced tests. Current evidence is of very low certainty. Better-quality data from more studies evaluating the results of semen analysis are needed to improve the certainty of evidence.

Current evidence on the estimated time that spermatogenesis takes is based on data from limited old studies. Some uncertainty exists based on biological plausibility *(22)* and observations from vivo studies *(23)*. Impact of sperm maturation and epididymal transport and storage on the duration is uncertain *(28)* and may require consideration in future studies. Further large studies are required to strengthen the evidence base regarding the duration of spermatogenesis.

The diagnostic scope of the guideline recommendation is limited, addressing only a subset of male infertility topics within the broader and evolving field of male infertility investigation. Specifically, this PICO provides guidance to the initial health care provider investigating a couple with infertility; guidance for male infertility specialists will be developed in the future. This approach acknowledges the positive momentum in diagnostic interventions for male-factor infertility. Emerging technologies have the potential to advance adjunct diagnostic tests that could complement semen analysis and improve the clinical diagnosis of male infertility; however, these have not been evaluated in this edition of the guideline and will be considered in future editions.

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5.8 Diagnosis of unexplained infertility

This section contains recommendations related to the diagnosis of infertility due to unexplained factors. Figure 5.1, near the start of this chapter, illustrates how a diagnosis of unexplained infertility is made.

Recommendation

WHO suggests making a diagnosis of unexplained infertility in a couple when all the following have occurred:

- failure to achieve 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 of evidence)*

Background and rationale

In a WHO multi-country study conducted in 25 countries and involving 8500 couples, no cause was identified in 10.8% of infertility cases *(1)*. As unexplained infertility is a diagnosis of exclusion, reported prevalence ranges vary widely, as demonstrated in several systematic reviews and meta-analyses from different global regions *(2–4)*. While there may be several detectable and undetectable reproductive defects that could hinder a couple from achieving pregnancy, different settings may apply different tests for exclusion based on the available resources.

This WHO guideline contains other conditional recommendations made based on a review of the evidence (rated as very-low certainty) about which tests to use to:

i. investigate anovulation and oligo-ovulation or tubal disease or blockage in females who have a normal physical examination and medical history;
ii. investigate uterine cavity abnormality, ovulation disorders and reduced ovarian reserve in females who do not have a normal physical exam and medical history; and
iii. assess males.

For (ii) and (iii) a diagnosis of infertility is based on the cause found through the investigations. However, for (i), when pathologies have not been identified, infertility remains unexplained, provided semen parameters are within the WHO reference ranges in a male with a normal history and physical examination (see **Fig. 5.1**).

Using a minimum set of criteria is probably feasible, acceptable and reduces costs in most resource settings. Therefore, the GDG agreed that at a minimum, a diagnosis of unexplained infertility should be arrived at if a couple has been unsuccessful in achieving pregnancy after 12 months of regular unprotected sexual intercourse; the physical examination and medical history in both the male and female are normal; ovulation and patent tubes in the female have been presumptively confirmed; and semen parameters are within the WHO reference ranges in the male.

Summary justification

Given that other recommendations for diagnosing infertility in this guideline are conditional, this recommendation for using a minimum set of tests that can rule out other causes of infertility is also conditional based on the very low certainty of the evidence. The minimum set of tests apply in couples with infertility who have normal physical examinations and medical histories with presumptively confirmed ovulation, tubal patency and semen parameters that are within the WHO reference ranges. The minimum set of tests are feasible, acceptable and require fewer resources to implement in many resource settings.

Implementation considerations

Specific details and recommendations regarding medical history-taking and physical examination in a couple, evaluation of ovarian function, tubal patency and uterine cavity in the female, and semen analysis in the male, are outlined in the relevant chapters of this guideline. Procedures for semen analysis are detailed in the *WHO laboratory manual for the examination and processing of human semen (5)*. Health care providers should ensure that physical examination and medical history-taking are conducted concurrently in both males and females as part of the initial diagnosis of unexplained infertility. If abnormalities affecting reproduction are found, diagnosis of unexplained infertility would not apply, as a cause would have been identified. Health care providers should be aware of, and mitigate, the psychological aspects of infertility, including when causes are unexplained (see **Chapter 3**). Health care providers should also be aware of, and whenever possible mitigate, the contextual issues that may affect the implementation of this recommendation related to the health system (e.g. personnel training and quality control of laboratories), economics (e.g. cost of tests) and social (e.g. stigma, masculine norms or other cultural) barriers to male testing.

Research gaps and future guideline update

Future studies are required to establish the magnitude of unexplained infertility using the above criteria, as available data are not current, and to understand the causes of infertility. Given that unexplained infertility is a diagnosis of exclusion, the fewer the number of diagnostics tests performed, the more likely infertility might be unexplained, while performing multiple tests could potentially result in an abnormal result, which may or may not be related to the failure to achieve pregnancy, and in the latter scenario, lead to unnecessary intervention. Future research is needed to determine whether any additional tests or criteria (such as an upper limit of female age) should be routine used in the initial evaluation of couples who would otherwise be classified as having unexplained infertility based on the above criteria. Implementation research is encouraged to validate data, document costs and inform whether the minimum diagnostic criteria should be resource-stratified.

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Chapters 6–10 Treatment of infertility

These chapters provide guidance on the treatment of infertility. These treatments are divided into three main groups:

Female-factor treatments

6.1 Treatment of infertility due to ovulatory dysfunction caused by PCOS

7.1 Use of surgery or IVF for treatment of tubal disease

7.2 Treatment of hydrosalpinx before IVF

8.1 Management of uterine septum in females with infertility

Male-factor treatments

9.1 Use of antioxidants

9.2 Treatment of varicocele

Unexplained infertility treatments

10.1 First-line management of couples with unexplained infertility

10.2 Second-line management of couples with unexplained infertility

10.3 Third-line management of couples with unexplained infertility

Relevant resources:

Figure 6.1 Treatment algorithm for anovulatory infertility due to PCOS

Figure 10.1 Treatment algorithm for unexplained infertility

Web Annex D. Evidence to decision tables for treatment of infertility due to ovulatory dysfunction, tubal disease and uterine cavity disorder

Web Annex E. Evidence to decision tables for treatment of infertility due to male factors

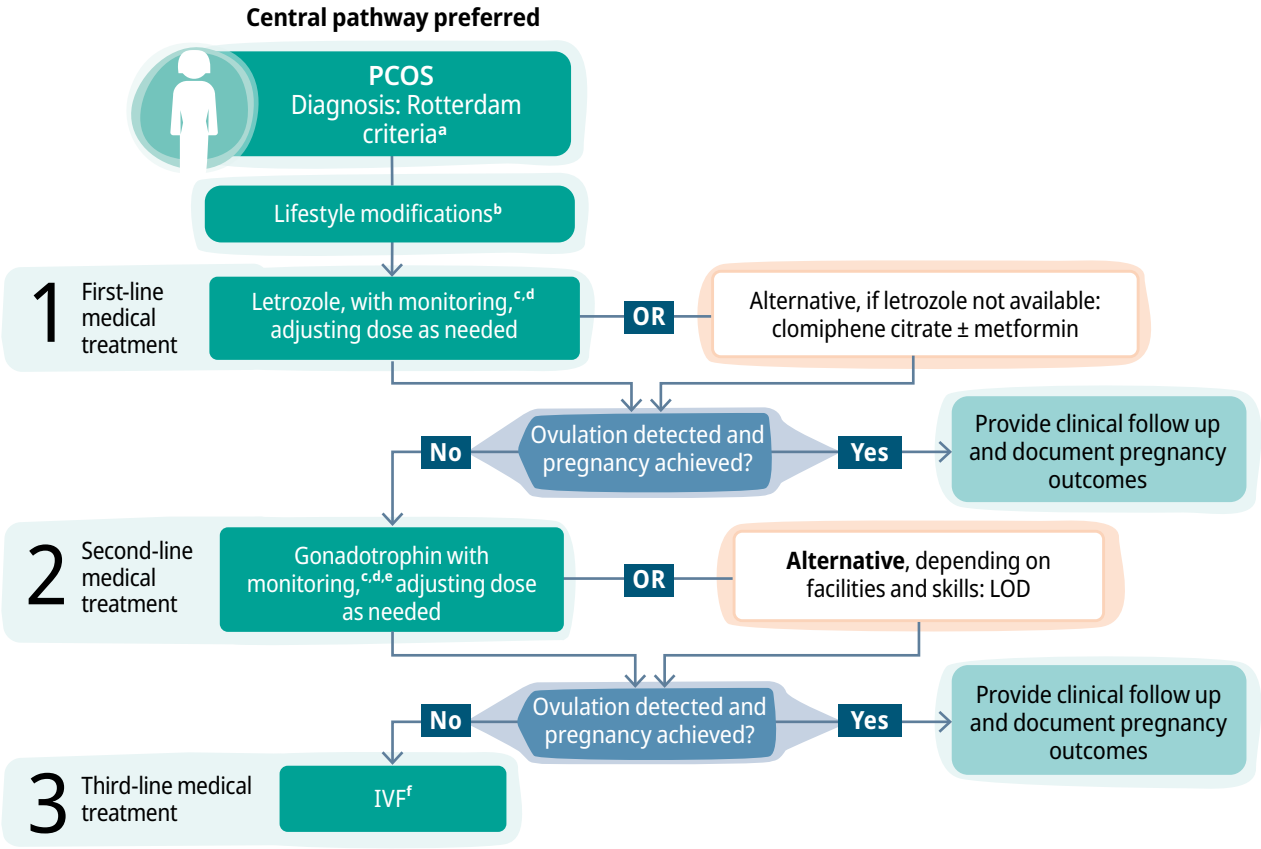
Web Annex F. Evidence to decision tables for treatment of couples with unexplained infertility

Chapter 6 Treatment of infertility due to ovulatory dysfunction

6.1 Treatment of infertility due to ovulatory dysfunction caused by PCOS

This section contains recommendations related to the management of infertility due to PCOS. **Figure 6.1** shows how these recommendations relate to each other. Specific recommendations are presented in the sections that follow.

Fig. 6.1. Management of 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**.
2. Additional assessment tests may be required, including during the pre-pregnancy period see **Chapter 3**.
3. Consider assessing tubal patency see **Chapter 5.5**.
4. Assess the male partner, including semen analysis see **Chapter 5.7**.

[b] As part of the management of PCOS, it is good practice to advise patients on lifestyle interventions, such as healthy diet and regular physical activity. (**Good practice statement**).

[c] Use repeated cycles based on shared decision-making considering age and resources.

[d] Monitor patients regularly (with US as needed) and manage potential risks that may occur during treatment see **Chapter 3** and **Chapter 6.1**.

[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**.

IVF, in vitro fertilization; LOD, laparoscopic ovarian drilling; PCOS, polycystic ovary syndrome; US, ultrasound.

Recommendation

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 citrate 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 healthy diet, regular physical activity and/or weight management. *(Good practice statement).*

Background and rationale

PCOS is a common condition affecting 6–13% of women of reproductive age, although the reported prevalence varies depending on the diagnostic criteria *(1, 2)*. Many women in the WHO Group II anovulation have PCOS. A diagnosis of PCOS in adults is based on the presence of two of the following three criteria: anovulation or oligo-ovulation; clinical or biochemical hyperandrogenism; or polycystic ovary morphology, and exclusion of related disorders (Rotterdam criteria) *(3)*.

PCOS has multiple reproductive, metabolic and psychosocial impacts *(4)*. Clinical features in PCOS commonly include irregular menstrual cycles, signs of androgen excess, such as hirsutism, and infertility *(3)*. PCOS is one of the most common causes of anovulatory infertility *(5)*. In addition, the prevalence of other comorbidities, such as obesity *(6)*, impaired glucose tolerance and metabolic syndrome *(7)*, is also high among women with PCOS, which may require identification and management.

Options for the treatment of infertility in PCOS include lifestyle interventions, pharmacological therapies, surgical laparoscopic ovarian diathermy or IVF. Pharmacological therapies include estrogen receptor modulators (such as clomiphene citrate), aromatase inhibitors (such as letrozole), insulin-sensitizing medications (such as metformin) and direct hormonal stimulation of the ovaries (with gonadotrophins). The costs and complexities of these interventions vary significantly (see **Fig. 6.1.** for the treatment algorithm for anovulatory infertility due to PCOS).

Pharmacological options include oral ovulation induction agents such as clomiphene citrate or letrozole, used alone or in combination with metformin. Clomiphene citrate is a selective estrogen receptor modulator *(8)* that acts primarily by binding with estrogen receptors at the hypothalamus *(9)*. It is administered orally, typically for 5 days from cycle days 3–7 or 5–9 *(10)* but can have side-effects, including changes to the endometrium and cervical mucus and hot flushes *(11)*. Ultrasound monitoring is often used to monitor follicular growth during a stimulation cycle *(12, 13)*.

Letrozole is a newer drug that blocks estrogen synthesis; it is also administered orally. It is an aromatase inhibitor *(14)* that has been used off-label for ovulation induction since 2001 *(15)*. It stimulates ovarian follicle development and maturation; compared to clomiphene citrate, it has a short half-life of 2–4 days *(16)*. It is usually administered daily from days 3–7 of the menstrual cycle *(10)*. Concerns have been raised about potential teratogenicity *(17)*, although reassuring data regarding safety are emerging *(18)*. Ultrasound may be used to monitor follicular development during a stimulation cycle and to mitigate the risk of multiple pregnancy.

Metformin is an antihyperglycaemic biguanide drug, which is widely used for lowering insulin levels *(19)*. Women with PCOS often present with insulin resistance and hyperinsulinaemia *(20–22)*. Insulin resistance and/or poor glycaemic control, is hypothesized to have an important role in the pathogenesis of PCOS *(23–25)*. Therefore, metformin is an (off-label) option used as an insulin-sensitizing medication in people with PCOS, as an adjunct to ovulation induction medications *(19, 26, 27)*, but it may cause gastrointestinal side-effects, and rarely, lactic acidosis and liver failure *(26)*. It is generally administered daily, and for longer durations, even when used in combination therapy with letrozole or clomiphene citrate *(26)*.

For this recommendation, the GDG addressed the following questions: (i) should letrozole versus clomiphene citrate or metformin be used for women with infertility due to ovulatory dysfunction caused by PCOS?; (ii) should clomiphene citrate versus clomiphene citrate + metformin or metformin be used for women with infertility due to ovulatory dysfunction caused by PCOS?; and (iii) should letrozole versus letrozole + metformin be used for women with infertility due to ovulatory dysfunction caused by PCOS?. The GDG assessed these oral pharmacological therapies as first-line treatment for PCOS.

Balancing harms and benefits

Use of monotherapy

Two systematic reviews *(18, 28)* and an RCT *(29)* provided relevant data related to the benefits and harms of letrozole compared to clomiphene citrate. There was a moderate increase in live births with letrozole (RR: 1.52; 95% CI: 1.28–1.82) and likely no difference in these effects based on BMI. Mixed results were observed across undesirable effects: miscarriages (small increase with letrozole); multiple birth rates (trivial decrease with letrozole); OHSS (small decrease with letrozole); and congenital malformations (inconsistent effect between RCTs and non-randomized studies). Given that there is likely no important uncertainty or variability among different populations in how people value benefits (live births) and harms (miscarriages, multiple birth rates and other side-effects), the GDG judged that, overall, the benefits are greater with letrozole and outweigh any harms that may be slightly increased (*low-certainty evidence*). The GDG emphasized that clomiphene citrate can be used as an alternative if letrozole is not available.

A systematic review and network meta-analysis by Wang et al. *(30)*, which was updated without retracted articles *(31)*, provided data comparing letrozole to metformin. Letrozole likely results in more live births (OR: 1.85; 95% CI: 1.02–3.45). The observed increase of 116 more per 1000 was judged by the GDG to be a large desirable effect. The use of letrozole may slightly increase miscarriages (OR: 1.30; 95% CI: 0.54–3.13) and multiple pregnancy (OR: 2.22; 95% CI: 0.47–11.11). Given the large benefits and small harms, the GDG judged that the balance of effects favours the use of letrozole over metformin (*moderate-certainty evidence*).

A systematic review by Sharpe et al. *(32)* provided relevant data for comparing metformin with clomiphene citrate. Metformin may result in fewer live births (OR: 0.71; 95% CI: 0.49–1.01), but fewer miscarriages (OR: 0.92; 95% CI: 0.51–1.66)

and fewer multiple pregnancy (OR: 0.29; 95% CI: 0.06–1.43) compared to clomiphene citrate. In addition, the potential benefit of metformin in reducing multiple pregnancy and miscarriages based on a BMI threshold of over or under 30 kg/m^2 was inconsistent. The GDG noted that the use of metformin alone is less effective than either clomiphene citrate or letrozole alone. The GDG judged that although there may be fewer harms with metformin alone in some populations, overall, there may be greater benefits with clomiphene citrate (*very-low-certainty evidence*).

Adjunct use of metformin in combination therapy

Two RCTs provided relevant data comparing letrozole in combination with metformin versus letrozole alone *(33, 34)*. The addition of metformin to letrozole may result in no difference in effect on live births (RR: 1.00; 95% CI: 0.61–1.65), while clinical pregnancies may increase slightly (by 58 per 1000 [from 58 fewer to 215 more] compared to letrozole alone (RR: 1.15; 95% CI: 0.85–1.56). There are no data to determine the effects based on insulin resistance or BMI (mean BMI in the two included studies was < 30 kg/m^2). In terms of undesirable effects, a small increase of miscarriages (60 per 1000 [from 41 fewer to 290 more] may occur when metformin is combined with letrozole compared to letrozole alone (RR 1.50; 95% CI: 0.66 to 3.43).

Gastrointestinal side-effects may occur when letrozole is combined with metformin, whereas there may be none with letrozole alone. The GDG noted that although clinical pregnancies may increase when metformin is combined with letrozole, there may be a similar increase in miscarriages and more gastrointestinal effects. Therefore, the balance of effects probably favours letrozole alone (*very-low-certainty evidence*).

A systematic review *(32)* compared metformin in combination with clomiphene citrate versus clomiphene citrate alone. Evidence showed that there is likely a moderate increase in live births (47 per 1000 [from 12 fewer to 123 more]; RR: 1.20;

95% CI: 0.95–1.52) and clinical pregnancies (111 more per 1000 [from 42 to 194 more]; RR: 1.40; 95% CI: 1.15–1.70) with metformin combined with clomiphene citrate compared to clomiphene citrate alone. Analyses using a BMI threshold of approximately < or >30 kg/m^2 found similar relative risks for live births and clinical pregnancy, suggesting that there are little to no differences in desirable effects based on BMI. Women with insulin resistance were identified and included in three of the 19 RCTs included in the review and had similar relative risks. In relation to harms, use of clomiphene citrate combined with metformin may slightly reduce OHSS (11 fewer per 1000 [from 11 to 10 fewer]; risk difference [RD]: -0.002; 95% CI: -0.033 to -0.027) and multiple pregnancy (8 fewer per 1000 [from 14 fewer to 13 more]; RR: 0.57; 95% CI: 0.19–1.72), but likely increases miscarriages (21 more per 1000 [from 9 fewer to 65 more]; RR: 1.27; 95% CI: 0.88–1.85) and gastrointestinal side-effects (180 more per 1000 [from 78 more to 343 more]; RR: 3.12; 95% CI: 1.92–5.05) compared to clomiphene citrate alone. Although miscarriages and gastrointestinal side-effects are likely greater when metformin is used with clomiphene citrate, the GDG agreed that they are comparatively less serious compared to OHSS and multiple pregnancy, and that there was still an increase in clinical pregnancies. The GDG judged that the use of clomiphene citrate with metformin may have moderate benefits and small harms when compared to clomiphene citrate alone (*moderate-certainty evidence*).

Other considerations

The GDG judged that it is probably feasible to provide oral medications for ovulation induction and noted that the exact cost of these medications may vary from country to country. Given that the use of letrozole could reduce equity, as it is may be more expensive than clomiphene citrate *(35)*, the GDG emphasized that clomiphene citrate can be used if letrozole is not available.

The GDG noted that either letrozole or clomiphene citrate may be acceptable for use by physicians in different settings, based on studies conducted among physicians in China *(36)*, Estonia, Denmark, Finland, Iceland, Norway and Sweden *(37)*, as well as the United States of America *(38)*. In one of these studies, Piltonen et al. *(37)* found that 29% of 382 medical and reproductive endocrinologists and obstetrician-gynaecologists in multiple countries prescribed clomiphene citrate in conjunction with metformin *(37)*.

The cost of metformin is generally low, but monitoring of metformin therapy is generally limited once the optimum dose is achieved. Therefore, the GDG judged that the additional resources required to add metformin to clomiphene citrate are probably negligible, and it is probably feasible.

Of note, there were no studies reporting the acceptability of these agents for ovulation induction among women with PCOS. In addition, the GDG noted that acceptability of letrozole among physicians could depend on its off-label use *(38)*, given that it is not currently approved by several regulatory authorities such as the U.S. Food and Drug Administration or European Medicines Agency for ovulation induction *(26)*.

Summary justification

Use of monotherapy

Overall, there may be greater benefits (live births) with letrozole compared to clomiphene citrate (low-certainty evidence) or metformin (low-certainty evidence), which outweigh any harms that may be slightly increased. Although the potentially higher cost of letrozole could negatively affect equity, it is feasible and probably acceptable to provide. However, letrozole may not be available in all settings for off-label use. Therefore, letrozole is suggested over clomiphene citrate, but clomiphene citrate with metformin can be used where off-label use of letrozole is not permitted or is unavailable.

Use of metformin in combination therapy

The balance of effects likely favours the use of clomiphene citrate with metformin over clomiphene citrate alone. The addition of metformin may result in moderate benefits and small undesirable effects. The use of clomiphene citrate with metformin is feasible and probably acceptable where off-label use (of metformin for PCOS) is allowed, and the additional costs of adding metformin to the stand-alone cost of clomiphene citrate alone is negligible.

There was very low certainty evidence that the benefits probably outweigh the harms of using letrozole alone compared to letrozole with metformin. The addition of metformin to letrozole may result in a small increase in clinical pregnancy but a corresponding small increase in miscarriages, resulting in no net effect on live births compared to letrozole alone. In addition, metformin may also increase gastrointestinal side-effects.

Implementation considerations

Health care providers should consider offering lifestyle advice (e.g. on healthy diet and regular physical activity) as part of the management of PCOS. In addition, health care providers need to be aware of the potential risk of comorbidities, such as impaired glucose tolerance, obesity and metabolic syndrome, among others, in patients with PCOS *(6, 7)*, which may require additional management.

Health care providers should be aware of and mitigate the overall impact of stimulating agents such as letrozole or clomiphene citrate by monitoring patients to optimize achieving a pregnancy, while mitigating undesirable outcomes. Monitoring ovarian stimulation with ultrasound may be considered to assess ovarian response and to mitigate the risk of multiple pregnancies. Health care providers should counsel patients regarding the potential morbidity that may result from multiple gestation.

Use of letrozole as an ovulation induction agent is not approved by several regulatory authorities such as the U.S. Food and Drug Administration or the European Medicines Agency *(26)*. The use of metformin in patients with PCOS is also off-label. Health care providers should familiarize themselves with applicable national regulations related to off-label use of medicines for ovulation induction. Where off-label use of letrozole as an ovulation induction agent is not permitted or is unavailable, health care providers should offer

treatment with other ovulation agents, such as clomiphene citrate.

Health care providers should take patients' values and preferences into account as no studies reporting the acceptability of ovulation induction agents among patients with PCOS were identified in the evidence reviewed for this guideline.

Research gaps and future guideline update

The uncertainty in the evidence related to the use of letrozole or clomiphene citrate in PCOS indicates the need for large, well-designed RCTs to evaluate the use of these agents, used alone or with metformin, in several subgroup populations stratified according to BMI, insulin resistance, PCOS phenotypes, AMH levels, testosterone levels and other relevant prognostic factors and parameters. Such research will be important in identifying which group of patients benefits most from letrozole, clomiphene citrate or clomiphene citrate with metformin. Although safety data are reassuring, ongoing surveillance on the long-term use of letrozole should be encouraged. Given the lack of data on acceptability among patients, future research should involve patients with PCOS to better understand their values and preferences. A wide array of interventions are often considered in the management of PCOS *(39, 40)* some of which are not explored in this guideline.

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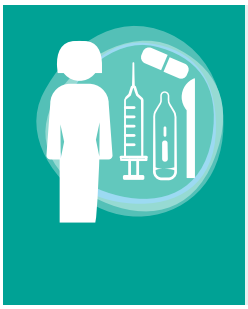


Recommendation

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)

Background and rationale

Treatment options for women who have been unsuccessful with oral pharmacological therapy with letrozole or clomiphene citrate with metformin include surgical treatment with LOD or pharmacological treatment with injectable gonadotrophins.

Gonadotropins include naturally occurring LH and FSH from the pituitary, and human chorionic gonadotrophin (HCG) from the placenta, as well as their recombinant glycoforms, rFSH, rLH and rHCG *(1, 2)*. Human menopausal gonadotrophins (hMGs) contain both FSH and LH *(3)*. In females, gonadotrophins influence follicular recruitment, oocyte maturation, E2 secretion, ovulation and progesterone production *(1)*. Based on these effects, gonadotrophins are an option for ovulation induction in the treatment of infertility *(4)*. However, they can cause adverse effects, such as multiple gestation and OHSS *(5)*, and need to be injected intramuscularly or subcutaneously *(6)*. Recombinant forms differ from urine-derived or serum-derived gonadotrophins in terms of purity and batch-to-batch consistency in biological activity *(7)*. To prevent multiple pregnancies and ovarian hyperstimulation, gonadotrophins are typically administered in individualized, step-up or (rarely) step-down regimens *(8, 9)*. Ultrasound is used to monitor follicular growth during a stimulation cycle.

LOD is a surgical procedure whereby multiple perforations are made in the ovarian surface and stroma (the inner area of the ovary) to stimulate follicle development and ovulation induction *(10, 11)*. LOD uses several cautery techniques to make perforations *(12, 13)*, and the number and depth of perforations, and dose and duration of energy may vary *(11)*. The precise mechanism through which LOD causes therapeutic effects is unknown, but is postulated to include changes in both circulating hormones and a pituitary feedback mechanism *(14, 15)*. LOD is typically performed as an outpatient procedure. For this recommendation, the GDG addressed the question: should LOD versus gonadotrophins be used for females with infertility due to ovulatory dysfunction caused by PCOS who fail oral pharmacological therapies such as letrozole or clomiphene citrate with metformin?

Balancing harms and benefits

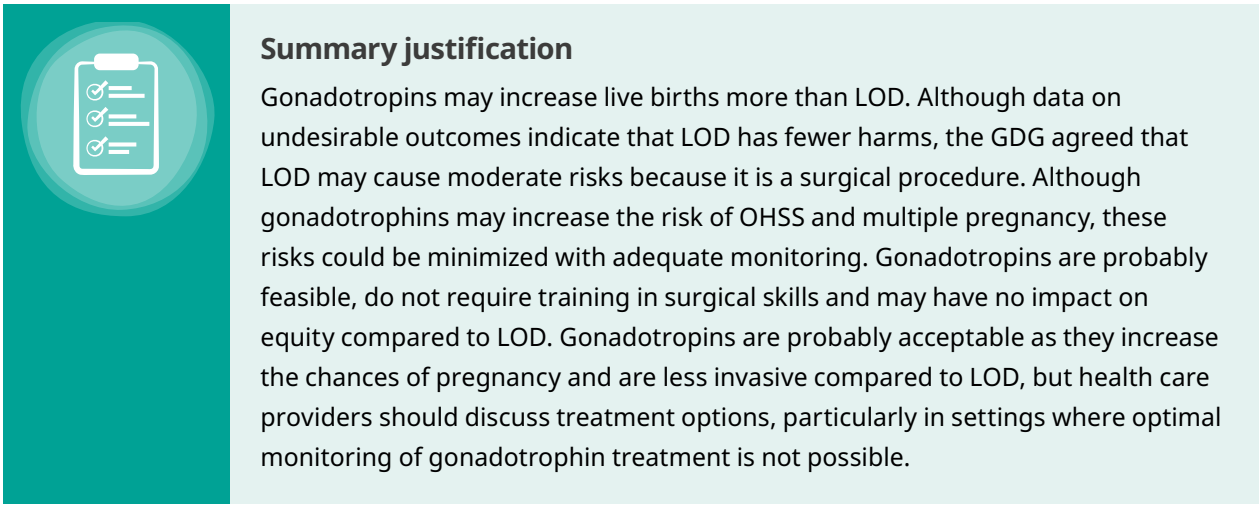
A systematic review of RCTs provided data for the benefits and harms of LOD compared with gonadotrophins *(16)*. There is likely little to no differences in live births (RR: 0.98; 95% CI: 0.79–1.21) and clinical pregnancies (RR: 1.02; 95% CI: 0.87–1.19), quality of life or depression between the two interventions. There may be large reductions in OHSS (RD: -0.02; 95% CI: -0.06 to 0.03) and multiple pregnancies (RR: 0.22; 95% CI: 0.09–0.54) and a small reduction in miscarriages (RR: 0.90; 95% CI: 0.57–1.45) with the use of LOD compared with gonadotrophins. Data on other adverse events were not reported, but the GDG noted that LOD is a surgical procedure requiring general anaesthesia, which could potentially increase the risks of bleeding, infection, thermal damage to adjacent organs and postoperative effects on ovarian reserve and adhesion formation. The GDG agreed that although gonadotrophins may increase the risk of OHSS and multiple pregnancies, these risks could be minimized with appropriate treatment regimens, surveillance and monitoring. Therefore, the GDG judged the benefits of LOD to be trivial and its

harms small compared to gonadotrophins. The overall certainty of evidence was low.

Other considerations

Although LOD is probably feasible, it requires training in surgical skills. The review reported costs from three RCTs and found that LOD was generally less costly than gonadotrophins *(16)*. However, a retrospective health-economic evaluation performed from a societal perspective comparing gonadotrophins with LOD (n = 35), followed by ovulation induction with clomiphene citrate and/or hMGs, reported that if spontaneous ovulation did not occur within 2 months, then the societal cost per patient was higher after LOD versus gonadotrophins *(17)*. Most of the cost in this retrospective study was due to productivity loss with LOD *(17)*. Two studies reported the comparative cost-effectiveness of LOD versus gonadotrophins per additional ongoing pregnancy and live birth, but the results were inconsistent *(17, 18)*. Based on these data, the GDG agreed that although LOD may cost less and may lead to cost savings because of a lesser need for monitoring (because of mono-ovulation), the harms that may occur with an invasive surgical intervention may lead to additional health care costs. Along with the additional greater training needs for LOD, this would balance out the potential cost savings, probably resulting in little difference in the cost-effectiveness of the two treatments.

There were no studies assessing equity, but the GDG judged that LOD probably has no impact on equity compared to gonadotrophins. One study that assessed patient preferences reported that couples were willing to accept LOD over ovarian stimulation if both treatments resulted in similar chances of pregnancy *(19)*; based on this finding, the GDG judged that there is probably no variability in how much people value pregnancy, noting that most people would want to minimize adverse effects and would probably opt for the treatment that most increases their chances of pregnancy and live births.



Summary justification

Gonadotropins may increase live births more than LOD. Although data on undesirable outcomes indicate that LOD has fewer harms, the GDG agreed that LOD may cause moderate risks because it is a surgical procedure. Although gonadotrophins may increase the risk of OHSS and multiple pregnancy, these risks could be minimized with adequate monitoring. Gonadotropins are probably feasible, do not require training in surgical skills and may have no impact on equity compared to LOD. Gonadotropins are probably acceptable as they increase the chances of pregnancy and are less invasive compared to LOD, but health care providers should discuss treatment options, particularly in settings where optimal monitoring of gonadotrophin treatment is not possible.

Implementation considerations

Health care providers should be aware of the risks of ovulation induction, including the occurrence of OHSS and multiple pregnancy on patients and health systems, and consider implementing monitoring strategies (e.g. with ultrasound or hormone measurement) to manage potential harms. Health care providers should counsel patients on treatment options, particularly in settings where optimal monitoring of gonadotrophin treatment is not possible. When gonadotrophins are used, it should be in settings where capacity for the management of side-effects and specified risk mitigation factors are in place (e.g. individualized, step-up or step-down protocols).

Research gaps and future guideline update

Future studies should report outcomes comprehensively, including cost-effectiveness, time to pregnancy, postoperative effects of LOD on ovarian reserve, thermal damage to adjacent organs, infections, adhesion formation and other longer-term outcomes. Future guidance will be needed on specific dosing regimens for ovulation induction with gonadotrophins.

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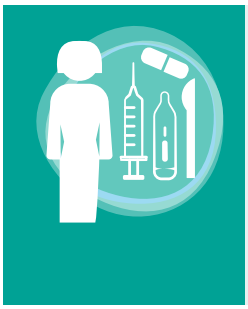

Recommendation

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 using in vitro fertilization (IVF) rather than expectant management. *(Conditional recommendation, very low certainty of evidence)*

Background and rationale

Women with infertility due to PCOS may fail to achieve pregnancy after treatment with letrozole, clomiphene citrate with metformin or gonadotrophins. Therefore, it is important to explore what approach should be followed when gonadotrophins have been unsuccessful. Options for women may include IVF or expectant management.

IVF is a procedure where oocytes and sperm are co-incubated outside the human body with the goal of achieving fertilization, after which the embryo is transferred to the uterus. IVF was first reported in humans in the late 1960s *(1)*; in 1978, the first birth resulting from IVF was reported *(2)*. IVF is traditionally the next line of treatment when most other approaches have been unsuccessful. The procedure involves several steps: (i) the retrieval of the woman's oocytes from the ovaries; (ii) exposure of the retrieved oocytes to sperm outside the body for fertilization; (iii) culture of the resulting embryo(s) for 3–5 days; and (iv) transfer of the embryo to the uterus *(3)*.

Globally, a significant number of people have conceived through IVF *(4)*, but it involves costs *(5)*, and may also have adverse effects, such as multiple pregnancy *(6, 7)* and OHSS, which is a serious and potentially fatal condition *(8)*. Ultrasound is typically used to monitor ovarian response and follicular growth during stimulation cycles for IVF *(9)*. IVF allows control over the number of embryos transferred, while allowing spare embryos to be cryopreserved for future use, obviating the need for further ovarian stimulation *(10)*. For this recommendation, the GDG addressed the question: should IVF versus expectant management be used for females with infertility due to ovulatory dysfunction caused by PCOS who fail pharmacological therapies such as letrozole, clomiphene citrate with metformin or gonadotrophins?

Balancing harms and benefits

The review team conducted a broad de novo search and did not identify any published systematic reviews, RCTs or non-randomized studies comparing IVF/ICSI versus no IVF/ICSI in women with ovulation dysfunction due to PCOS. Evidence from nine non-comparative, single-arm, non-randomized studies among women receiving IVF for ovulation dysfunction due to PCOS were identified *(11–19)*. Of these, only one study *(12)* reported that women (n = 1508) had been unsuccessful on other treatments.

Evidence from observational non-comparative studies indicated that the use of IVF may result in 550 clinical pregnancies (proportion: 0.55; 95% CI: 0.43–0.66) and 520 live births per 1000 women (proportion: 0.52; 95% CI: 0.34–0.70). In terms of undesirable effects, for every 1000 women receiving IVF, there may be 50 cases of OHSS (proportion: 0.05; 95% CI: 0–0.10) and 180 cases of multiple pregnancy (proportion: 0.18; 95% CI: 0.12–0.25) and a low incidence of miscarriages (proportion: 0.16; 95% CI: 0.13–0.20). The GDG noted the difficulty of judging the magnitude of undesirable effects by looking at proportions, but also noted that OHSS and multiple pregnancy are inherently associated with IVF. Although IVF may cause harms such as OHSS and multiple pregnancy, these can be mitigated with appropriate treatment

regimens, surveillance, monitoring and policies regarding embryo transfer.

Direct evidence is lacking with respect to patients' values and preferences comparing IVF with no IVF (i.e. expectant management). Indirect evidence from two discrete experimental studies that involved 297 Dutch women with infertility (n = 206 and n = 91) eligible for IVF showed that acceptability of IVF was increased by its potential to increase pregnancies and live births, but was reduced by out-of-pocket costs and potential risk of OHSS *(20, 21)*. The GDG judged that the benefits of IVF probably outweigh the potential harms for women with infertility due to PCOS when other initial treatments have been unsuccessful. The overall certainty of evidence was judged to be very low given the lack of appropriate comparative studies.

Other considerations

IVF is probably feasible but requires investments in health systems because of the costs involved *(5, 22)*. Safe provision of IVF requires specialized equipment and training of health care providers. The GDG judged that resource requirements on health systems and individuals are moderate to large, noting that costs to individuals and the health system may result from the IVF procedure itself or from the management of OHSS, multiple pregnancy and other complications that may result from IVF. IVF probably reduces equity if it is only available to select people, for example, in settings where IVF facilities are not available or physically or financially accessible. To mitigate the impact on equity, appropriate assisted reproduction policies and services are required to ensure access to those that need it.

In the absence of direct evidence on acceptability, values and preferences from patients with PCOS, the GDG agreed that women with infertility value live births over potential harms and considered that ethically, such patients should have options when other treatments have been unsuccessful. Overall, the GDG judged that IVF is probably acceptable if the frequency of OHSS and costs are reduced.

Summary justification

The higher number of live births, relatively low undesirable effects, feasibility and acceptability of IVF probably favours the use of IVF over expectant management.

Implementation considerations

Women with PCOS undergoing IVF should be informed about the potential benefits, costs and risks of IVF, such as OHSS and multiple pregnancy. Health care providers should consider ways of minimizing potential harms, including through appropriate treatment regimens and protocols, surveillance and monitoring, and policies on the number of embryos to transfer *(7, 23–26)*.

Given the lack of direct evidence on patients' values and preferences, health care providers should seek to understand patients' acceptability of IVF when other treatment options have been unsuccessful, as well as social, cultural, economic and other concerns that patients may have. Acceptability of IVF may be affected by a range of individual and sociocultural factors *(27, 28)*. Health care providers should inform patients about prognostic factors such as female age, duration of subfertility and number of oocytes, among others *(29)*, and support patients to make informed decisions in keeping with the principles of shared decision-making based on their values and preferences. Health care providers should also be aware and, whenever possible, mitigate contextual issues that may affect the implementation of this recommendation related to the health system

(e.g. availability of IVF facilities, personnel training and quality control of laboratories), economics (e.g. costs of IVF) and sociocultural factors (e.g. religious beliefs related to ART).

Research gaps and future guideline update

Further guidance will be required on the role of the GnRH agonist trigger, in vitro maturation, single embryo transfer, minimal ovarian stimulation and other prognostic factors, protocols and strategies that may increase the efficiency and effectiveness of IVF, while reducing any potential harms. Future research should involve patients and identify their values, preferences and acceptability of IVF interventions. In addition, future research is needed to assess strategies for making IVF more affordable *(30, 31)* given that IVF is economically out of reach for many individuals *(31, 32)*.

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Recommendation

For females with infertility due to ovulatory dysfunction caused by hyperprolactinaemia, WHO suggests using cabergoline over bromocriptine.
(Conditional recommendation, low certainty of evidence)

Background and rationale

Hyperprolactinaemia is a common endocrine disorder of the hypothalamic–pituitary axis. Normal prolactin (PRL) levels in women and men are below 25 µg/L and 20 µg/L, respectively *(1)*. Data on the global prevalence of hyperprolactinaemia are sparse; however, an analysis of 1607 medically treated patients with hyperprolactinaemia reported a prevalence of 10.8 per 100 000 in men and 29.5 per 100 000 in women, with a peak incidence among women aged 25–34 years *(2)*. Although hyperprolactinaemia is diagnosed in less than 1% in the unselected general population, it is reported to occur in 5–17% of women with secondary amenorrhoea *(3–6)* and in 6.7% of those with infertility *(7, 8)*.

There are many possible causes of hyperprolactinaemia, including physiological, pharmacological, pathological or idiopathic etiologies *(9)*. Pituitary adenoma or prolactinoma is one of the most frequent pathological cause of hyperprolactinaemia *(10)*. Physiological states such as pregnancy can cause PRL elevation *(11)*, while pharmacological causes include side-effects from some antipsychotics, opiates, antihypertensives and antidepressants *(12)*.

PRL exerts many physiological functions; clinical manifestations of hyperprolactinaemia are exerted through its effects on the hypothalamic–pituitary–gonadal axis, mammary glands (i.e. breast) and adenoma mass effects in the region of the sella turcica *(13)*. In women, hyperprolactinaemia often leads to oligomenorrhoea, amenorrhoea, infertility and galactorrhoea *(14)*. These symptoms are related to the physiological actions of PRL on lactogenesis and also result in hypogonadotropic hypogonadism, low estrogen and oligo-ovulation or anovulation. Other symptoms may include headaches and visual disturbances because of local mass effects of pituitary adenomas and prolactinomas *(14)*.

Dopamine agonists are often the first-line treatment for patients with hyperprolactinaemia due to a pituitary adenoma *(1)*. Pituitary PRL secretion is mainly under inhibitory control by dopamine in the hypothalamic tuberoinfundibular pathway. It is secreted into the hypophyseal portal system and reaches the pituitary lactotrophs where it activates dopamine D2 receptors to suppress PRL secretion *(15)*. Because dopamine inhibits PRL secretion, dopamine agonists, such as bromocriptine and cabergoline, reduce serum PRL levels by directly stimulating dopamine receptors in pituitary lactotrophs, thereby lowering circulating PRL levels. A reduction in PRL levels subsequently leads to the resumption of ovulatory menstrual cycles, shrinking of pituitary prolactinomas, resolution of visual field defects and resolution of galactorrhoea *(16)*.

For this recommendation, the GDG addressed the question: should cabergoline versus bromocriptine be used for the treatment of anovulatory infertility caused by hyperprolactinaemia? Bromocriptine is the primary dopamine agonist against which newer ergot derivatives are typically compared *(17)*; it has side-effects common to all ergot derivatives, such as nausea and vomiting *(18)*. Although it is generally effective, some patients may not tolerate bromocriptine at therapeutic doses *(19, 20)* and are resistant to it *(21)*. Cabergoline is a newer ergot derivative with a longer half-life allowing it to be taken only once or twice weekly, which may improve therapeutic compliance *(18, 22)*. The outcomes of

interest for this recommendation were live births, clinical pregnancy rates and adverse effects of these medications. Although return of ovulation is an important intermediate step towards live births in women with anovulatory infertility secondary to hyperprolactinaemia, it was not independently assessed as an outcome; instead, the GDG prioritized pregnancies and live births as primary outcomes.

Balancing harms and benefits

A systematic search for randomized and non-randomized studies was conducted in MEDLINE, Embase and the Cochrane Central Register of Controlled Trials from 1990 until June 2019. The search identified five relevant RCTs that compared cabergoline and bromocriptine *(23–27)*. There is low-quality evidence from these RCTs that cabergoline may be more effective in terms of both biochemical (RR: 1.65; 95% CI: 0.95–2.86) and clinical (RR: 1.46; 95% CI: 1.19–1.78) pregnancy, assessed at 4 and 6–7 weeks of gestation, respectively. In these RCTs, live birth rates were not assessed.

In terms of undesirable effects, there is moderate to very-low evidence from RCTs that medication side-effects are likely less common with cabergoline compared to bromocriptine, suggesting that cabergoline is likely more tolerable. Two studies *(24, 25)* reported on miscarriages, which were rare, but these studies were rated as being of very low quality for failing to report results between comparison groups, incomplete outcome data and having very few events. In all studies, the route of administration was oral for both medications, although the GDG noted some variations in the dosages of the two medications administered across the studies. These studies used lower levels of bromocriptine than what is typical in clinical practice. The overall certainty of evidence was rated as low. Data are lacking on patient values and preferences; however, the GDG judged that there is no important uncertainty in how people value the main outcomes. Because patients are likely to prefer the option that is more effective and better tolerated, the GDG judged that the balance of effects probably favours cabergoline compared to bromocriptine.

Additional considerations

There is a lack of studies assessing the acceptability of dopamine agonists among patients. However, given the less frequent oral dosing and better tolerability of cabergoline compared to bromocriptine, the GDG judged that it is probably acceptable. Although there was limited evidence regarding feasibility, the GDG judged that provision of cabergoline, including management of side-effects, is likely feasible. Two studies reported that cabergoline is slightly more expensive than bromocriptine when analysed per tablet *(28, 29)*. However, costs are likely to be comparable, given the less frequent dosing schedule of cabergoline *(29)*. Therefore, the GDG concluded that overall, recommending cabergoline would result in negligible costs compared to bromocriptine, although costs may differ slightly across countries.

Summary justification

Overall, there is low quality evidence that cabergoline may be more effective in increasing the rate of both clinical and biochemical pregnancy and is likely more tolerable. Live birth rates were not reported in the studies. Because patients are likely to prefer the option that is more effective while having fewer side-effects, the balance of effects probably favours cabergoline. In addition, cabergoline is probably acceptable and is feasible. Although the cost per tablet of cabergoline could be higher than bromocriptine, the dosing regimen can reduce cabergoline costs. Therefore, women with ovulatory dysfunction infertility due to hyperprolactinaemia are more likely to benefit more from cabergoline than bromocriptine.

Implementation considerations

Once hyperprolactinaemia is confirmed, the primary cause needs to be investigated before initiating treatment with dopamine agonists. Evaluation is aimed at excluding pharmacological or extra-pituitary causes of hyperprolactinaemia, such as medication use, renal failure, primary hypothyroidism and parasellar tumours *(9)*, and may include history-taking, visual and physical examination, and laboratory and imaging tests. The higher the level of PRL in general, the greater the likelihood of a pituitary adenoma and the greater the likelihood it will be a macroadenoma. Higher levels of PRL are associated with prolactinomas and macroadenomas *(30, 31)*.

Macroadenomas of the pituitary can be associated with visual field defects and may alter secretion of other pituitary hormones. Clinically significant tumour growth can occur during pregnancy.

After commencement of treatment, health care providers should monitor whether dopamine agonists are working effectively, including regularly assessing PRL levels, side-effects and return of ovulation. Further evaluation should be considered if menses do not return, or if new symptoms appear or persist, which may indicate possible pregnancy or persistent hyperprolactinaemia requiring dose adjustment.

Research gaps and future guideline update

In terms of future research, studies comparing cabergoline and bromocriptine should assess live birth outcomes, as well as patient-centred outcomes, including acceptability and quality of life. Current studies focus on reporting pregnancy rates and normalization of PRL levels. Future research and guidance will be required on whether to discontinue bromocriptine or cabergoline therapy in women who become pregnant after normalization of PRL levels. Such guidance will need to consider the potential risk of continuing dopamine agonists vis-à-vis the risk of recurrence of hyperprolactinaemia on medication withdrawal.

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Chapter 7 Treatment of infertility due to tubal disease

The following **sections 7.1–7.2** present recommendations related to the management of tubal blockage and hydrosalpinx.

7.1 Use of surgery or IVF for treatment of tubal disease

Recommendation

For females aged < 35 years with mild-to-moderate tubal disease (Hull and Rutherford grades I and II), WHO suggests surgery rather than in vitro fertilization (IVF). *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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.

For females aged < 35 years with severe tubal disease (Hull and Rutherford grade III), WHO suggests in vitro fertilization (IVF) rather than surgery. *(Conditional recommendation, very low certainty of evidence)*

Remark:

- This recommendation does not apply to females who have had previous tubal sterilization.

For females aged ≥ 35 years with any tubal disease, WHO suggests IVF rather than surgery. *(Conditional recommendation, very low certainty of evidence).*

Background and rationale

Tubal factor infertility occurs when some pathology proximally at the uterotubal junction or more distally in the fallopian tube(s), caused by disease, obstruction, damage, scarring, congenital malformations or other factors, prevents oocyte pickup by the fimbriated ends of the tube or sperm access to the oocyte for fertilization in the tube, or impedes the fertilized egg and developing embryo from descending into the uterus, thereby preventing pregnancy or resulting in ectopic pregnancy. Of the different causes, the most prevalent is PID or salpingitis. In a large WHO multi-country study, bilateral tubal occlusion and acquired tubal abnormalities accounted for 17.7% and 11.6%, respectively, of all identifiable causes of female infertility *(1, 2)*, although the distribution can vary between high-income, middle-income and low-income settings (see **Annex 1. Distribution of the causes of infertility**). Given the role of the fallopian tube in gamete and embryo transport *(3)*, assessment of tubal disease, particularly tubal patency is important in the investigation of female infertility.

The two modalities for managing (or overcoming) tubal factor infertility, such as blockage, are IVF and tubal surgery. IVF is an ART procedure that involves combining eggs and sperm outside the body in a laboratory. The resulting embryos are transferred into the uterine cavity, without the need for open fallopian tubes. Surgical procedures include salpingostomy (formation of an opening at the distal end of an occluded fallopian tube), fimbrioplasty (removal of scar tissue around the distal end of the tube or reconstructing the fimbriae to approximate normal anatomy) and adhesiolysis (performed to remove scar tissue around the tube) *(4)*.

Given that fecundity of women decreases with age *(5)*, time to pregnancy is an important consideration when comparing surgery versus IVF. Apart from age, other important considerations include site and the extent of the tubal disease.

The Hull and Rutherford classification of tubal disease uses clinical descriptive characteristics, including tubal mucosal status, fibrosis and distension, and the extent of peritubal-ovarian adhesions; it groups patients (< 40 years old and excluding endometriosis) according to the prognosis for pregnancy *(6)*. Classification according to severity is related to the prognosis for spontaneous (i.e. unassisted) pregnancy after surgery (indicated by the expected 3-year pregnancy rate). Grade I refers to minor disease (with favourable surgical prognosis of 85% clinical pregnancy rate [CPR] and 69% live birth rate [LBR]/3 years). Grade II indicates intermediate disease (with intermediate surgical prognosis of 72% CPR and 48% LBR/3 years), while grade III indicates severe disease (with unfavourable or poor surgical prognosis of 28% CPR and 9% LBR/3 years) *(7)*. For these recommendations, the GDG addressed the question: should surgery versus IVF be used for women with infertility due to tubal disease? For these recommendations, surgical procedures for tubal disease exclude tubal re-anastomosis after sterilization (sterilization reversal). These recommendations assume that no significant male factor exists.

Balancing harms and benefits

A systematic review of the literature for randomized and non-randomized studies from 1990 to July 2019 was conducted. No RCTs comparing pregnancy rates after tubal surgery versus IVF were identified. Available evidence was identified from comparative non-randomized studies *(8–10)*; the certainty of the evidence was very low because of potential confounding, low number of events and wide CIs, and the heterogeneity of surgical approaches. Studies providing data on tubal re-anastomosis were excluded. The balance of desirable and undesirable effects for tubal surgery or IVF was arrived at considering patient age and the severity of the disease.

The overall data showed that compared to IVF, surgery may result in more live births (212 more per 1000 [from 156 to 279 more]; RR: 3.36; 95% CI: 2.74–4.11) over a follow-up duration of at least 5 years and may also result in more clinical pregnancies over the same follow-up period (369 more per 1000 [from 300 to 447 more]; RR: 4.34; 95% CI: 3.72–5.05), suggesting the benefit of surgery in younger patients with a good prognosis based on the Hull and Rutherford classification, that is, grade I or II tubal disease. In addition, surgery may result in fewer miscarriages (10 fewer per 1000 [from 28 fewer to 18 more]; RR: 0.84; 95% CI: 0.54–1.30). Of note, the benefits from surgery were mainly from microsurgical techniques. The GDG judged these desirable effects to be large.

In terms of harms, the data showed that surgery may result in more ectopic pregnancies (120 more per 1000; risk difference (%): 12; 95% CI: 9–15). Data on multiple gestations and OHSS were not reported in the studies included. The GDG noted the absence of data on important outcomes such as bleeding, infection, injury to internal organs and blood vessels, risks of general anaesthesia, OHSS and high-order multiple pregnancy (HOMP). The GDG considered that there is very little risk, if any, of OHSS and HOMP with surgery but IVF may increase the risk of OHSS and HOMP; however, effective strategies to

mitigate these risks of IVF, such as elective single embryo transfer, exist. However, the GDG noted that the greater risk of ectopic pregnancy, which may occur with surgery, may be more relevant in rural settings. However, in most cases these can be well managed by instituting heightened awareness and appropriate surveillance. The GDG considered that the outcomes of surgery are highly operator-dependent and may also be dependent on the extent and site of tubal disease. The GDG judged the undesirable effects to be small.

Although no evidence was found regarding values, the GDG agreed that women with infertility value pregnancy and live birth highly as the main outcomes of the intervention, as well as minimizing risks.

Based on these data, the GDG judged that the overall balance of effects probably does not favour either surgery or IVF. The GDG also noted that IVF outcomes and tubal surgery outcomes may vary in different settings depending on several factors, including the quality of the IVF laboratory and surgeon experience and expertise. In addition, the GDG considered the varying benefits of surgery for different subgroups, noting that the outcomes appear to be potentially influenced by several factors, including age and duration of follow-up. Cumulative pregnancy outcomes with surgery accrue over a longer duration of follow-up that ranges from 1 to 5 years, compared to IVF. Therefore, it is reasonable to offer surgery to younger patients (< 35 years) with mild and moderate disease (Hull and Rutherford grades I and II) because younger women may have time to explore other assisted reproduction options if pregnancy is not achieved after surgery. Given the resources expended in providing surgery, and the time required to achieve spontaneous (i.e. unassisted) pregnancy after surgery, it is recommended that health providers wait for a reasonable time (at least 1 year) after surgery before providing other interventions such as IVF. Most pregnancies occur within 1–2 years of surgical treatment of distal tubal disease *(7, 11)*; therefore, waiting a minimum of 1 year may be reasonable. It should be noted that this recommendation does not apply to women desiring pregnancy after tubal ligation or sterilization.

For younger women aged < 35 years with severe disease (Hull and Rutherford grade III) the harms of surgery probably outweigh its benefits. Although younger women aged < 35 years may have time to explore other assisted reproduction options if pregnancy is not achieved after surgery, severe disease (Hull and Rutherford grade III) has poor prognosis; therefore, IVF is recommended over surgery for these women.

Given concerns related to age-related fertility decline, IVF is also suggested over surgery in women aged ≥ 35 years regardless of the severity of tubal disease. For older women (≥ 35 years) the additional time required to undergo surgery and wait for spontaneous (i.e. unassisted) pregnancy means that women would be much older before exploring other options such as IVF, should pregnancy not be achieved after surgery; therefore, they would have a much lower chance of achieving pregnancy. For older women, the benefits of IVF probably outweigh the harms compared to surgery. For women who are older, women with severe tubal disease and couples with male-factor infertility, IVF could be offered. The overall certainty of evidence was judged to be very low; all studies included were observational.

Other considerations

Performing tubal reconstructive surgery with good results requires a well-equipped health system and a high level of expertise or training. Although it is probably feasible to train health professionals to provide surgery *(12)*, the resource requirements are often not available or met in many low-resource settings. Thus, the GDG judged that large resources are required for surgery and that compared to IVF, surgery would probably have no or limited effect on equity as IVF also involves high costs to be set up and operate.

Tubal surgery is often a one-time procedure that may be conducted as a minimally invasive outpatient procedure. It is more invasive than IVF. Given the impact of both age and severity of disease on pregnancies and live births, surgery is probably acceptable in younger patients with Hull and Rutherford grade I or II tubal disease, while in severe tubal disease (Hull and Rutherford grade III), IVF would probably be acceptable.

Summary justification

Surgery may increase pregnancies and live births after 5 years of follow-up more than IVF. Although surgery may increase the risk of ectopic pregnancy, a heightened awareness of its possibility with appropriate surveillance and management may minimize this risk. Surgery also may have fewer harms, including reduced risk of OHSS and HOMP. The overall desirable effects of clinical pregnancy and live births probably outweigh the risk of ectopic pregnancy. In addition, surgery is probably feasible to provide, is probably acceptable, and it probably has no impact on equity compared to IVF.

Younger women (< 35 years) can pursue other assisted reproduction interventions if pregnancy fails to occur after surgery. However, for older women (≥ 35 years), the additional time required to undergo surgery and then receive IVF if surgery fails, means they would be much older and have a further reduced chance of pregnancy. Therefore, for older women the benefits of IVF probably outweigh its harms compared to surgery. Although IVF can increase the risk of OHSS and HOMP, these risks can be mitigated by strategies such as single embryo transfer.

Time to pregnancy in patients with good, intermediate and poor prognosis (3-year rates) justify an age cut-off of 35 years because this age allows up to 3 years of follow-up at a time when women's fertility potential is narrowing.

The minimum time to wait after surgery before offering IVF is similar to the duration for the definition of infertility for women < 35 years, that is, failure to conceive within 1 year. Although the treatment timeline can be different from the diagnostic timeline, data show that most pregnancies occur within 1–2 years after surgery.

Implementation considerations

Health care providers should counsel patients, communicate the prognosis, clearly discuss the options and costs of surgery and IVF, and consider patient preferences. In settings where the infrastructure for tubal surgery or IVF does not exist, patient referrals to adequately equipped centres should be considered. Health care providers should be trained to adequately monitor, mitigate and manage the undesirable effects of surgery (such as ectopic pregnancy) and IVF (such as OHSS and HOMP).

In implementing this recommendation, health care providers should consider whether patients have hydrosalpinges which may have a negative effect on pregnancy and IVF success rates *(13)*. If hydrosalpinx is present in women planning to undergo IVF, health care providers should implement recommendations related to treatment of hydrosalpinx before IVF, as described in the next section. In addition, these recommendations assume that no significant male factor exists.

Research gaps and future guideline update

Ovarian reserve may be an additional factor to consider; however, data were not available on the subgroup of women with decreased ovarian reserve, which should be addressed in future studies. Future studies should also assess important outcomes such as bleeding, infection, injury to internal organs and vessels, risks of general anaesthesia, OHSS and HOMP, and patients' values, including attitudes towards surgery or IVF, and preferences related to time to pregnancy and desired family size.

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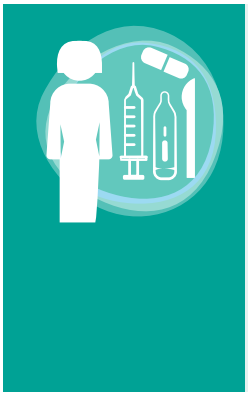
7.2 Treatment of hydrosalpinx before IVF



Recommendation

For females with tubal factor infertility due to hydrosalpinx, WHO suggests either salpingectomy or tubal occlusion before provision of in vitro fertilization (IVF).
(Conditional recommendation, very low certainty evidence)

Remark:

- When selecting whether to use salpingectomy or tubal occlusion, consider feasibility, availability of trained health care providers and presence of adhesions.

Background and rationale

In cases of tubal disease or blockage, women may develop hydrosalpinx, a condition where fluid accumulates inside the fallopian tubes. The presence of hydrosalpinx may have a negative effect on successful embryo implantation and affect IVF outcomes *(1)*. Therefore, the GDG agreed that guidance is needed regarding the management of hydrosalpinx in patients who are scheduled to undergo IVF.

Treatment of hydrosalpinx is aimed at preventing the hydrosalpingeal fluid from reaching the uterine cavity *(2)*. Options for hydrosalpinx treatment include surgically resecting and removing the affected fallopian tubes (salpingectomy), isolating the hydrosalpinx from the uterine cavity using laparoscopic or hysteroscopic tubal occlusion, transvaginal aspiration of hydrosalpingeal fluid under ultrasound guidance or draining the hydrosalpingeal fluid by means of salpingostomy *(3)*.

For this recommendation, the GDG addressed the question: should salpingectomy or tubal occlusion versus none be used to treat tubal disease due to hydrosalpinx in women due to undergo IVF?

Balancing harms and benefits

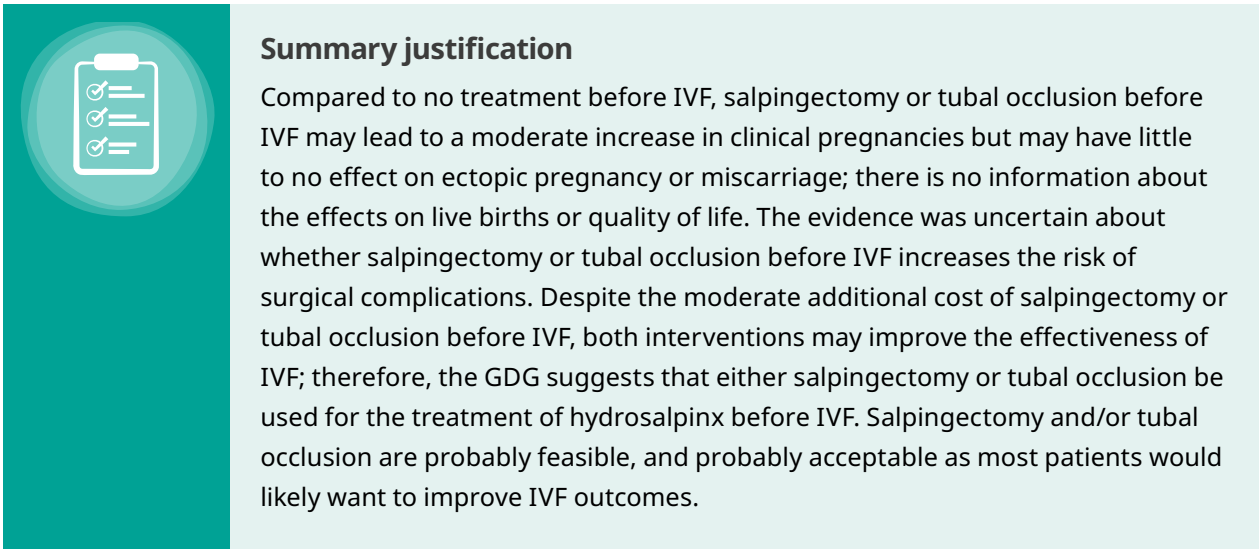
A systematic review published in 2020 was identified, with a search date from inception of the databases up to January 2020 *(3)*. From this systematic review, four RCTs published between 1998 and 2006 provided data for the outcomes *(4–7)*.

The results showed that compared to no treatment, conducting salpingectomy or tubal occlusion before IVF may result in slightly greater pregnancies and no difference in ectopic pregnancy and miscarriage. There were 151 more pregnancies (from 58 to 287 more) per 1000 (RR: 2.01; 95% CI: 1.39–2.91), three fewer miscarriages (from 32 fewer to 71 more) per 1000 (RR: 0.94; 95% CI: 0.36–2.41) and nine fewer ectopic pregnancies (from 14 fewer to 15 more) per 1000 (RR: 0.39; 95% CI: 0.08–1.97). Live births and quality of life outcomes were not reported. Compared to no treatment before IVF, conducting salpingectomy or tubal occlusion before IVF may result in 10 more conversions to laparotomy (RD: 0.01; 95% CI: -0.02 to 0.03) and 10 more pelvic infections per 1000 (RD: 0.01; 95% CI: -0.02 to 0.03). Although not measured, the GDG noted that the risk of other potential complications, such as visceral injuries, injury to blood vessels and bleeding, may exist with salpingectomy or tubal occlusion conducted before IVF. The GDG agreed that there were moderate benefits, but small harms, based on the very low certainty of the evidence because of few events or participants. Therefore, the GDG judged that the balance of effects probably favours surgery over no treatment before IVF.

Other considerations

No studies documented patient values; however, the GDG agreed that most couples would place higher value on maximizing pregnancy and birth outcomes and minimizing harms. The GDG agreed that the resources for surgery (e.g. equipment) and personnel training would result in moderate costs, although some cost variations between countries is expected.

No evidence was found on cost-effectiveness. The GDG noted that because of the costs, treatment with salpingectomy or tubal occlusion before IVF would probably reduce equity in settings with limited public health financing of infertility treatment. The GDG judged that surgery is probably acceptable, noting that while most couples would prefer to avoid invasive treatment, someone with confirmed hydrosalpinx who understands the impact of the condition on their IVF outcome would probably opt for treatment with salpingectomy or tubal occlusion to optimize the chance of success with subsequent IVF. The GDG judged that salpingectomy and tubal occlusion are probably feasible but require surgical facilities and training.



Summary justification

Compared to no treatment before IVF, salpingectomy or tubal occlusion before IVF may lead to a moderate increase in clinical pregnancies but may have little to no effect on ectopic pregnancy or miscarriage; there is no information about the effects on live births or quality of life. The evidence was uncertain about whether salpingectomy or tubal occlusion before IVF increases the risk of surgical complications. Despite the moderate additional cost of salpingectomy or tubal occlusion before IVF, both interventions may improve the effectiveness of IVF; therefore, the GDG suggests that either salpingectomy or tubal occlusion be used for the treatment of hydrosalpinx before IVF. Salpingectomy and/or tubal occlusion are probably feasible, and probably acceptable as most patients would likely want to improve IVF outcomes.

Implementation considerations

Caution should be taken during salpingectomy for hydrosalpinx conducted before IVF to avoid compromising the vascular supply to the ovaries, which could potentially result in suboptimal ovarian stimulation. Health care providers may consider several factors to determine whether to offer salpingectomy or tubal occlusion before IVF, for example, the presence of dense adhesions and patient preferences. Health care providers should monitor patients for potential complications after salpingectomy or tubal occlusion.

Research gaps and future guideline update

Future studies should report outcomes related to live birth rates, complications and quality of life, and should compare the different techniques of salpingectomy or tubal occlusion. Future guidance will be required on subgroups that may benefit optimally, for example, based on whether the hydrosalpinx is communicating or not. Future guidance will be required regarding the optimal timing of salpingectomy or tubal occlusion in relation to ovarian stimulation and egg retrieval.

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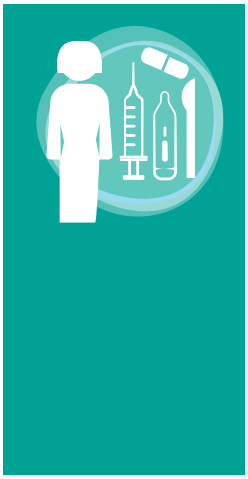

Recommendation

For females with tubal factor infertility due to hydrosalpinx, WHO suggests either salpingectomy or tubal occlusion rather than transvaginal aspiration of hydrosalpingeal fluid before provision of in vitro fertilization (IVF). *(Conditional recommendation, very low certainty of evidence for salpingectomy compared with tubal occlusion, and very low certainty of evidence for transvaginal aspiration compared to no treatment)*

Remark:

- In settings where salpingectomy and tubal occlusion are not available or feasible, transvaginal aspiration may be offered.

Background and rationale

Options for hydrosalpinx treatment include surgically resecting and removing the affected fallopian tubes (salpingectomy), isolating the hydrosalpinx from the uterine cavity using laparoscopic or hysteroscopic tubal occlusion, transvaginal aspiration of hydrosalpingeal fluid under ultrasound guidance or draining the hydrosalpingeal fluid by means of salpingostomy *(1)*. For this recommendation, the GDG addressed the question: should transvaginal aspiration of hydrosalpingeal fluid versus no treatment be used in tubal disease in women with hydrosalpinx who are due to undergo IVF?

Balancing harms and benefits

A systematic review published in 2020 was identified, with a search date from inception of the databases up to January 2020 *(1)*. From this systematic review, three RCTs published between 2008 and 2015 provided data for the outcomes *(2–4)*.

The results showed that transvaginal aspiration before IVF may result in a small increase in pregnancies and no differences in ectopic pregnancy or miscarriage compared to no treatment before IVF. There may be 96 more clinical pregnancies (from 12 to 226 more) per 1000 with transvaginal aspiration (RR: 1.64; 95% CI: 1.08–2.51), 12 more miscarriages (from 27 fewer to 118 more) per 1000 (RR: 1.24; 95% CI: 0.46–3.36) and five fewer ectopic pregnancies (from 13 fewer to 54 more) per 1000 (RR: 0.69; 95% CI: 0.10–4.62). Live births and quality of life outcomes were not reported. In addition, there may be no difference in pelvic infection, but a slight increase in multiple pregnancy, which is likely attributable to IVF treatment: transvaginal aspiration may result in zero fewer pelvic infections per 1000 (RD: 0; 95% CI: -0.03 to 0.03) and 53 more multiple pregnancies (from 19 fewer to 373 more) per 1000 (RR: 2.33; 95% CI: 0.52–10.32). There may also be an important proportion of women with recurrence after transvaginal aspiration; the number of other major or minor complications is low. Overall, recurrence with or without sclerotherapy occurred in 27% (18–39%). More specifically, without sclerotherapy, recurrence was 53% (46–60%); with sclerotherapy, it was 14% (8–22%). Major complications occurred in 10 out of 1297 (0.7%) and minor complications (e.g. pain, extravasation, ruptured cyst, flush reactions and gastrointestinal discomfort) in 80 out of 1297 (6%). Based on these data, the GDG judged that there may be small desirable and undesirable effects of transvaginal aspiration compared to no treatment before IVF.

The certainty of evidence was judged to be very low because of inconsistent blinding of participants and outcome assessors, loss to follow-up and few events or participants; some studies were not comparative. Although the GDG agreed that most people would place higher value on pregnancy and birth outcomes, while wanting to minimize harms, they judged that the balance of effects probably does not favour either transvaginal aspiration or no treatment.

Other considerations

The GDG agreed that the resources for transvaginal aspiration would result in moderate costs. No data were found on cost-effectiveness; however, the GDG considered that transvaginal aspiration would probably not be cost-effective because of the moderate costs, small benefits and small harms. No studies of the impact on health equity were available; however, the GDG judged that in women receiving IVF, the addition of transvaginal aspiration of hydrosalpingeal fluid before IVF would probably reduce equity because of additional costs.

No data were identified on acceptability; however, the GDG judged that transvaginal aspiration would probably not be acceptable given that most people would like to avoid an invasive procedure when there may be little benefit compared to harm. Nevertheless, the GDG judged that transvaginal aspiration is probably feasible, noting that ultrasound is available in most settings as a basic tool for gynaecological assessment; training of health care providers is required to perform transvaginal aspiration safely.

Summary justification

Transvaginal aspiration before IVF may lead to a small increase in clinical pregnancies, but it may have little to no effect on ectopic pregnancy or miscarriage; there are no data about its effects on live births or quality of life. There may be a slight increase in multiple pregnancy when transvaginal aspiration is conducted before IVF, and a clinically important proportion of women may experience recurrence after aspiration; however, the rates of other complications are low. As the benefits may be small, the GDG agreed that other procedures for the treatment of hydrosalpinx with greater benefits, that is, salpingectomy or tubal occlusion be used instead of transvaginal aspiration. However, in settings where salpingectomy and tubal occlusion are not available or feasible, transvaginal aspiration may be considered.

Implementation considerations

Health care providers should monitor patients for potential complications after treatment of hydrosalpinx, including post-aspiration infection, recurrence of fluid accumulation and accumulation of fluid in the endometrial cavity. Health care providers should note that transvaginal aspiration may only be offered if salpingectomy and tubal occlusion are not available or feasible.

Research gaps and future guideline update

Future guidance comparing transvaginal aspiration with salpingectomy or tubal occlusion should report outcomes related to live birth rates and surgical complications, optimal timing of procedures in relation to ovarian stimulation and oocyte retrieval or embryo transfer, and quality of life. Further guidance will be required regarding whether antibiotic prophylaxis should be used routinely if transvaginal aspiration is provided before IVF.

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Chapter 8 Treatment of infertility due to uterine cavity disorder

This section presents recommendations related to the management of uterine cavity disorders. Abnormalities of the uterine cavity may be congenital and acquired; rarely, they have an unknown etiology. Congenital abnormalities stem from aberrations in the development of the genital tract in the female *(1)*. Examples of acquired abnormalities include intrauterine adhesions, adenomas, fibroids or polyps, among others (see the *WHO manual for the standardized investigation and diagnosis of the infertile couple [2]* and its annexes). This chapter discusses the management of congenital abnormalities of the uterine cavity prioritized by the GDG, specifically uterine septum in women with infertility. Further guidance for other uterine conditions will be provided in a subsequent edition of this guideline.

8.1 Management of uterine septum in females with infertility

Recommendation

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)*

Background and rationale

Congenital uterine malformations represent a variety of anomalies of the female reproductive tract, which result from the abnormal differentiation, formation, migration, fusion, canalization or resorption of the Müllerian system during the fetal period *(3)*. The prevalence of congenital uterine malformations has been estimated at 4.3% in fertile women, 3.5–8.0% in women with infertility and 13–13.3% in women with recurrent pregnancy losses *(4, 5)*. Discrepancy in the prevalence rates has been reported in the literature, potentially because of different classifications *(4, 6–12)* and the use of different diagnostic methods, with variable ability of identifying and distinguishing these uterine malformations *(5)*. There is a lack of a single universally accepted evidence-based system for the definitions and diagnostic criteria of Müllerian anomalies.

Uterine malformations include:

- Müllerian agenesis, which is characterized by a failure of the Müllerian ducts to develop.
- Arcuate uterus, which is characterized by a mild concave indentation at the uterine fundus.
- Unicornuate or bicornuate uteri or uterus didelphys, which is characterized by varying abnormalities in fusion or unification defects of the Müllerian ducts.
- Subseptate or septate uteri characterized by varying abnormalities in canalization of the Müllerian ducts.

Of these malformations, septate, bicornuate and arcuate uteri are the most commonly reported among unselected populations *(4, 5)*; however, a septate uterus is likely more prevalent among populations at the highest risk of poor reproductive outcomes *(5, 13)*. A 2011 systematic review and meta-analysis found that presence of a subseptate or septate uterus is associated with reduced fertility (RR: 0.86; 95% CI: 0.77–0.96), increased first-trimester miscarriage rates (RR: 2.9; 95% CI 2.0 0–4.1) and increased preterm births (RR: 2.1; 95% CI 1.5–3.1) *(14)*. In the same meta-analysis, arcuate uteri were associated with increased rates of second-trimester miscarriage (RR: 2.39; 95% CI, 1.33–4.27), while unification defects (unicornuate or bicornuate uteri or uterus didelphys) were associated with increased rates of preterm birth (RR: 2.97; 95% CI: 2.08–4.23) *(14)*. Given that a septate uterus is among the most common uterine malformations *(4, 5)* and has the most data available from studies, the GDG guideline prioritized management of septate uterus over other uterine anomalies.

Options for managing uterine septae include expectant management, or surgery through hysteroscopic septum resection *(13)*. Although hysteroscopic septum resection is widely reported in the literature and is not uncommon in clinical practice, there is uncertainty regarding its benefit. For this recommendation, the GDG addressed the question: should hysteroscopic metroplasty (resection of uterine septum ["septoplasty"]) versus no treatment (i.e. expectant management) be used for women with infertility and uterine septae? Therefore, the population of interest for this recommendation are women with infertility and without recurrent pregnancy loss. Although the literature often includes women with miscarriage as part of the infertile population *(13, 15)*, this recommendation considered these as separate groups.

Balancing harms and benefits

Evidence was identified from a recent review *(16)*, a recent RCT *(17)* and nine non-randomized comparative studies *(18–26)*.

Low-certainty evidence showed that both the benefits and harms of septoplasty are small. In terms of benefits, data showed that providing hysteroscopic septoplasty may increase clinical pregnancies slightly (RR: 1.13; 95% CI: 0.74–1.74; 65 more, [from 130 fewer to 370 more], per 1000), but may have little to no difference on live births compared to expectant management (RR: 0.92; 95% CI: 0.48–1.75; 24 fewer, [from 156 fewer to 225 more], per 1000). In terms of harms, hysteroscopic septoplasty in the context of infertility treatment may result in slightly more multiple pregnancies (RD: 0.06; 95% CI: -0.03 to 0.15; 60 more, [from 30 fewer to 150 more], per 1000) and slightly more miscarriages (RR: 1.83; 95% CI: 0.70–4.81; 249 more, [from 90 fewer to 1000 more], per 1000), and little to no difference in preterm births, ectopic pregnancies or other adverse reproductive outcomes when compared to expectant management. In addition, there may be a small risk of uterine perforation with surgical resection. No reports of fluid overload were reported in one study that evaluated this outcome *(17)*. Most of the studies included contributed equally to most of the outcomes assessed. Most also included populations with infertility without recurrent pregnancy loss. Some studies included women with an arcuate uterus. Despite the heterogeneity of the studies included, the results were quite consistent across studies, except for one study by Li et al. *(21)*, which reported worse results with septoplasty. In this study *(21)*, indications for surgery were (i) septum depth ≥ 10 mm; (ii) septum depth between 5 and 10 mm with unexplained recurrent miscarriage or infertility; and (iii) recurrent failures of IVF and embryo transfer. Notably, this study reported higher miscarriage and lower live birth rates with surgery, which potentially changed the overall result to null in the adjusted analyses. The inclusion of data from women with an arcuate uterus, for which septoplasty may not be indicated, did not seem to affect the balance of effects. These results suggested that there is no clear evidence that the benefits of septoplasty outweigh its harms. The GDG judged that the balance of desirable and undesirable effects probably did not favour either septoplasty or expectant management.

Other considerations

Evidence on patient values and acceptability was limited. However, the GDG noted that some women may prefer to avoid invasive surgery, especially when the benefit is small. Among health care providers, acceptability for septoplasty varied. In a randomized study involving 191 gynaecologists from 43 countries, the agreement on the need for surgery once a septate uterus had been diagnosed was low *(27)*. Although hysteroscopic septoplasty is probably feasible, it involves moderate costs. Equipment and training of health care providers are required for the safe provision of hysteroscopic septoplasty, including prevention of fluid overload, which may not be available in all settings. The GDG acknowledged that contextual differences may exist in terms of the costs associated with hysteroscopic septoplasty and may also depend on differences in the availability of funding for infertility treatment. No relevant studies comparing the cost-effectiveness of hysteroscopic septoplasty versus expectant management were found. While limited evidence related to the impact of hysteroscopy on cost-effectiveness *(28)* or equity exists, the GDG judged that hysteroscopic septoplasty would likely reduce equity if only select people can afford it, which is likely given the potential costs to both individuals and health care systems.

Summary justification

Low-certainty evidence shows that there may be small undesirable effects with hysteroscopic uterine septum resection, particularly miscarriage, ectopic pregnancy and preterm birth, which balance with the small overall increase in benefits (including clinical pregnancy and live birth) that may result from the procedure. The balance of desirable and undesirable effects probably does not favour either hysteroscopic septoplasty or expectant management for treatment of infertility. Although hysteroscopic septoplasty is probably feasible to provide, it involves moderate cost or resources compared to expectant management. Acceptability of hysteroscopic septoplasty among health providers varies; in the absence of direct evidence from patients, it is possible that some women would likely want to avoid invasive procedures, especially when the benefit is small.

Implementation considerations

Health care providers should be aware that this recommendation also applies to women with an arcuate uterus, which is regarded as a variant of normal morphology for which hysteroscopic septum resection is generally not indicated. This recommendation does not address intrauterine polyps, a bicornuate uterus or uterine fibroids. Health care providers should take caution regarding different or changing definitions of what constitutes a uterine septum or an arcuate uterus. Definitions of septate and arcuate uteri vary widely (e.g. length, width of septum).

Research gaps and future guideline update

Large randomized controlled studies are required to provide high-quality evidence on the effects of hysteroscopic septoplasty and to identify specific subgroups with infertility that could benefit from septoplasty. Future studies should be large enough to measure outcomes stratified according to types, depth or width of uterine septae, and other subgroup categories of interest to health practitioners (including those due to undergo IVF). Careful attention to inclusion and exclusion criteria is warranted to ensure that any future studies are meaningful. These efforts should be complemented

by strengthening and consistent use of evidence-based definitions and diagnostic criteria of Müllerian anomalies.

This recommendation relates to populations of women with infertility but not those with recurrent pregnancy loss. Future guidance will be required on the role of septoplasty in fertile women (with a septate uterus) who have recurrent pregnancy losses after achieving a pregnancy. In addition, this recommendation does not assess the harms or benefits of septoplasty in women (with a septate uterus) who have implantation failure; future guidance will be required to address this question.

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Chapter 9 Treatment of infertility due to male factors

The following sections 9.1–9.2 present recommendations related to the management of male-factor infertility.

9.1 Use of antioxidants

Recommendation

For males with infertility and one or more semen parameters that are outside the WHO reference ranges 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.

Remark:

- 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.

Background and rationale

Globally, the main cause of infertility reported in a large WHO multi-country study involving 8500 couples in 25 countries was due to female factors alone in 30.6% of cases, both male and female factors in 26.3% and male factors alone in 18.7% of cases *(1)*. Based on this study, male factors contributed wholly or in part to 45.1% of infertility cases (see **Annex 1. Distribution of the causes of infertility**).

Reactive oxygen species (ROS), such as superoxide ($O_2^{\cdot-}$), nitric oxide ($NO^{\cdot}$) and hydrogen peroxide (H_2O_2), are by-products of oxygen metabolism under normal physiological conditions *(2, 3)*. However, an imbalance in reduction–oxidation reactions is thought to increase intracellular concentration of ROS and to potentially have a role in disease processes *(4, 5)*. In the context of infertility, oxidative stress may increase the levels of ROS in the male tract or seminal secretions, which is hypothesized to negatively affect male fertility *(6, 7)*. Oxidative stress can result from several sources, including seminal leukocytes *(8, 9)*.

Although there is still a need for definitive evidence (for a validated or certain test, assay or proof) linking reduction–oxidation imbalances with fertility outcomes *(8)*, as indicated in some studies *(10, 11)*, it is accepted that oxidative stress is probably an important modulator of human sperm function *(8)*. In this context, oral antioxidant therapy has been increasingly investigated for the possibility that it could ameliorate oxidative stress, and improve human sperm function *(12)*, under an overarching hypothesis that individuals exposed to increased oxidative stress may have raised antioxidant requirements.

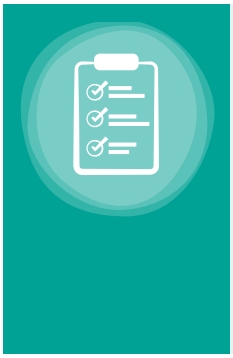
In general, a dietary antioxidant is a substance in foods that significantly decreases the adverse effects of ROS, reactive nitrogen species or both,

on normal physiological function in humans *(13)*. While fruits and vegetables typically contain safe levels of dietary antioxidants *(3, 14, 15)*, the GDG agreed that an important question is whether oral antioxidant supplements are beneficial or harmful for men with male-factor infertility, and what types and amounts of antioxidants are useful for this population. The GDG agreed and noted that clinicians may be suggesting antioxidants for men with infertility, particularly those who have semen parameters outside the WHO reference ranges, and also that men may be asking about whether to take antioxidants, yet there have been uncertainties about the general health effects and potential harms of supplementation with antioxidants supplements, as reported in some studies *(16)*.

In the context of male-factor infertility, an antioxidant is a substance that has the ability to protect spermatozoa against oxidative damage, for example, through neutralizing actions, or by functioning as a component of an antioxidant enzyme *(12)*. These antioxidant properties may also contain membrane stability effects *(3, 17)*. Oral antioxidant supplements typically include some types of vitamins, trace elements and other mineral compounds that are chemically synthesized and packaged as pills. They are generally dispensed without prescription, either separately or in any combination among themselves, or in combination with other vitamins, trace elements or mineral compounds that do not have antioxidant effects. For this recommendation, the GDG addressed the question: should oral antioxidant supplements versus no oral antioxidant supplements be used by men with infertility and semen parameters outside the WHO reference range? In this recommendation, the GDG was interested in fertility outcomes rather than changes in specific semen parameters. Herbal preparations are not included.

Balancing harms and benefits

Data were obtained from a systematic review *(12)* and a targeted search for RCTs. Based on the evidence, the GDG concluded that no recommendation can be made about the use of antioxidant supplements for men in couples with infertility and semen parameters that are outside the WHO reference range attempting to achieve pregnancy with or without medically assisted reproduction (see **Web Annexes A–F** for the detailed evidence to decision tables).



Summary justification

The available studies from a systematic review *(12)* and a targeted search for RCTs up to April 2024 were in men with different pathologies for infertility and evaluated a variety of antioxidants in combination or as a single supplement and in different doses in men with one or more semen parameters outside the WHO reference ranges. This evidence could not be used to inform a recommendation about the use of antioxidants for this population.

Research gaps and future guideline update

Overall, stronger evidence is still needed to demonstrate clear reversal of imbalance in reduction–oxidation equilibrium reactions, which forms the basis of the use of oral supplemental antioxidants in men with infertility, while precluding the risk of possible reductive stress *(18–20)*. In particular, large, good-quality RCTs on oral supplemental antioxidants are required among men in couples with infertility, particularly men with one or more semen parameters that are outside the WHO reference ranges, noting simple diagnostic tests that can identify men with oxidative stress may also be needed *(21)*. Such studies should focus on cases where female factors have been excluded. Such studies should be well-powered

trials with low risk of attrition and other bias and should report live birth as a primary outcome. Studies should harmonize the types, doses and durations of the antioxidant compounds being tested. Harmonization of eligibility and outcomes would also facilitate comparison, interpretation and pooling of results. Further efforts are required to harmonize regulatory parameters and quality control related to antioxidant formulation, production and storage.

Future trials should be independent, be of sufficiently long duration and with adequate patient retention. Future studies should focus on outcomes beyond changes in semen parameters to also include clinical pregnancy and live births. Future studies should focus on researching compounds at comparable standard doses, formulation, durations and combinations that may undergo evaluation as part of the WHO model list of essential medicines update process *(22)*. Better understanding of the potential for antioxidants to cause reductive stress is also needed. At present, there are several micronutrient compounds included on the WHO model list of essential medicines *(22)*, but the optimal plasma or tissue concentrations of nutrients required to counter oxidant stress in tissues are not known *(3)*. Future research is required to address this gap.

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9.2 Treatment of varicocele

This section contains several recommendations related to the management of varicocele regarding treatment, treatment modalities or approaches that should be read together.

Recommendation

For males with infertility and clinical varicocele, WHO suggests surgical or radiological treatment over expectant management. *(Conditional recommendation, low certainty of evidence)*

Remarks:

- Males with clinical varicocele and semen parameters 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 clinical varicocele in couples with infertility who are not undergoing treatment with assisted reproductive technology (ART).

Background and rationale

Varicoceles are vascular lesions resulting from the dilation and distention of the internal spermatic vein and pampiniform plexus within the spermatic cord in the scrotum. While most varicoceles are left-sided, they may occur on the right or bilaterally *(1)* and they are a common finding among men being evaluated for infertility. In a large WHO multi-country study involving 8500 couples in 25 countries, varicocele constituted 13.1% of male infertility cases *(2)*. In the same study, varicocele was found in 25.4% of male partners with abnormal semen parameters, compared with 11.7% of male partners with normal semen parameters *(3)*. While varicoceles occur more frequently in infertile compared to fertile men, not all men with a varicocele have infertility *(4)*.

Common symptoms of varicoceles include pain or discomfort. Varicoceles may also have negative *(5, 6)* and possibly progressive effects *(7)* on semen parameters and sperm function *(8)*. The exact mechanisms according to which varicoceles cause negative effect on spermatogenesis are unknown; however, testicular temperature elevation, venous reflux and oxidative stress are hypothesized to have important roles *(9)*. Others include reflux of renal and adrenal products, hormonal dysfunction, autoimmunity, apoptosis, hypoxia, genetics, defects in acrosome reaction and DNA damage, among others *(9–13)*. Despite ongoing research, the pathophysiological mechanisms through which varicoceles impair testicular function remain inconclusive; many of these factors may act in concert.

A varicocele may be clinical or subclinical.
A subclinical varicocele is not palpable (nor visible) on scrotal examination; it requires additional diagnostic aids to detect. A clinical varicocele is palpable and is diagnosed by physical examination through palpation before and during a Valsalva manoeuvre with the patient in a standing position at room temperature. Clinical varicoceles are further graded as follows:

- grade I: palpable during a Valsalva manoeuvre only;
- grade II: palpable but not visible;
- grade III: palpable and visible.

Initial options for management of varicocele include surgical or radiological treatment or expectant management. Surgical treatment involves varicocelectomy, conducted via retroperitoneal or conventional inguinal open techniques, microsurgical inguinal or subinguinal approaches, or laparoscopic repairs *(14–16)*. Radiological treatment involves either varicocele embolization or sclerotherapy. Embolization involves blocking one or more blood vessels or abnormal vascular channels using a coil or a balloon or other embolic agents *(17)*, whereas sclerotherapy involves injecting a sclerosing agent into the spermatic vein, resulting into shrinkage and lumen occlusion *(18)*. The goal of both surgical and radiological treatment is to stop reflux in the internal spermatic vein. The halting of venous reflux is frequently followed by an improvement in semen parameters *(19, 20)*.

For this guideline, distinction was made between clinical and subclinical varicocele, given the documented link between the treatment of clinical varicoceles and improvement in fertility. Although men with varicoceles may also be candidates for ART, this recommendation does not address the use of surgical or radiological treatment before, or in combination with, ART. GDG agreed that an issue of central concern is whether treatment (surgical or radiological) of a varicocele should be used for the male partner of a couple with infertility who are not undergoing other ART procedures based on (i) whether the varicocele is clinical or not, and (ii) whether semen parameters are within the WHO reference ranges or not. Therefore, for this recommendation, the GDG addressed the question: should surgical or radiological treatment versus no treatment be used for men with clinical varicocele in couples with infertility?

Balancing harms and benefits

Evidence was obtained from a recent systematic review of RCTs by Persad et al. *(21)*. The search date was up to April 2020. The review pooled together studies comparing any repair to no treatment (or non-surgical methods). We included studies from the Persad et al. review with couples experiencing infertility and men who had clinical varicocele; we also performed a subgroup analysis of men with semen parameters within the WHO reference ranges *(22–29)* or outside the WHO reference ranges *(30)*. Several studies were excluded because of the inclusion of couples with multiple pregnancy losses or recurrent pregnancy loss *(31)*, failure to separate clinical from non-clinical varicoceles in analysis *(32, 33)*, undefined eligibility criteria *(34)* or other reason *(35)* (see **Web Annexes A**–**F**).

Evidence showed that treatment of varicocele may result in a moderate increase in clinical pregnancies among men with semen parameters outside the WHO reference ranges (RR: 1.94; 95% CI: 1.23–3.05). However, the effect was uncertain among men with subclinical varicocele and semen parameters within the normal range (RR: 1.09; 95% CI: 0.55–2.26). Live births were not reported in the studies. In absence of data on live births, clinical pregnancies were assessed. The GDG noted that the effect of treatment on live births would be expected to be less than the effect on pregnancies; the certainty of evidence from this review was judged to be low.

In terms of undesirable effects, in the studies in the review by Persad et al. *(21)* comparing surgical treatments to each other and to radiological treatments (to each other), the incidence of varicocele recurrence was between 3% and 20%. Pain with surgery was approximately 2–20%, testicular atrophy with surgery 0–4%, hydrocele formation with surgery 5–10%, and wound infection approximately 4%. The GDG judged these to be small harms. The GDG agreed that certainty of evidence is low for men with clinical varicocele with semen parameters outside the WHO reference range and very low for men with clinical varicocele with semen parameters within the WHO reference range; overall, the overall certainty of evidence was judged to be very low.

Limited data were identified related to patient values on treatment or expectant management. Nevertheless, the GDG judged that patients would likely value pregnancies and live births, and would

seek to minimize adverse events; probably, no important variability exists in how people value these outcomes. Given that more value is placed on the potential for small benefits and less on adverse events, treatment is probably favoured in men with clinical varicocele with semen parameters outside the normal range. For men with clinical varicocele with semen parameters within the normal range, treatment is probably not favoured.

Other considerations

Limited data exist concerning the acceptability and feasibility of surgical or radiological treatment of varicocele. However, the GDG judged that surgery would probably be acceptable to men to improve fertility. In addition, the GDG judged that it is probably feasible to provide varicocele treatment. However, training and expertise is required to ensure safety and minimize complications. Based on data from studies in Kuwait *(36)*, China *(37)* and Canada *(38)*, the GDG judged that surgery involves moderate costs compared to no treatment. However, a variation in costs to individuals and health systems may exist from country to country. Subsequently, the GDG judged that equity may be reduced with treatment if some populations are unable to access it, especially in settings without public financing or insurance cover for infertility treatment.

Summary justification

Treatment of varicocele may have a small desirable effect by increasing clinical pregnancies, and a small undesirable effect resulting from complications of surgical or radiological procedures (very low certainty of evidence). Given the higher value that people ascribe to pregnancy compared to the undesirable effects, the balance of effects favours the intervention. Treatment may incur moderate costs and probably reduce equity if some populations cannot access it; however, it is probably acceptable and probably feasible.

Implementation considerations

This recommendation focuses on treatment of varicocele to improve current fertility among adult males with infertility and clinical varicocele who are not undergoing ART. Treatment of varicocele to improve other outcomes (e.g. to relieve pain or to prevent future reproductive problems) is beyond the scope of this recommendation.

For optimal benefit, varicocele treatment is suggested for men with infertility intending to conceive if they have (i) a clinical varicocele and (ii) semen parameters that are outside the WHO reference range. In addition, patients should be clearly informed that the impact on live births is unknown. In implementing this recommendation, health care providers should note that it is likely to involve moderate costs and potential exposure to harms associated with surgery or radiological treatments. Results of semen analysis based on the procedures outlined in the *WHO manual for the examination and processing of human semen (39)* should be used to identify men who are likely to benefit from the intervention. After treatment, patients should be monitored for potential complications, such as hydrocele, recurrence and ultimately improvement in fertility status.

Research gaps and future guideline update

Current evidence is of very low quality. Large, randomized studies are required to provide high-quality evidence. In addition, future studies should include live births as an outcome. The overall impact of the grade of a clinical varicocele (i.e. grade I, II or III) on treatment outcome could not be determined from the current evidence. Future studies should be designed to identify

which grades of a clinical varicocele may optimally benefit from treatment, including one-sided versus bilateral varicocele. Further research is needed on the pathophysiological mechanisms and potential new therapies. Future guidance is required in relation to treatment options among infertile men with clinical varicocele who do not respond to surgical or radiological therapy. The evidence reviewed in this recommendation relates to men with clinical varicocele in couples with infertility who are not undergoing ART. Future guidance is required in relation to the role of treatment of varicocele before ART.

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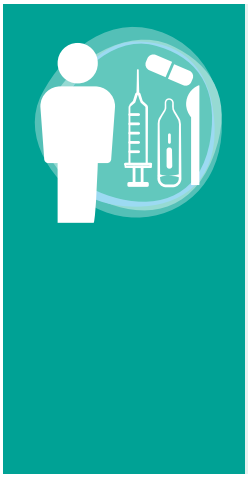

Recommendation

For males with infertility undergoing treatment of varicocele, WHO suggests using either surgical or radiological treatment. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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 varicocele in couples with infertility who are not undergoing treatment with assisted reproductive technology (ART).

Background and rationale

This guideline suggests surgical or radiological treatment over expectant management of clinical varicocele in men with infertility, with certainty of evidence that is low (see previous sections of this chapter).

Once a decision to treat clinical varicocele has been arrived at, options for treatment include surgical repair or radiological treatment. Surgical treatment involves varicocelectomy, conducted via retroperitoneal or conventional inguinal open techniques, microsurgical inguinal or subinguinal approaches, or laparoscopic repairs *(1–3)*. Radiological treatment involves varicocele embolization or sclerotherapy. Embolization involves blocking one or more blood vessels or abnormal vascular channels using a coil or a balloon, while sclerotherapy involves injecting a sclerosing agent into the spermatic vein, resulting in shrinkage and lumen occlusion *(4)*.

Surgical repair of varicoceles is widely practised using different techniques; however, it may be complicated by varicocele persistence, recurrence or injury to surrounding tissue; depending on the procedure, it may also require general anaesthesia or a longer time to operate *(2, 5)*.

Radiological treatments may be complicated by failure, recurrence, thrombosis, scrotal subcutaneous emphysema, injury to blood vessels, haemorrhage, epididymitis, scrotal pain and allergic reaction to contrast agents *(5, 6)*. However, radiological treatments are generally less invasive than most surgical treatments, may be performed under local anaesthesia *(7)*, and patients often require a shorter time to recover *(8)*. As embolization is intravascular, it may minimize the risks of injury to adjacent vessels and lymphatics.

Given the potential advantages and disadvantages of surgical and radiological treatments *(6)*, the GDG agreed that there is need for guidance on which treatment modality between the two is preferred. Therefore, for this recommendation, the GDG addressed the question: should surgical versus radiological treatment be used for men with clinical varicocele in couples with infertility? It does not assess the use of these treatments before or in combination with ART.

Balancing desirable and undesirable effects

Evidence from a recent systematic review of RCTs was included *(9)*. The search date was up to April 2020. The review pooled together studies comparing surgical versus radiological procedures. From that review, only studies in men with confirmed clinical varicocele were included *(10–15)*. Importantly, all included studies directly comparing surgical versus radiological procedures concern the use of non-microsurgical techniques (high or inguinal open methods).

Results showed that compared to radiological treatments, surgery may result in 54 more live

births (from 37 fewer to 261 more,) per 1000 (RR: 1.49; 95% CI: 0.66–3.37), and likely 28 more pregnancies (from 60 fewer to 155 more) per 1000 (RR: 1.11; 95% CI: 0.76–1.62). The GDG judged these desirable effects of surgical repair to be trivial compared to radiological treatment.

In terms of undesirable effects, data showed that surgery may result in 35 more varicocele recurrences or persistence (from 29 fewer to 137 more) per 1000 (RR: 1.25; 95% CI: 0.79–1.98), and 11 fewer complications, such as extravasation, wound infection and hydrocele formation, (from 56 fewer to 68 more) per 1000 (RR: 0.91; 95% CI: 0.53–1.57), when compared to radiological treatments. The GDG judged the magnitude of these differences to be trivial. The GDG agreed that couples would likely value pregnancies and live births and would want to minimize adverse events, and judged that there was probably no important uncertainty or variability in how much people valued these outcomes. The GDG concluded that the balance of effects probably does not favour either surgery or radiological treatment. The overall certainty of evidence for the effects was very low, primarily because the studies compared non-microscopic surgical methods with radiological treatment, which was considered indirect evidence of the effect of surgery. Studies comparing microsurgical varicocele repair with radiological treatment were lacking. In addition, there were few participants and events in the analyses. Despite the evidence being indirect regarding the overall effects of all surgical procedures (i.e. both microsurgical and non-microsurgical methods [retroperitoneal or inguinal vein ligation]), it was still used to inform the recommendation.

Other considerations

Both surgical and radiological treatments involve costs. A Canadian simulation study *(16)* showed that embolization may be less cost-effective than surgery. However, the GDG considered that given that there are trivial differences in benefits or harms and negligible cost differences, both may have similar cost-effectiveness. The GDG also considered that costs and insurance coverage between surgery and radiological treatment may vary from country to country and that equity may be reduced if some populations are unable to access treatment, especially in those countries and settings with limited public financing of insurance for infertility treatments.

No data were found comparing acceptability between surgery and embolization. However, in the absence of data, the GDG judged that both surgical and radiological treatments are probably acceptable. In terms of feasibility, the GDG agreed that both procedures are feasible in most settings. However, training is required to assure safety and minimize complications. However, availability of trained surgeons and interventional radiologists may vary, especially in LMICs.

Summary justification

Overall, there is very-low-certainty evidence that there are trivial differences between surgical and radiological treatments in terms of benefits, harms and costs. Studies comparing microsurgical varicocele repair with radiological treatment were scarce, thus contributing to the GDG's assessment that the evidence was indirect. Compared to each other, both treatments are probably feasible, acceptable and have little difference in impact on equity.

Implementation considerations

This recommendation focuses on the treatment of clinical varicocele to improve fertility in men with infertility who are not undergoing ART. This recommendation does not address the role of varicocele treatment before ART. Treatment of clinical varicocele to improve other outcomes (e.g. to relieve pain or to prevent future reproductive problems) is beyond the scope of this recommendation. Health care providers should appropriately monitor all patients after any surgical or radiological treatment procedures. Patients should be monitored for potential complications after treatment, such as hydrocele, recurrence and persistence. Given that there was limited information on all surgical procedures (i.e. both microsurgical and non-microsurgical methods [retroperitoneal or inguinal vein ligation]), consideration of patient preferences regarding the type of treatment procedure is important.

Research gaps and future guideline update

Certainty of evidence for this recommendation was very low. Studies comparing microsurgical varicocele repair with radiological treatment were lacking. Future studies should include comparing microsurgical techniques versus embolization, and comparing acceptability between surgery and embolization. Given the small numbers of events and participants and the absence of recent research on embolization, high-quality randomized controlled studies comparing radiological treatments to surgery are needed. Future guidance will be needed regarding the management of recurrence, and persistence after initial treatment with either surgical or radiological treatment. Future guidance will be required to address the role of varicocele treatment before ART.

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Recommendation

For males with infertility undergoing surgical treatment of varicocele, WHO suggests using microscopic surgery rather than other surgical procedures.
(Conditional recommendation, very low certainty of evidence)

Remarks:

- 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 assisted reproductive technology (ART).

Background and rationale

This guideline suggests the use of either surgical or radiological treatment of varicocele in men with infertility, with certainty of evidence that is low (see previous sections). If surgical methods are selected, further decisions would be needed to choose which surgical methods would be used to treat clinical varicocele.

Options for surgical varicocelectomy include retroperitoneal or conventional inguinal open techniques, microsurgical inguinal or subinguinal approaches, or laparoscopic repair *(1–4)*. Surgical repair of varicocele using different techniques may be complicated by varicocele persistence, recurrence or injury to surrounding tissue; depending on the procedure, general anaesthesia or longer time to operate may be required *(2, 5)*. Postoperative hydrocele formation is a frequent complication of varicocelectomy resulting from the disruption of lymphatic vessels. Different techniques have been developed in an attempt to minimize such complications, for example, to reduce recurrence rates, which may be more common with some surgical approaches *(6, 7)*.

Microscopic varicocelectomy is typically performed using a subinguinal approach, which involves making a 2–3-cm transverse skin incision centred over the external inguinal ring to approach the spermatic cord, with the aid of an operating microscope, after which the spermatic veins are ligated while preserving the testicular arteries and lymphatics. Microscopic inguinal varicocelectomy is less common and involves making an incision in a way that provides access to the ilioinguinal nerves, applying similar procedural principles of ligating the spermatic veins while preserving the testicular arteries and lymphatics.

For this recommendation, the GDG addressed the question: should microscopic varicocelectomy versus other non-microscopic surgical varicocelectomy techniques be used for men with clinical varicocele in couples with infertility? This question was identified by the GDG as a priority and is provided in the context of the recommendation related to the treatment of clinical varicocele in men with infertility. It does not assess the use of surgical treatment before or in combination with ART.

Balancing desirable and undesirable effects

A systematic review *(8)* reported the effects of surgical and radiological treatment of varicoceles in subfertile men. We used the data from studies that included men with clinical varicocele as reported by the authors of the original studies.

Sixteen studies that compared microscopic surgical treatment to other surgery were included *(9–24)*. Subinguinal microsurgery was the most common surgical varicocelectomy procedure assessed in the

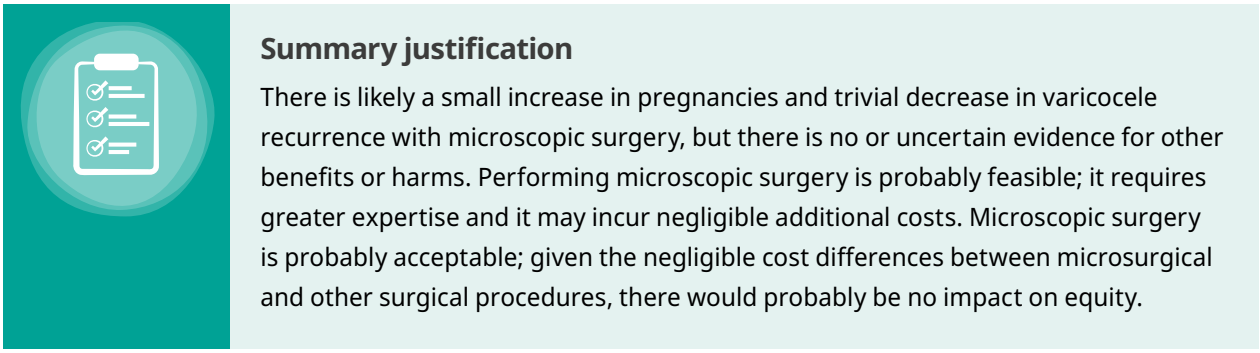
studies. Results showed that there is likely a small increase in pregnancies with microscopic subinguinal surgery (60 more [from 3 to 126 more] per 1000; RR: 1.20; 95% CI: 1.01–1.42) when compared to other surgical approaches. Data on live births and quality of life were not reported. In relation to undesirable effects, microscopic surgery may slightly reduce varicocele recurrence, but the effects on other adverse events, such as hydrocele formation, testicular atrophy, wound infection and haematoma, are very uncertain and not consistently less. Most studies did not report on the randomization or allocation method and had incomplete follow-up; there were few participants or events related to adverse effects. Because of the uncertainty of the evidence for adverse events, the overall certainty of evidence is rated very low. Although no data on patient values were available, the GDG agreed that most patients valued pregnancy and live births, while seeking to minimize harms. Therefore, based on the likely small increase in pregnancies and decrease in varicocele recurrence, the GDG agreed that microscopic treatment is probably favoured over other treatments.

Other considerations

Based on data from studies *(25, 26)*, the GDG agreed that microscopic surgery may cost slightly more than most non-microscopic surgical approaches (and may vary across countries) and that training may be required; however, these additional costs were considered negligible because most other surgical procedures involve large costs.

Although a modelling study *(25)* suggested that microscopic surgery is more cost-effective than non-microscopic surgery, the pregnancy estimates in the model were much higher than reported in the systematic review of RCTs by Persad et al. *(8)*. Given the trivial differences in benefits and harms from the systematic review, and the negligible cost differences between microscopic and other procedures in most countries, the GDG judged that cost-effectiveness did not favour either microscopic or other surgical procedures.

The GDG judged that microscopic surgical procedures are probably feasible to provide but may require expertise, equipment or training to perform safely. As surgical procedures are likely available and involve similar large costs, there is probably no impact on equity. In addition, although there were no data regarding patient preferences for any of the procedures, the GDG agreed that microscopic surgery is probably acceptable to patients.



Summary justification

There is likely a small increase in pregnancies and trivial decrease in varicocele recurrence with microscopic surgery, but there is no or uncertain evidence for other benefits or harms. Performing microscopic surgery is probably feasible; it requires greater expertise and it may incur negligible additional costs. Microscopic surgery is probably acceptable; given the negligible cost differences between microsurgical and other surgical procedures, there would probably be no impact on equity.

Implementation considerations

When implementing these recommendations, health care providers should monitor patients for complications to ensure safety. To ensure good-quality outcomes from microscopic surgery, expertise and training may be required. In low-resource and other settings where the expertise to perform microscopic surgery is not available, other surgical techniques may be considered, bearing in mind patients' preferences.

Research gaps and future guideline update

Future studies should include live births and quality of life as outcomes, and patient preferences, and should also endeavour to report adverse events alongside desirable outcomes. Blinding of outcome assessors in future studies would be important. Future guidance is needed on the effects of microsurgical versus other treatment modalities in subgroups of patients with recurrent clinical varicoceles.

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Recommendation

For males with infertility undergoing non-microscopic surgical treatment of varicocele, WHO suggests using either inguinal or retroperitoneal surgical procedures. *(Conditional recommendation, very low certainty of evidence)*

Remarks:

- 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 assisted reproductive technology (ART).

Background and rationale

Once a decision to treat clinical varicocele has been arrived at, options for treatment include surgical repair or radiological treatment. Options for surgical varicocelectomy include retroperitoneal or conventional inguinal open techniques, microsurgical inguinal or subinguinal approaches, or laparoscopic repair *(1–3)*.

Surgical repair of varicocele using different techniques may be complicated by varicocele recurrence or injury to surrounding tissue; depending on the specific procedure, it may require general anaesthesia, microsurgical expertise or longer operative time *(2, 4)*. Postoperative hydrocele formation is a frequent complication of varicocelectomy resulting from the disruption of lymphatic vessels. Different techniques have been developed in an attempt to minimize such complications and to reduce recurrence rates, which may be more common with some surgical approaches *(5, 6)*.

This guideline suggests surgical or radiological treatment over expectant management of clinical varicocele in men with infertility, with certainty of evidence that is low. In addition, this WHO infertility guideline suggests microsurgical subinguinal varicocele repair over other surgical procedures to treat clinical varicocele in men in couples with infertility (see previous sections). In settings where the expertise to perform microsurgical subinguinal varicocele repair is unavailable, other surgical techniques may be considered. Such options include inguinal or retroperitoneal procedures.

Inguinal varicocelectomy involves an incision over the inguinal canal, starting at the external inguinal ring and extending 3–4 cm laterally parallel to the inguinal ligament, which allows the identification of the spermatic cord and exposure of the enlarged pampiniform veins for ligation *(7)*. This is an open surgical procedure, typically performed without a microscope. The conventional non-magnified open inguinal varicocelectomy is also referred to as the Ivanissevich technique *(8)*.

Retroperitoneal varicocelectomy, also referred to as suprainguinal, Palomo, high-ligation, highest entry point or abdominal varicocelectomy, is an open varicocelectomy procedure that involves a medial inferior incision to the ipsilateral anterior superior iliac spine through the external and internal oblique fascia to access and ligate the internal spermatic vein *(9, 10)*.

For this recommendation, the GDG addressed the question: should surgical treatment of clinical varicoceles be performed using conventional non-magnified open inguinal techniques (Ivanissevich technique) versus a retroperitoneal surgical technique? This recommendation does not assess the use of surgical treatment before or in combination with ART.

Balancing desirable and undesirable effects

We used the data from a systematic review *(9)* that addressed the effects of surgical and radiological treatment for clinical varicoceles in subfertile men. We used data from studies that compared inguinal to retroperitoneal surgery among men with clinical varicoceles only *(11–21)*. Results showed that there may be no difference in the number of pregnancies with either procedure. There were five more pregnancies (46 fewer to 70 more) per 1000 (RR: 1.02; 95% CI: 0.82–1.27) with inguinal surgery compared to retroperitoneal surgery. There were no data for live births or quality of life. In terms of undesirable effects, the evidence showed that there may be no difference with the inguinal approach in varicocele recurrence compared to the retroperitoneal approach (three more [from 64 fewer to 164 more] per 1000; RR: 1.03; 95% CI: 0.43–2.46) or hydrocele formation (two more [from 45 fewer to 161 more] per 1000; RR: 1.03; 95% CI: 0.31–3.47). Evidence is also uncertain for other adverse events, including testicular atrophy, haematoma and wound infection. In addition, most studies did not report the randomization or allocation method and had incomplete follow-up; there were also few participants or events related to desirable and undesirable effects. Given these limitations, the overall certainty of evidence was very low. The GDG agreed that individuals with infertility place greater value on live births and pregnancies and would likely avoid harms. Since there were trivial differences in desirable effects and harms, and the evidence is very uncertain for other adverse events, the GDG agreed that one procedure is probably not favoured over the other.

Other considerations

The GDG agreed that there would likely be a negligible difference in the costs between the two techniques. Evidence is uncertain for no differences in benefits and harms between the two procedures; cost differences are probably negligible. Therefore, the GDG agreed that cost-effectiveness does not favour either procedure. The GDG judged that both inguinal and retroperitoneal approaches are similarly available and are likely to involve similar costs; therefore, there would be no impact on equity if either is recommended over the other. No evidence on acceptability was identified. However, the GDG agreed that either procedure is probably acceptable to patients. No specific evidence was available on feasibility. However, the GDG judged that both procedures would be probably feasible given that training, equipment and time required for surgery are probably similar.

Summary justification

There may be little difference in pregnancies, varicocele recurrence or hydrocele formation with either procedure, and the evidence is uncertain for other harms. Performing either procedure would likely result in similar costs and likely be similarly acceptable and feasible, and would probably have no impact on equity.

Implementation considerations

Health care providers should monitor patients for complications. To ensure the safety of procedures, training of health care providers may be required.

Research gaps and future guideline update

Future studies should comprehensively report live births, quality of life, patient preferences and adverse events. Future studies should assess whether either procedure evaluated separately improves these outcomes, compared to no treatment. Blinding of outcome assessors in such future studies would be important.

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Chapter 10 Treatment of couples with unexplained infertility

This section contains recommendations related to the management of unexplained infertility. **Figure 10.1** shows how these recommendations relate to each other, illustrated in a diagnostic algorithm. Specific recommendations are presented in the sections that follow.

10.1 First-line management of couples with unexplained infertility

Recommendation

For couples with unexplained infertility, WHO suggests expectant management rather than unstimulated intrauterine insemination (U-IUI).
(Conditional recommendation, low certainty of evidence)

Remarks:

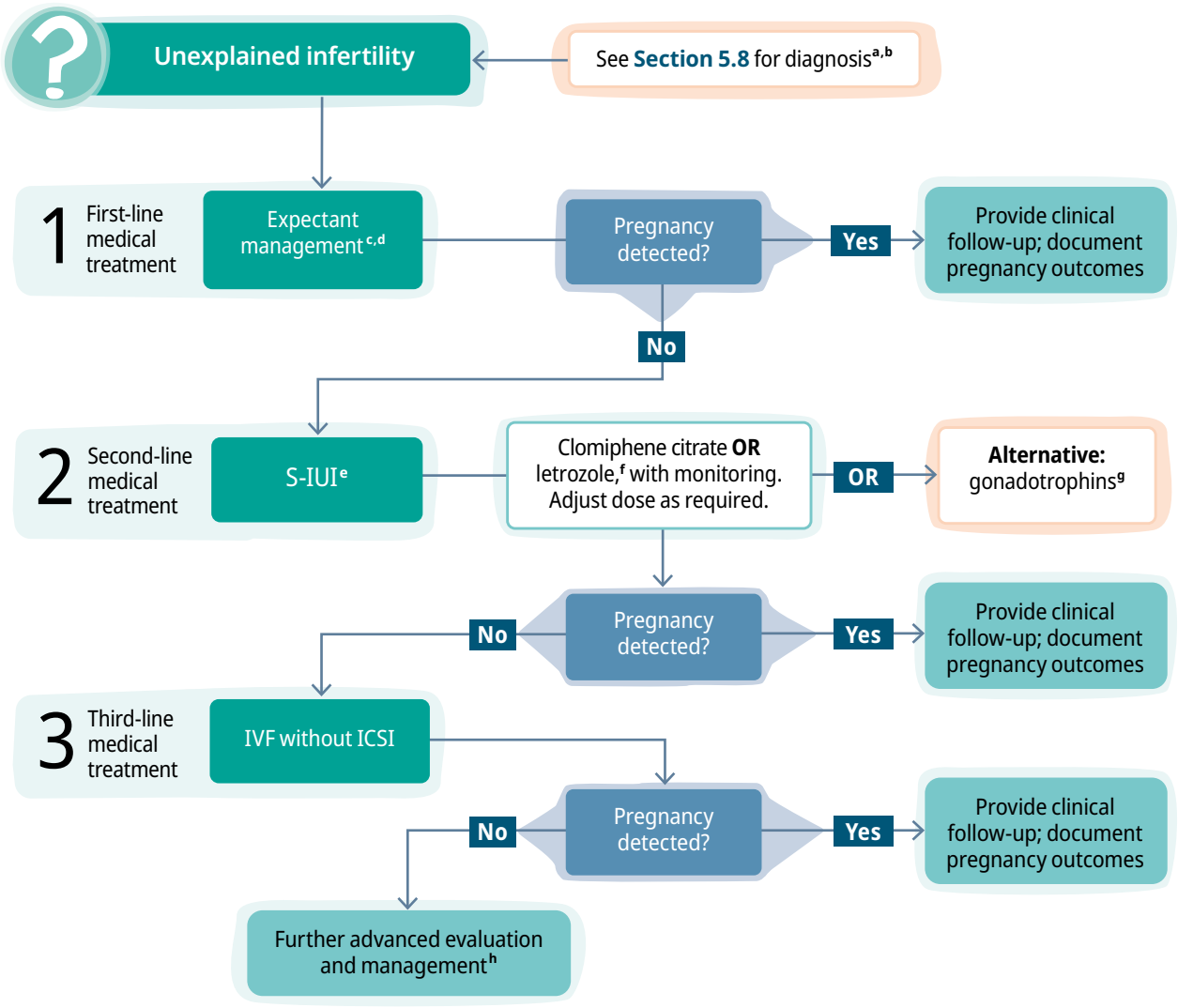
- Expectant management refers to monitoring the couple with the expectation that pregnancy will be achieved without medical intervention. It includes providing advice on lifestyle and the most fertile days of the menstrual cycle, and monitoring if pregnancy will occur; however, no medical intervention is provided.
- The duration of expectant management was typically 3–6 months in studies informing this recommendation.

Background and rationale

Unexplained infertility is diagnosed when there is failure to achieve pregnancy after 12 months of regular unprotected intercourse, and when investigations fail to identify a cause in either the female or male partner (such as tubal disease or uterine cavity abnormalities, ovulation dysfunction in the female partner, or semen parameters that are outside the WHO reference ranges in the male partner) (see **section 5.8** for the criteria for diagnosis of unexplained infertility). For this recommendation, the GDG addressed the question: should U-IUI versus expectant management be used for couples with unexplained infertility? This was assessed in the context of first-line management of unexplained infertility.

Expectant management refers to monitoring the couple with the expectation that pregnancy will be achieved without medical intervention. While the likelihood of spontaneous (i.e. unassisted) pregnancy without medical intervention among couples with unexplained infertility varies from study to study *(1–6)*, it is typically greater than zero but less than that of fertile couples *(5)*. Therefore, expectant management could reduce overtreatment *(7)* as some couples with infertility may conceive during expectant management *(8–10)*. Based on this possibility for spontaneous (i.e. unassisted) pregnancy, couples with unexplained infertility are advised on lifestyle, provided information regarding their most fertile days and monitored if they will become pregnant, but are not provided any treatment (see **Fig. 10.1** for the treatment algorithm for unexplained infertility).

Fig. 10.1. Treatment algorithm for unexplained infertility



[a] Infertility is defined as failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse.
[b] Criteria for the diagnosis of unexplained infertility:
- failure to achieve 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.

[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.
ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; S-IUI, stimulated intrauterine insemination.

IUI is a fertility treatment that places processed sperm directly into the uterus at the time of ovulation. In IUI, the male partner's semen is processed using established standards *(10)* and the sperm placed into the uterus with a suitable transcervical catheter around the time of ovulation. Thus, IUI bypasses the cervix and increases the number of motile sperm that reach the uterus and the fallopian tubes. To ensure accurate timing of the insemination, cycle monitoring is performed through ultrasound assessment of follicle growth or by monitoring the preovulatory LH levels. IUI can occur in a natural cycle (U-IUI) or after ovarian stimulation with a medication such as clomiphene citrate, letrozole or gonadotrophins.

Balancing harms and benefits

A systematic review with network meta-analysis by Wang et al. *(12)* provided evidence for expectant management versus U-IUI. We also extracted results from pairwise meta-analyses and examined the primary studies included in the review for additional outcomes.

The evidence showed that the benefits of U-IUI are likely trivial when compared to expectant management, with only 28 more live births (from 58 fewer to 160 more) per 1000 (OR: 1.21; 95% CI: 0.61–2.43) and 26 more clinical pregnancies (from 55 fewer to 148 more) per 1000 women treated (OR: 1.20; 95% CI: 0.61–2.36). In the studies where desirable outcomes were observed, clinical pregnancies occurred within 3–6 months' duration. The differences in undesirable effects are also trivial between U-IUI and expectant management. Compared to expectant management, U-IUI may result in a trivial increase in ectopic pregnancy (15 more, ranging from 18 fewer to 279 more per 1000; OR: 1.70; 95% CI: 0.15–19.35), pain (42 more [from five fewer to 155 more], per 1000; OR: 2.43; 95% CI: 0.84–7.07) and bleeding (36 more [from six fewer to 149 more], per 1000; OR: 2.52; 95% CI: 0.77–8.20). However, U-IUI may reduce miscarriages (140 fewer [from 235 fewer to 32 more], per 1000; OR: 0.45; 95% CI: 0.17–1.16) and may slightly reduce preterm birth (22 fewer [from 119 fewer to 209 more], per 1000; OR: 0.84; 95% CI: 0.23–3.06), depression (12 fewer [from 21 fewer to 38 more], per 1000; OR: 0.49; 95% CI: 0.09–2.70) and hospitalizations (10 fewer [from 12 fewer to 36 more], per 1000; OR: 0.19; 95% CI: 0.01–4.07). There may be no differences in gastrointestinal symptoms (vomiting and bloating) between U-IUI and expectant management. Because of lack of sufficient studies reporting outcomes according to age, a planned subgroup analysis according to age was not performed by Wang et al. *(12)*; only one study reported these data. The GDG considered that people with unexplained infertility highly value live births and do not desire negative outcomes, and that these values are unlikely to vary among different groups. Given the trivial benefits and trivial harms, the GDG judged that the balance of effects probably does not favour either U-IUI or expectant management.

Other considerations

The GDG considered evidence from two studies *(4, 13)* showing that U-IUI requires personnel, laboratory equipment, materials, medication and overhead costs, and judged that the procedure is associated with moderate costs compared to expectant management. The GDG judged that U-IUI is probably feasible and noted that although the U-IUI technique itself is not complex, training is still needed to perform it correctly and ensure optimal timing of the insemination. The GDG considered evidence from one study *(14)* showing that U-IUI was acceptable to most women if it increases the chances of pregnancy; however, data showed that it has minimal benefits compared to expectant management. Because of the costs involved, U-IUI may result in decreased equity compared to expectant management, especially in settings where fertility treatment is not publicly funded. Given that U-IUI involves costs and yet it has trivial benefits, the GDG concluded that cost-effectiveness probably favours expectant management.

Summary justification

U-IUI may have trivial benefits on live births and pregnancies compared to expectant management and trivial differences in adverse events. Although U-IUI is probably acceptable and feasible, it is not cost-effective and may reduce equity compared to expectant management. Therefore, expectant management was suggested rather than U-IUI.

Implementation considerations

Couples with unexplained infertility should be informed of the rationale and success rate with expectant management, noting that age and ovarian reserve may have an impact on the outcomes of expectant management. Unstimulated IUI is no better than expectant management and is not recommended. Health care providers should inform couples regarding the duration of expectant management, and counsel them regarding the possibility of offering second-line treatments if expectant management is not successful. Adequate counselling and education regarding expectant management and its duration is essential given that some couples with unexplained infertility may have low confidence with spontaneous (i.e. unassisted) pregnancy *(15)*.

Research gaps and future guideline update

Future guidance will require availability of sufficient data from studies to perform subgroup analyses for prognostic factors, such as age, duration of unexplained infertility and ovarian reserve, among others, for example, using prognostic models or other approaches.

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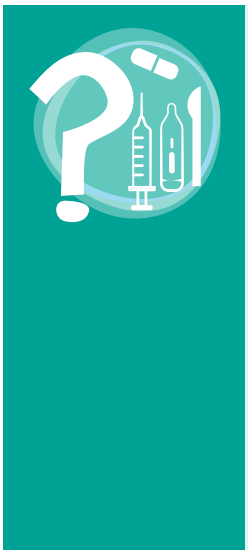

Recommendation

For couples with unexplained infertility, WHO suggests expectant management rather than ovarian stimulation with timed intercourse.
(Conditional recommendation, low certainty of evidence)

Remarks:

- 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 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.

Background and rationale

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 (see the previous section for the rationale for expectant management).

Ovarian Stimulation (OS) refers to the pharmacological treatment to induce the development of (typically multiple, and ideally three or fewer) ovarian follicles and hence oocytes available for fertilization. Commonly used medications for ovarian stimulation include clomiphene citrate, letrozole and gonadotrophin modulators *(1–4)*. Because of their mechanism of action and effects on follicle development, medications used for ovarian stimulation such as clomiphene citrate, letrozole or gonadotrophins may increase the risk of adverse events, such as multiple pregnancy and OHSS *(1, 5)* (see **Chapter 6.1** for details on the mechanisms of actions of these medications).

When ovarian stimulation is provided in combination with timed intercourse, couples with unexplained infertility are prescribed ovarian stimulation medications and advised to have sexual intercourse during the fertile period, which is typically a few (≈6) days up to and including the day of ovulation *(6–8)*. For this recommendation, the GDG addressed the question: should ovarian stimulation with timed intercourse versus expectant management be used for couples with unexplained infertility? It was assessed in the context of first-line management for unexplained infertility.

Balancing harms and benefits

A systematic review by Wang et al. *(9)* provided data for this comparison. The review included 13 RCTs comparing ovarian stimulation using several medications (e.g. clomiphene citrate, letrozole, or gonadotrophins) with timed intercourse or IUI to no treatment. Results comparing ovarian stimulation with timed intercourse versus expectant management were extracted. Data for additional relevant outcomes were extracted from the primary studies included in the network meta-analysis.

The analysis reported that although ovarian stimulation with timed intercourse likely results in 77 more clinical pregnancies (from 1 fewer to 180 more) per 1000 women treated (OR: 1.64; 95% CI: 0.99–2.73) and one more live birth (from 74 fewer to 117 more) (OR: 1.01; 95% CI: 0.51–1.98), when compared to expectant management. In the studies where desirable outcomes were observed, clinical pregnancies occurred within 3–6 months' duration. In terms of harms, ovarian stimulation likely results in 12 more multiple pregnancies (from zero to 48 more) (OR: 3.07; 95% CI: 1.00–9.41),

and may result in 156 more miscarriages (from 190 fewer to 654 more) per 1000 women treated (OR: 2.08; 95% CI: 0.16–26.37) compared to expectant management. Slight increases in pain (205 more [from 75 to 416 more] per 1000; OR: 9.55; 95% CI: 3.66–24.91) and nausea (107 more [from 24 to 287 more] per 1000; OR: 5.92; 95% CI: 1.99–17.59) may occur, but there may be no difference in anxiety (OR: 1.09; 95% CI: 0.63–1.87), depression (OR: 0.98; 95% CI: 0.24–3.97) or hospitalization (OR: 0.95; 95% CI: 0.13–6.84). There were no data on OHSS. A planned subgroup analysis according to age was not conducted in the systematic review by Wang et al. *(9)* because of lack of sufficient studies reporting outcomes according to age; only one study reported these data. The GDG judged that ovarian stimulation with timed intercourse may result in small benefits and moderate undesirable effects. The GDG also judged that people with unexplained infertility highly value live births and do not desire negative outcomes, and that these values are unlikely to vary among different groups. Therefore, the balance of effects probably favours expectant management over ovarian stimulation with timed intercourse. The overall certainty of evidence was low.

Other considerations

The GDG judged that although ovarian stimulation with timed intercourse is probably feasible, it involves moderate resources because of the cost of medications, ultrasound monitoring or hormone assays *(10)*. The GDG noted that the costs of stimulating agents vary from country to country, but are likely higher for gonadotrophins. Although the costs of some medications, such as clomiphene citrate, could be low, overall, ovarian stimulation would probably reduce equity, especially in settings where fertility treatments are not publicly financed. Based on data presented from two studies *(11, 12)*, the GDG judged that the acceptability of ovarian stimulation among patients varies.

Summary justification

Overall, there is low certainty evidence for small desirable effects and moderate undesirable effects with ovarian stimulation with timed intercourse compared to expectant management. In addition, ovarian stimulation with timed intercourse involves moderate costs, which may reduce equity compared to expectant management, and its acceptability varies. Therefore, the undesirable consequences of ovarian stimulation with timed intercourse probably outweigh the desirable consequences; therefore, expectant management is suggested.

Implementation considerations

Health care providers implementing expectant management should counsel couples on lifestyle and their most fertile days and monitor if they will become pregnant. Health care providers should inform couples about the duration and potential outcomes of expectant management, and ensure that couples understand the rationale for expectant management. They should also counsel patients about the possibility of offering second-line treatments if expectant management is not successful.

Research gaps and future guideline update

Further guidance is needed on whether and how the duration of unexplained infertility, age, ovarian reserve and other prognostic factors can further inform expectant management.

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10.2 Second-line management of couples with unexplained infertility

Recommendation

For couples with unexplained infertility, where expectant management has been unsuccessful, WHO suggests stimulated intrauterine insemination (S-IUI) with either clomiphene citrate or letrozole. *(Conditional recommendation, low certainty of evidence)*

Remarks:

- 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.

Background and rationale

This guideline suggests expectant management as first-line management in couples with unexplained infertility rather than ovarian stimulation with timed intercourse or U-IUI. S-IUI involves the use of ovarian stimulation medications to increase the number of mature oocytes available for fertilization. Commonly used medications for ovarian stimulation include anti-estrogens (e.g. clomiphene citrate), aromatase inhibitors (e.g. letrozole) and gonadotrophins (e.g. FSH and LH) (see **Chapter 6.1** for a description of these agents and their mechanisms of actions). For this recommendation, the GDG addressed the question: should S-IUI with letrozole versus S-IUI with clomiphene citrate be used for couples with unexplained infertility? It was assessed in the context of second-line management of unexplained infertility.

Balancing harms and benefits

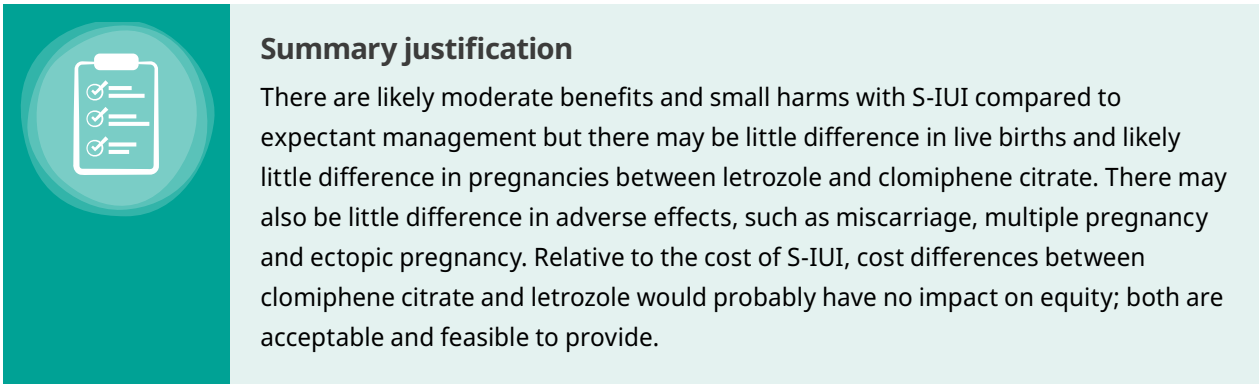
We used evidence from two systematic reviews: Wang et al. *(1)* for the effects of expectant management compared to S-IUI and existing RCT data comparing clomiphene citrate to letrozole in S-IUI from a review by Eskew et al. *(2)*. Eight eligible RCTs were identified by the review authors, but only six investigated ovulation stimulation paired with IUI *(3–8)*. One of the studies, Badawy et al. *(8)* was retracted; therefore, it is not included in this analysis. Another study by Badawy et al. *(9)* was excluded because it focused on stimulation for timed intercourse rather than IUI and it is under investigation *(10)*.

Data showed that there are likely greater pregnancies with S-IUI than expectant management (approximately 100–200 more per 1000) but likely little to no difference between the ovarian stimulation drugs. There may also be little to no difference in live births between the drugs. Compared to clomiphene citrate, stimulation with letrozole may result in similar number of live births per 1000 pregnancies (RR: 1.00; 95% CI: 081–1.22) and likely 80 more biochemical pregnancies [from 43 fewer to 272 more] per 1000 (RR: 1.32; 95% CI: 0.83–2.09). In terms of harms, there may be little to no difference in harms or adverse events between letrozole and clomiphene citrate, but greater harms compared to expectant management (e.g. OHSS may occur in 11 per 1000 with ovarian stimulation but not with expectant management). Compared with clomiphene citrate, letrozole may result in similar outcomes in terms of miscarriage (134 fewer, [from 224 fewer to 106 more] per 1000; RR: 0.52; 95% CI: 0.20–1.34), multiple (twin) pregnancies (17 fewer per 1000; RR: 0.76; 95% CI: 0.22–2.64), ectopic pregnancies and congenital anomalies. Based on 599 participants in one

study, the review *(2)* reported similar rates of abdominal bloating (16.8% versus 18.6%), breast pain (6.4% versus 7.2%) and headache (34.9% versus 41.9%) between clomiphene citrate and letrozole. Hot flushes (30.9% versus 16.8%) and constipation (9.4% versus 2.7%) were higher with clomiphene citrate, while joint and limb pain were more common with letrozole (5.8% versus 2.7%). In the RCTs, different numbers of cycles were provided, ranging from one to six, with more recent studies providing three to six cycles. Overall, the certainty of the evidence was low because the numbers of events in the analyses were small. Although data on patient values were not available, the GDG judged that people highly value live births and seek to minimize harms, such as multiple pregnancy, miscarriage or congenital anomalies. Given the moderate benefits and small increase in harms compared to expectant management, but trivial differences in harms and benefits between the drugs, the GDG judged that the balance of effects probably favours S-IUI but does not favour either letrozole or clomiphene citrate.

Other considerations

Stimulation with either clomiphene citrate or letrozole is feasible; it requires similar access to specialist care and ultrasound monitoring. The GDG judged that use of clomiphene citrate and letrozole is probably acceptable *(11)*, but noted that the acceptability of letrozole may also depend on whether off-label use is permitted *(12)*. The cost and access to letrozole may vary substantially between countries; although it could be more expensive compared to clomiphene citrate in some contexts, the GDG agreed that relative to the overall cost of IUI, choosing letrozole would have negligible effects on overall costs and equity in access. No evidence on cost-effectiveness was found; however, the GDG judged that given the trivial differences in benefits and harms and negligible differences in costs, cost-effectiveness probably does not favour either medication.



Summary justification

There are likely moderate benefits and small harms with S-IUI compared to expectant management but there may be little difference in live births and likely little difference in pregnancies between letrozole and clomiphene citrate. There may also be little difference in adverse effects, such as miscarriage, multiple pregnancy and ectopic pregnancy. Relative to the cost of S-IUI, cost differences between clomiphene citrate and letrozole would probably have no impact on equity; both are acceptable and feasible to provide.

Implementation considerations

Health care providers should be aware and mitigate the potential risks of stimulating agents, including clomiphene citrate and letrozole. Health care providers should consider monitoring ovarian response with US to minimize the risk of multifollicular development and multiple pregnancy. Health care providers may consider switching clomiphene citrate and letrozole based on patient symptoms and ultrasound monitoring. Relevant stakeholders should familiarize themselves with applicable national laws and regulations related to the off-label use of letrozole.

Research gaps and future guideline update

Future research and guidance will be required on the timing of IUI in stimulated cycles, and whether to use single or double IUI in stimulated cycles. Ongoing research and surveillance of fetal outcomes should be encouraged. Future research is required regarding the impact of age and other prognostic factors on the outcome of stimulated IUI.

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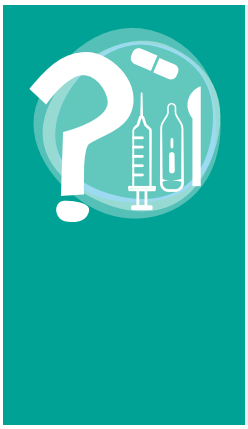


Recommendation

For couples with unexplained infertility, where expectant management has been unsuccessful, WHO suggests S-IUI with either clomiphene citrate or letrozole rather than with gonadotrophins. *(Conditional recommendation, very low certainty of evidence)*

Remark:

- 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.

Background and rationale

Ovarian Stimulation is a pharmacological treatment used to induce the development of (typically multiple and ideally three or fewer) ovarian follicles; hence more oocytes available for fertilization. Commonly used medications for ovarian stimulation include anti-estrogens (e.g. clomiphene citrate), aromatase inhibitors (e.g. letrozole) and gonadotrophins (e.g. FSH and LH) *(1–4)*.

In the previous section, this WHO guideline suggests the use of S-IUI with either letrozole or clomiphene citrate for ovarian stimulation (*conditional recommendation, low certainty of evidence*). While both clomiphene citrate and letrozole are oral medications, gonadotrophins are injected. Because of their mechanism of action and effects on follicle development, medications used for ovarian stimulation such as clomiphene citrate, letrozole or gonadotrophins, may increase the risk of multiple pregnancy to varying extents; gonadotrophins may also increase the risk of OHSS *(1)* (further details on these ovulation-stimulating agents are described in **Section 6.1**).

Given the potential differences in benefits, the GDG considered it a priority to determine whether to preferentially provide the oral medications (letrozole or clomiphene citrate) or gonadotrophins as stimulation agents for treatment of unexplained infertility. For this recommendation, the GDG addressed the question: should S-IUI with gonadotrophins versus S-IUI with clomiphene citrate or S-IUI with letrozole be used in couples with unexplained infertility? This was assessed in the context of second-line management of unexplained infertility.

Balancing harms and benefits

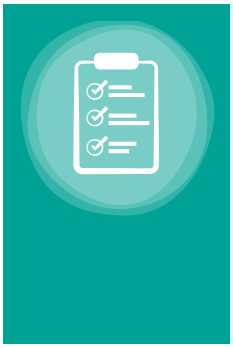
To compare clomiphene citrate with gonadotrophins, evidence was obtained from a review by Athaullah et al. *(5)*, consisting of five RCTs *(6–10)* that compared stimulation with clomiphene citrate versus gonadotrophins in patients with unexplained infertility undergoing IUI. The results showed that compared to gonadotrophins, clomiphene citrate may result in 105 fewer live births (from 193 fewer to 79 more), (OR: 0.51; 95% CI: 0.18–1.47), and 90 fewer pregnancies (from 137 to one fewer) per 1000 women (OR: 0.44; 95% CI: 0.19–0.99). The mean pregnancy rate per cycle was 25% with gonadotrophins and 8% with clomiphene citrate. However, clomiphene citrate may also result in 97 fewer miscarriages (from 185 fewer to 254 more), (OR: 0.46; 95% CI: 0.06–3.33) and 140 fewer multiple pregnancies (from 230 fewer to 198 more), per 1000 pregnancies (OR: 0.37; 95% CI: 0.06–2.43). None of the RCTs reported cases of OHSS. The GDG noted that the higher pregnancy rate that may occur with gonadotrophins was at the expense of a higher multiple pregnancy rate and other adverse effects. Based on these data, the GDG concluded that the balance of effects probably favours clomiphene citrate over gonadotrophins. The certainty of the evidence was considered very low because of very few events across the RCTs.

To compare letrozole with gonadotrophins, a new search and review of evidence were conducted. Three eligible RCTs comparing letrozole to gonadotrophins in patients with unexplained infertility were identified *(11–13)*. The evidence showed that letrozole may result in fewer live births and pregnancies compared to gonadotrophins: 103 fewer live births (from 138 to 57 fewer), (RR: 0.59; 95% CI: 0.45–0.77) and 108 fewer clinical pregnancies (from 150 to 57 fewer), per 1000 women treated (RR: 0.64; 95% CI: 0.50–0.81). The GDG judged that the magnitude of these effects was small. Letrozole may also result in moderate reductions in undesirable effects. Evidence suggests 140 fewer multiple pregnancies (from 193 to 40 fewer), (RR: 0.44; 95% CI: 0.23–0.84), 32 fewer miscarriages (from 86 fewer to 48 more), (RR: 0.84; 95% CI: 0.57–1.24), and six fewer cases of OHSS, (from 11 fewer to 34 more per 1000), (RR: 0.43; 95% CI: 0.05–4.07). In the RCTs, different numbers of cycles were provided, which ranged from one to six, with more recent studies providing 3–6 cycles. The GDG noted that although pregnancy and live birth rates are higher with gonadotrophins compared to letrozole, this comes at the expense of higher multiple pregnancy rates. The GDG judged that most patients value live births and would want to minimize serious side-effects, and that these values likely do not differ among couples with unexplained infertility. Thus, the GDG concluded that the balance of effects probably favours letrozole over gonadotrophins. The certainty of the evidence was low because of few events and wide CIs.

Other considerations

Ovarian stimulation involves the cost of medications, ultrasound monitoring, hormone assays and skilled personnel. Although the overall cost of S-IUI may vary from country to country, the GDG agreed that the cost of oral agents is considerably lower than that of gonadotrophins; moderate savings would be achieved with the use of either clomiphene citrate or letrozole compared to gonadotrophins. The GDG considered studies showing the importance of treatment costs to couples and health systems *(11, 14–16)* and judged that use of oral agents would be expected to increase equity of access to fertility treatment as they are considerably cheaper than gonadotrophins.

Based on two studies *(17, 18)*, the GDG judged that ovarian stimulation with IUI is probably feasible. Variations in gonadotrophin treatment protocols (e.g. doses) can affect the ability of health systems to respond to the complications of gonadotrophins, such as OHSS. Health systems capacity to implement gonadotrophins safely and manage their potential side-effects varies widely. While using low-dose gonadotrophins could reduce the risk of HOMP and OHSS, this is applied inconsistently across different jurisdictions and studies. On the other hand, the GDG judged that clomiphene citrate and letrozole have similar feasibility, in contexts where the off-label use of letrozole is permitted. Although direct evidence from patients was lacking, the GDG noted that the injectable nature of gonadotrophins, the need for more frequent monitoring (because of the higher risk of multiple follicle recruitment and the associated risks of multiple pregnancy and OHSS) and refrigerated storage requirements could potentially reduce their acceptability.



Summary justification

Although there may be slightly fewer pregnancies and live births when providing S-IUI with either clomiphene citrate or letrozole, these oral agents may have fewer adverse effects compared to gonadotrophins. In addition, clomiphene citrate and letrozole are less expensive compared to gonadotrophins, and their use is likely to result in moderate resource savings and higher equity; they are probably acceptable and feasible.

Implementation considerations

This guideline suggests that clomiphene citrate or letrozole are preferable to gonadotrophins as stimulation agents during S-IUI. When gonadotrophins are used, it should be in settings where capacity for the management of side-effects and specified risk mitigation factors are in place (e.g. low-dose, step-up protocols) and where the use of clomiphene citrate or letrozole is not feasible.

Couples should be informed of the success rate, risks and costs associated with these options. Health care providers should be aware of and mitigate the potential risks of stimulating agents and should consider monitoring ovarian response with ultrasound to minimize the risk of multiple pregnancy. Relevant stakeholders should familiarize themselves with applicable national laws and regulations related to the off-label use of letrozole for ovulation induction. Where off-label use is allowed, health professionals should inform their clients, discuss the evidence and address possible concerns or side-effects, and discuss any alternatives.

Research gaps and future guideline update

Future guidance is required on how to take into account prognostic factors, such as the age of the female partner and duration of infertility, during S-IUI, for example, using prognostic models. Future research and guidance will be required on the timing of IUI in stimulated cycles, and whether to use single or double IUI in stimulated cycles.

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10.3 Third-line management of couples with unexplained infertility

Recommendation

For couples with unexplained infertility, where stimulated intrauterine insemination (S-IUI) has been unsuccessful, WHO suggests in vitro fertilization (IVF) rather than expectant management. *(Conditional recommendation, low certainty of evidence)*

Background and rationale

For couples with unexplained infertility who fail to achieve pregnancy with S-IUI, options for management include IVF or expectant management. 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 most fertile days of the menstrual cycle, and monitoring if pregnancy will occur; however, no treatment is provided (see **section 10.1** for the rationale for expectant management).

Conventional IVF is an insemination procedure where oocytes and sperm are co-incubated outside the human body with the goal of achieving fertilization, after which the embryo is transferred to the uterus. IVF allows control over the number of embryos transferred, while allowing spare embryos to be cryopreserved for future use, obviating the need for further ovarian stimulation *(1)*. However, IVF involves costs *(2, 3)* and may have undesirable outcomes *(4)* warranting its comparison with expectant management. For this recommendation, the GDG addressed the question: should IVF (with or without ICSI) versus no treatment be used for couples with unexplained infertility?

Balancing harms and benefits

Evidence was reviewed from a network meta-analysis *(5)*, two RCTs *(6, 7)* and a non-randomized study *(8)*. When comparing IVF to expectant management, IVF may result in 204 more clinical pregnancies (from 40 to 407 more), (OR: 3.03; 95% CI: 1.32–6.94) and 106 more live births (from 27 fewer to 300 more), (OR: 1.88; 95% CI: 0.81–4.38), but 10 more multiple pregnancies (from two fewer to 53 more), per 1000 women treated (OR: 2.66; 95% CI: 0.68–10.43). This difference was considered moderate, and the GDG noted the possibility of further mitigating the risk of multiple pregnancy through the adoption of elective single embryo transfer. **In the studies, one to six cycles of IVF were provided.** The GDG concluded that the balance of effects probably favours IVF over expectant management and judged the certainty of the evidence to be low.

Other considerations

When comparing IVF to expectant management, the GDG judged that IVF is feasible because the infrastructure can be developed and training provided, making it possible to implement it with strong collaborations and support. IVF is expensive and may not be readily accessible in some settings because of lack of infrastructure and its high cost. Thus, IVF likely reduces equity compared to expectant management. Data on the values and acceptability of IVF compared to expectant management; however, the GDG acknowledged that the trade-offs patients undergoing infertility treatments are willing to make may vary depending on different factors, including burden, effectiveness, safety and financial costs *(9)*. Thus, although values were not directly assessed, the GDG agreed that patients are likely to value live births highly while avoiding side-effects, and this is unlikely to vary among different patient groups. In addition, the GDG judged that for patients who have been unsuccessful with other treatments, IVF is probably acceptable; ethically, such patients should have options when other treatments have been unsuccessful.

Summary justification

In couples with unexplained infertility, there may be large benefits in live births and clinical pregnancies with IVF compared to expectant management. Although there may be a moderate risk of multiple pregnancy, the balance of effects probably favours IVF compared to expectant management. Although IVF is expensive, it reduces time to pregnancy, which may be of greater benefit for couples with unexplained infertility where S-IUI has been unsuccessful. Although IVF may probably reduce equity, it is probably acceptable and probably feasible.

Implementation considerations

In implementing these recommendations, health care providers should consider and mitigate the risks associated with IVF, such as OHSS, and the surgical risks associated with oocyte retrieval. Health care providers should provide information about benefits, costs and the potential risks of IVF to couples with unexplained infertility undergoing IVF.

Research gaps and future guideline update

Future research and guidance on how to incorporate possible prognostic factors is needed, including the age of the female partner and the duration of infertility *(10, 11)*. Future research and guidance are needed to determine the optimal or maximum number of IVF cycles that should be provided. Further research and guidance on management options when IVF fails to achieve pregnancy in couples with unexplained infertility is needed.

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Recommendation

For couples with unexplained infertility undergoing in vitro fertilization (IVF) after stimulated intrauterine insemination (S-IUI) has been unsuccessful, WHO recommends using IVF alone rather than IVF with intracytoplasmic sperm injection (ICSI). *(Strong recommendation, low certainty of evidence)*

Background and rationale

Conventional IVF is an insemination procedure where oocytes and sperm are co-incubated outside the human body with the goal of achieving fertilization. Introduced in 1992, ICSI involves injecting a single sperm into an oocyte with the goal of achieving fertilization *(1, 2)*. It is often performed as an additional procedure to conventional IVF for male-factor infertility. However, the rationale for the use of ICSI for non-male-factor infertility, including unexplained infertility, is unclear *(3)*, and the procedure increases costs *(4)*. The GDG agreed that guidance was needed regarding the addition of ICSI to conventional IVF in the management of unexplained infertility. For this recommendation the GDG addressed the question: should IVF versus ICSI be used for couples with unexplained infertility in whom other treatments have been unsuccessful?

Balancing harms and benefits

Evidence was reviewed from two RCTs *(5, 6)* and a non-randomized observational study *(3)*. In the studies, the IVF/ICSI cycles provided ranged from one to six. Evidence showed that, when comparing IVF to ICSI for the treatment of unexplained infertility, IVF likely results in up to 28 fewer clinical pregnancies (from 66 fewer to 18 more), (RR: 0.93; 95% CI: 0.82–1.06), and likely up to 28 fewer live births (from 72 fewer to 24 more), per 1000 (RR: 0.91; 95% CI: 0.78–1.06) compared to ICSI. These differences were considered trivial by the GDG. There may also be little or no difference in adverse effects when comparing IVF with ICSI, such as multiple pregnancy (RR: 0.87; 95% CI: 0.62–1.21), although the studies were unclear on whether a similar number of embryos were transferred in all participants; miscarriages (RR: 0.96; 95% CI: 0.58–1.61); ectopic pregnancies (RR: 1.00; 95% CI: 0.42–2.38); and OHSS (RR: 1.17; 95% CI: 0.39–3.45). The GDG judged these differences in both benefits and undesirable effects to be trivial; the evidence was of low quality because of small events contributing to the data, and the risk of confounding for adverse events from the comparative non-randomized study.

Other considerations

When comparing IVF to ICSI, the GDG considered that ICSI requires additional laboratory resources, personnel, time and expertise compared to IVF. Therefore, the use of IVF is expected to lead to large cost savings compared to ICSI. A 2013 modelling study *(7)*, which compared all IVF versus a 50:50 split between IVF and ICSI, found a 3% increase in cumulative births from ICSI for an additional cost of US$ 1763. However, the GDG noted that these data did not necessarily show that ICSI was cost-effective. Given the trivial differences in live births and clinical pregnancies and the high additional cost of ICSI, the GDG judged that IVF is probably more cost-effective than ICSI for the treatment of unexplained infertility. The GDG judged that if IVF is recommended, it would lead to increased equity and significant cost savings compared to ICSI. In addition, the GDG judged that IVF is probably feasible, and probably more feasible than ICSI, given the additional training, expertise and resources necessary for ICSI. Based on existing GRADE criteria *(8)*, the GDG made a strong recommendation despite the low certainty of evidence, given that the two interventions being compared may have equivalent benefits (low or very low certainty in benefits), while one option (in this case IVF) is less risky or less costly.

Summary justification

In couples with unexplained infertility, IVF and ICSI likely result in similar clinical pregnancies and live births, and similar harms such as miscarriage, OHSS and ectopic pregnancy. However, the costs and resources needed for ICSI are considerably higher. Compared to ICSI, IVF results in large cost savings and is probably more cost-effective. In addition, IVF is probably more feasible compared to ICSI.

Implementation considerations

Health care providers should note that unexplained infertility implies semen parameters that are within the WHO reference ranges as indicated in the *WHO laboratory manual for the examination and processing of human semen (9)*.

Research gaps and future guideline update

Future research and guidance are needed to determine the optimal or maximum number of IVF cycles that should be provided. Further research and guidance is needed on further advanced evaluation and management options that are available when IVF fails to achieve pregnancy in couples with unexplained infertility.

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Chapter 11 Dissemination, local adaptation, implementation, monitoring and evaluation

This chapter provides information on how the guideline recommendations could be adapted, implemented and continuously monitored.

11.1 Dissemination

The recommendations in this guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, other United Nations agencies, international development agencies, universities, professional societies and nongovernmental organizations, including non-state actors in official relations with WHO. The guideline will be published on the WHO website in English; the executive summary will be available in all six United Nations languages. A summary of recommendations aimed at policy-makers, programme managers and health care providers will be developed and disseminated in the six United Nations languages. A commentary summarizing the guideline recommendations will be published in English in an open access academic journal. The guideline will also be disseminated through a global fertility care community of practice. Infographics, social media kits and web stories will be developed, and webinars and scientific sessions organized to further raise awareness of the guideline.

11.2 Local adaptation

The recommendations in this guideline have been developed for a global audience. It is expected that countries will 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. It is anticipated that national adaptation will be based on the epidemiological profile related to the burden of infertility and needs assessments, and will consider the capacity of the health care system, required resources, as well as the local health, social, cultural and economic contexts. Guideline adaptation may involve translation into national or local languages. In 2023, WHO published updated estimates on the global prevalence of infertility *(1)*, which will be useful to countries adapting these guidelines. In settings lacking the local data needed for adaptation, the recommendations in this guideline could be adopted as presented because evidence has been assessed globally. Countries will be encouraged to hold key stakeholder consultations to inform the decisions to introduce the guideline recommendations into national programmes. During adaptation, policy-makers are expected to consider how the recommendations in this guideline align and complement existing WHO guidance on other issues related to sexual and reproductive health.

11.3 Implementation

Successful implementation of the recommendations in this guideline will require endorsement by multiple stakeholders at the country level, including ministries of health, local professional societies, nongovernmental organizations, civil society and patient groups. 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 departments, health and other policies (e.g. educational or social), strategic plans, services and financing, as well as ensuring that fertility care medicines are included in essential medicines list, training health care providers on infertility, modifying health information systems to incorporate data on infertility and developing national clinical guidelines on infertility. WHO has updated its model lists of essential medicines *(2)* and the WHO model list of essential in vitro diagnostics *(3)* to include relevant medications and reproductive hormone-related infertility care; countries will be encouraged to consult these when quantifying, costing and procuring relevant supplies. Political support is essential, as is the need to embed a reproductive rights-based approach to implementation. Providers of fertility care should consider the needs of, and provide equal care to, all individuals. Demographic trends such as total fertility rates should not be used to prioritize or deprioritize guideline implementation; rather, efforts should aim to support individuals and couples achieve their fertility preferences, reproductive goals and aspirations *(4)*. Additionally, implementation research should be encouraged to inform guideline adaptation, implementation and continuous quality improvement. Adaptation of the recommendations into digital and app format is also encouraged, where feasible.

11.4 Monitoring and evaluation

WHO will aim to collect regular feedback from key stakeholders to understand the usefulness and impact of this guideline. WHO will monitor the uptake of the guideline in national policies and programmes by reviewing the number of countries that have adapted or endorsed it. Implementation research related to this guideline, including to evaluate how practice is aligned with the recommendations, will be encouraged. Monitoring and evaluation should be built into the implementation process to provide important lessons to continually improve implementation. The implementation of the guideline recommendations should involve national programmes (and relevant partners) collecting and reporting data on services provided to prevent, diagnose or treat infertility. This may require review of existing health information systems, including ART and other medically assisted reproduction (MAR) registries, which capture data related to fertility care, medical electronic records and other patient electronic reporting and vital registration systems, to ensure that service provision data are adequately captured and reported. WHO plans to develop a core and expanded set of indicators for the prevention, diagnosis and treatment of infertility, which will aid monitoring and impact evaluation. Some indicators that can be used to monitor progress may already be available in the existing health management information systems, national surveillance systems or ART and other MAR registries that capture data related to fertility care; for others, periodic surveys or evaluations may be required.

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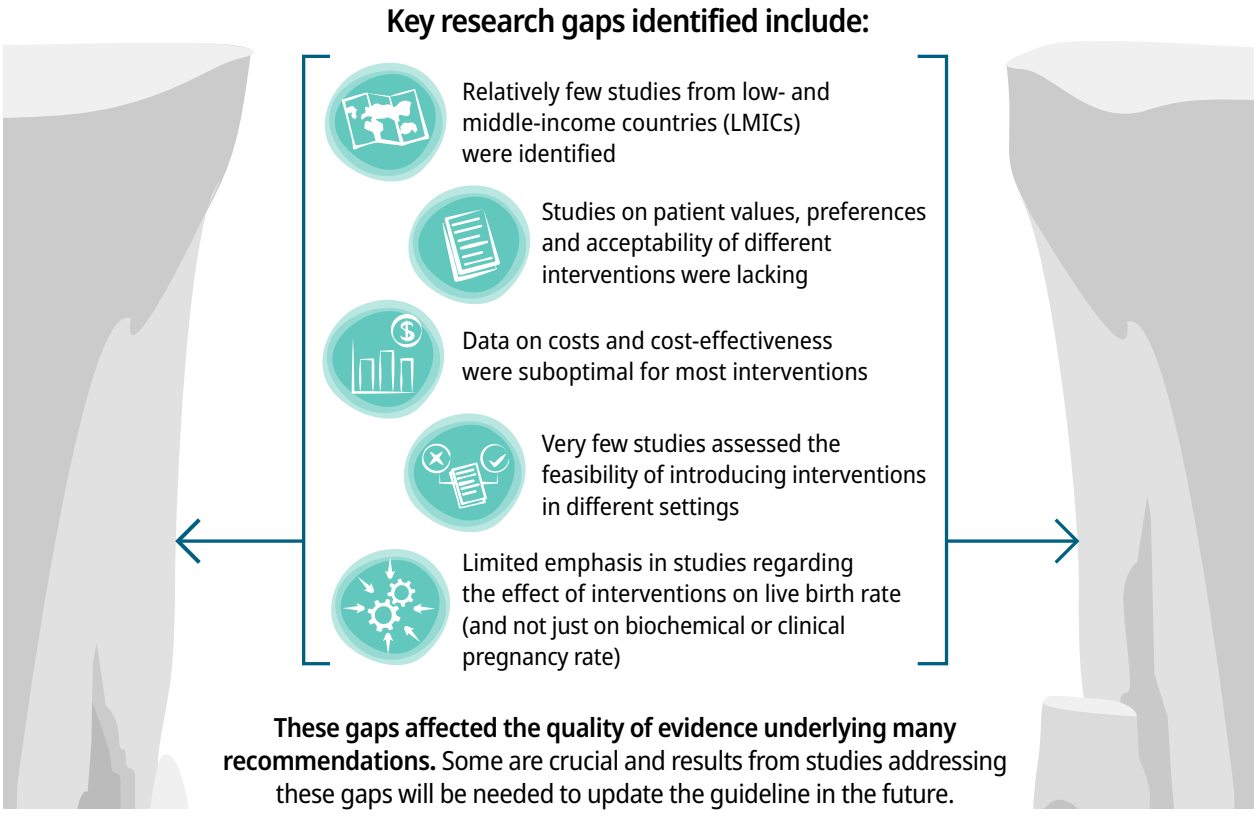
Chapter 12 Research gaps, future scope and updating the guideline

This chapter provides a summary of research gaps and future updating of this guideline.

12.1 Research gaps

The recommendations in this guideline are based on the best global evidence available at the time of compilation. The GDG identified important gaps in research that need to be addressed through primary research studies and RCTs of interventions. Research gaps for specific interventions are many and are summarized under each relevant section throughout this guideline. Overall, relatively few studies from LMICs were identified. Additionally, there was a dearth of studies on patient values, preferences and acceptability of different interventions. 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. Less emphasis was placed in studies regarding the effect of interventions on live birth rate (and not just on biochemical or clinical pregnancy rate). These gaps affected the quality of evidence underlying the many recommendations. Some of these research gaps are crucial and results from these studies will be needed to update the guideline in the future. WHO will continue to track relevant results from the research community.

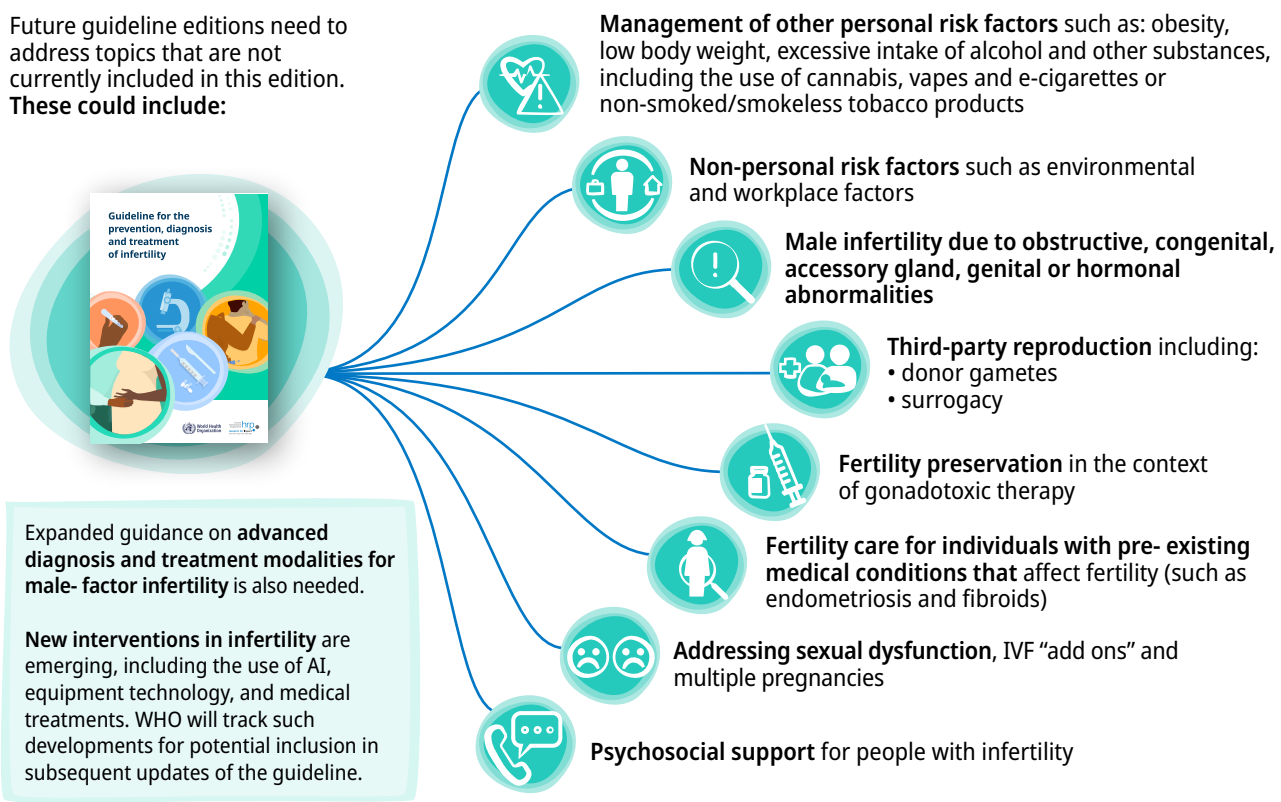
Fig. 12.1. The need to address critical research gaps



12.2 Future scope and updating this 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, and important gaps remain. 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 and 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), or with obstructive, congenital, accessory gland, genital or hormonal abnormalities associated with male infertility, as well as psychosocial support for people with infertility. 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. Guidance is also needed on the use of adjunct IVF "add-ons", and how to further minimize multiple pregnancies. These topics received relatively limited attention in this initial guideline (based on the initial scoping by the GDG) and will need to be considered in subsequent editions. Similarly, subsequent editions of this guideline will need to consider expansion of critical outcomes, as appropriate, to incorporate outcomes that are increasingly important to patients, such as time to pregnancy.

Fig. 12.2. Future guideline scope and updates.



An expanded guideline is expected to be available in five years. Feedback from key stakeholders will help guide the next edition of this guideline. WHO Secretariat, in consultation with technical experts, will continue to follow research development in infertility, particularly for questions in which the certainty of evidence was found to be of low or very low certainty. New and experimental interventions in infertility are emerging, including use of artificial intelligence, equipment technology, medical treatments (such as uterine transplants), among others.

WHO will track these and other developments for potential consideration in subsequent updates of the guideline. If the guideline merits an update in the interim, or if new evidence emerges or other important developments arise that may have an impact on the validity of current recommendations in this version, the Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing will coordinate the guideline update, adhering to the formal procedures outlined in the *WHO handbook for guideline development (1)*.

Reference

1. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/145714).

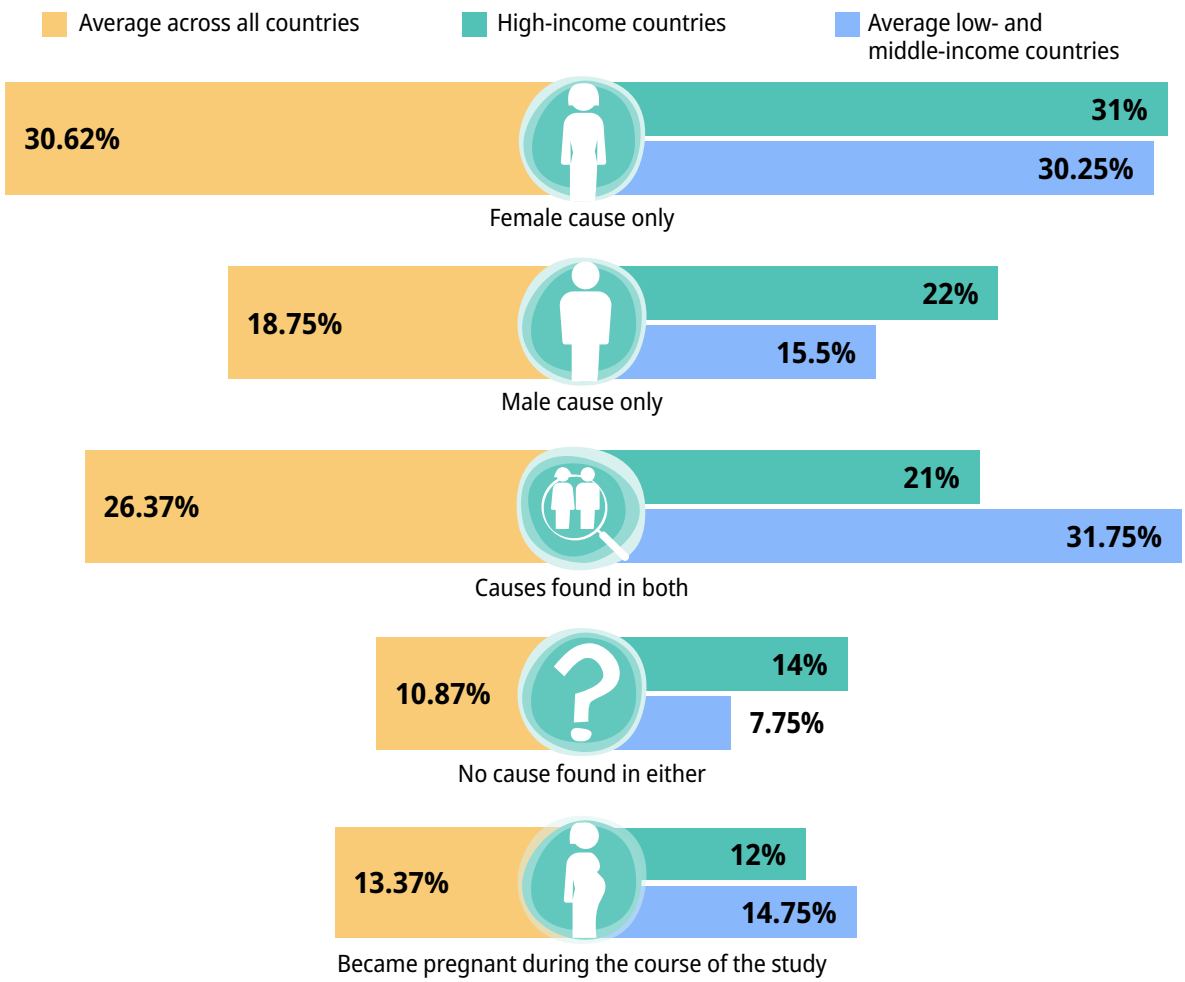
Annex 1. Distribution of the causes of infertility

Table A1.1. General categories of infertility (percentages of couples)[a,b,c,d,e]

	High-income countries	Regions in LMICs				Average LMICs	Average across all countries[f]
		Africa	Asia	Latin America	Eastern Mediterranean		
Female cause only	31.00	37.00	34.00	25.00	25.00	30.25	**30.62**
Male cause only	22.00	8.00	13.00	22.00	19.00	15.5	**18.75**
Causes found in both	21.00	35.00	24.00	30.00	38.00	31.75	**26.37**
No cause found in either	14.00	5.00	13.00	10.00	3.00	7.75	**10.87**
Became pregnant during the course of the study	12.00	15.00	16.00	13.00	15.00	14.75	**13.37**
Total	100.00	100.00	100.00	100.00	100.00	100.00	**99.98**

[a] Data adapted from Cates et al., 1985 *(1)*; see also WHO, 1992 *(2)*.
[b] Study involved 8500 couples in 33 medical centres in 25 countries representing high-, middle- and low-income countries.
[c] 8500 couples were enrolled and just over 5800 (≈69%) completed the investigation to the point of a diagnosis being made for both partners.
[d] Couples were admitted to the study if they had been infertile for at least 1 year (i.e. inclusion criteria).
[e] Classifications of income categories of countries as at the time of the original study.
[f] The average across all countries was derived by summing the prevalence in the "high-income countries" and "average LMICs" columns and dividing this by 2.

Fig. A1.1. Causes of infertility[a]



[a] Data adapted from Cates et al., 1985 *(1)*; see also WHO, 1992 *(2)*.

Table A1.2. Specific diagnoses of infertility (percentages of couples)[a,b,c,d,e,f]

	High-income countries	LMICs				Average LMICs	Average across all countries[g]
		Africa	Asia	Latin America	Eastern Mediterranean		
Female diagnosis							
No demonstrable cause	40.00	16.00	31.00	35.00	26.00	27.00	**33.50**
Bilateral tubal occlusion	11.00	49.00	14.00	15.00	20.00	24.50	**17.75**
Pelvic adhesions	13.00	24.00	13.00	17.00	13.00	16.75	**14.87**
Acquired tubal abnormality	12.00	12.00	12.00	12.00	9.00	11.25	**11.62**
Anovulatory regular cycles[h]	10.00	14.00	9.00	9.00	15.00	11.75	**10.87**
Anovulatory oligomenorrhoea[h]	9.00	3.00	7.00	9.00	11.00	7.50	**8.25**
Ovulatory oligomenorrhoea[h]	7.00	4.00	11.00	5.00	8.00	7.00	**7.00**
Hyperprolactinaemia	7.00	5.00	7.00	8.00	6.00	6.50	**6.75**
Endometriosis	6.00	1.00	10.00	3.00	1.00	3.75	**4.87**
Male diagnosis							
No demonstrable cause	49.00	46.00	58.00	41.00	28.00	43.25	**46.12**
Varicocele	11.00	20.00	10.00	19.00	12.00	15.25	**13.12**
Primary testicular failure	10.00	7.00	11.00	13.00	25.00	14.00	**12.00**
Accessory gland infection	7.00	11.00	3.00	12.00	3.00	7.25	**7.12**
Abnormal sperm morphology[i]	8.00	5.00	3.00	4.00	3.00	3.75	**5.87**
Low sperm motility[i]	3.00	1.00	5.00	8.00	5.00	4.75	**3.87**

[a] Data adapted from Cates et al., 1985 *(1)*; see also WHO, 1992 *(2)*.
[b] Study involved 8500 couples in 33 medical centres in 25 countries representing high-, middle- and low-income settings.
[c] 8500 couples were enrolled and just over 5800 (≈69%) completed the investigation to the point of a diagnosis being made for both partners.
[d] Couples were admitted to the study if they had been infertile for at least 1 year (i.e. inclusion criteria).
[e] Classifications of income categories of countries as at the time of the original study.
[f] Not all diagnostic categories were listed in the original publication; some patients had more than one diagnosis or cause.
[g] The average across all countries was derived by summing the prevalence in the "high-income countries" and "average LMICs" columns and dividing this by 2.
[h] Categories merged and reported under anovulatory and oligo-ovulatory disorders in this guideline, with a total prevalence of 26.1% across all countries.
[i] Categories merged and reported under abnormal semen parameters in this guideline, with a total of 9.7% across all countries.

Fig. A1.2. Specific diagnoses of infertility (male)[a]

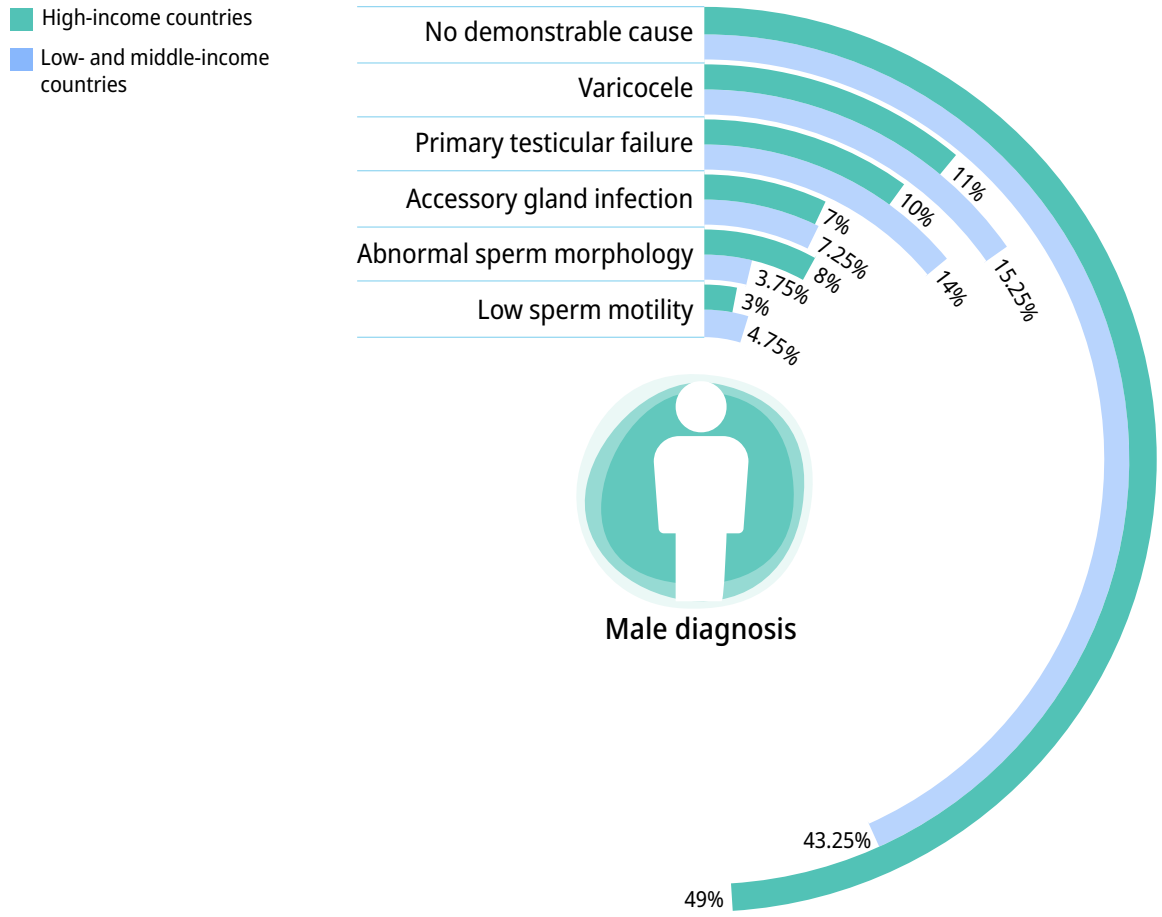
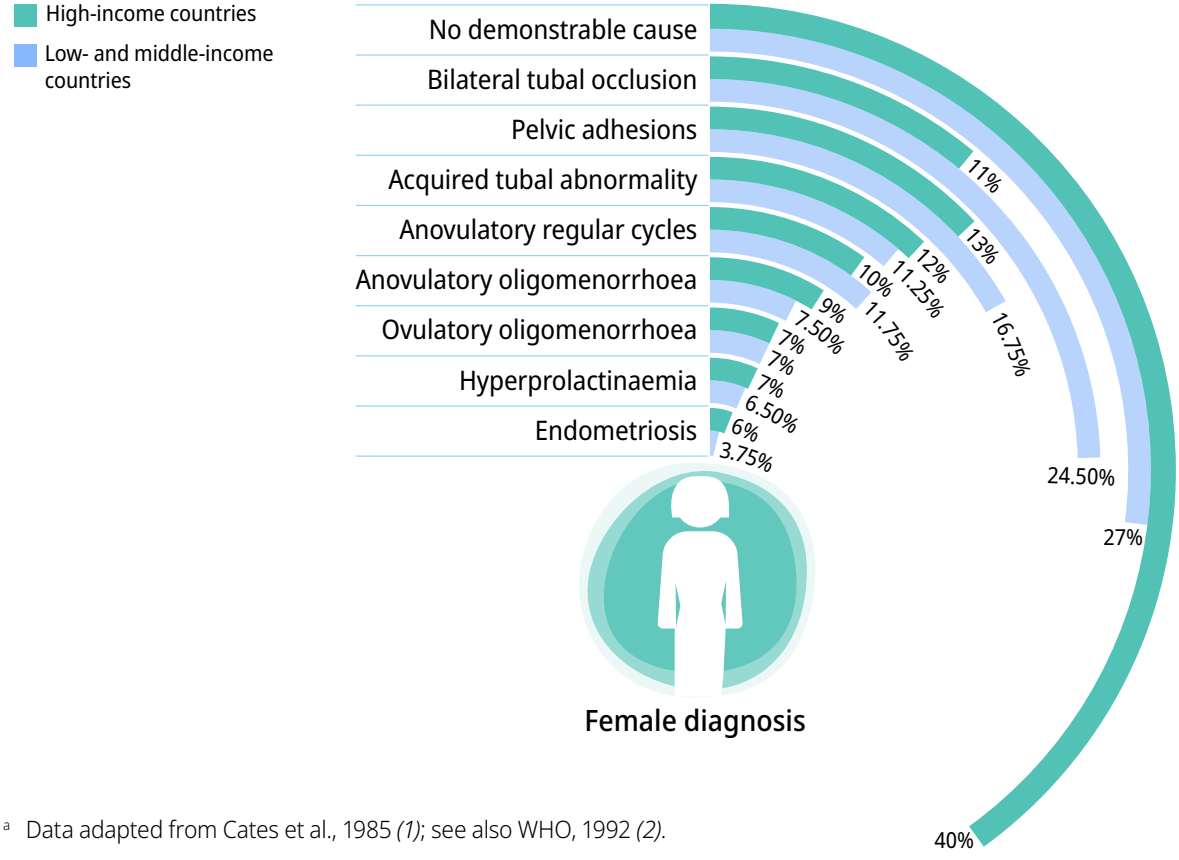


Fig. A1.3. Specific diagnoses of infertility (female)[a]



[a] Data adapted from Cates et al., 1985 *(1)*; see also WHO, 1992 *(2)*.

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Annex 4. Summary of declared interests from members of the GDG

GDG member[a]	Affiliation	Nature of declared interest[b]
Adam H. Balen	Leeds Teaching Hospitals, Leeds, United Kingdom of Great Britain and Northern Ireland	Shareholding, Consulting or Chair (CARE Fertility, Leeds, United Kingdom, and UK Innovation and Research Board); Advisory board membership, (Novo Nordisk Pharmaceuticals). Director and/or Partner (Balance Reproductive Health Ltd; Partner Balance Mind Ltd, and Balance Fertility Ltd); Trustee, Chair or Past Chair (British Fertility Society, NHS England IVF Pricing Development Expert Advisory Group); Fellows' Representative, RCOG Council (until 2023). Guideline member (PCOS Global Guideline Group); Member, FIGO Steering Group on Anovulatory Infertility. No amounts declared for these roles.
Jacky Boivin	School of Psychology, Cardiff University, Cardiff, United Kingdom	Non-monetary support £250 (ESHRE). Research support (£100 219, Merck Serono Ltd, paid to Cardiff University) non-interventional investigator led study on treatment planning. Consulting (£14 907, Ferring Pharmaceutical UK, United Kingdom, the Netherlands, Global). Public statements (total: £1750). Speaker fees (£26 107, Ferring Pharmaceutical, Merck, Gedeon-Richter, British Fertility Society, IVI-RMA).
Barbara Collura	The National Infertility Association (RESOLVE), Washington DC, United States of America (USA)	Employment (Resolve); non-monetary support valued >US$ 1000; public statements.
Ben Cohlen	Isala Fertility Centre, Zwolle, the Netherlands	Research support for clinic projects (grants) from Merck (US$ 30 000), Ferring (US$ 10 000), Gideon Richter (US$ 10 000).
Christopher J. De Jonge	University of Minnesota, Minneapolis, USA	No interests declared.
Sandro C. Esteves	ANDROFERT, Andrology and Human Reproduction Clinic, Campinas, Brazil	Research support grant (Merck) US$ 90 000. Speaker fees (Merck, US$ 20 000; MedE.A./Med.E.A, US$ 9000). Non-monetary support valued at over US$ 1000 (Merck KGaA). Public statements.
Cynthia Farquhar	University of Auckland, Auckland, New Zealand	No interest declared.
Richard Kennedy	Birmingham Women's and Children's NHS Foundation Trust, United Kingdom	No interest declared.

GDG member[a]	Affiliation	Nature of declared interest[b]
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Linda Giudice	UCSF School of Medicine, San Francisco, USA	Investments in stocks (Merck), US$ 5000, (Pfizer) US$ 5000. Public statements as President of IFFS. Speaker fees (IBSA Pharma).
Luca Gianaroli	Reproductive Medicine Unit, S.I.S.Me.R., Bologna, Italy	Employment and stakeholder in SISMER (up to 2024); consulting; non-monetary support valued at over US$ 1000; speaker fees; public statements; investments up to 2020 except in SISMER. Non-recurring fees from Merck, Theramex, InMed, MedThink. Consultant at Interdisciplinary Institute of Reproductive Medicine (IIRM) and at ART Fertility Clinic and Next Clinic (since 2025).
Carin Huyser	Steve Biko Academic Hospital, University of Pretoria, South Africa	No interest declared.
Dmitry Kissin	Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, USA	No interest declared.
Tansu Kucuk	Department of Obstetrics and Gynaecology, Acıbadem Maslak Hospital, Istanbul, Türkiye	No interest declared.
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Ragaa Mansour	The Egyptian IVF Center, Ma`adi, Cairo, Egypt	No interest declared.
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Willem Ombelet	Genk Institute for Fertility Technology, Genk, Belgium	No interest declared.
Allan Pacey	Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom	Monetary support to employer valued at over US$ 1000 for consultancy/public speaking (Carrot Fertility [current], Cryos International [current], IBSA Institut Biochimique SA, Mealis Group). Several unpaid positions: Member of Advisory Board of Progress Educational Trust; Co-Chair, UKNEQAS Reproductive Sciences Advisory Committee; Member, Science Media Centre Advisory Board; Patron, Fertility Alliance (United Kingdom).

GDG member[a]	Affiliation	Nature of declared interest[b]
Guido Pennings	Department of Philosophy and Moral Sciences, Ghent University, Ghent, Belgium	Non-monetary support valued at over US$ 1000 (Merck). Honorarium of speaker fees (Merck, US$ 2000; Teva Pharma, US$ 2000). Consulting fees (IVIRMA for membership of Ethics Committee, €20 000; Cryos Int. for membership of External Scientific Advisory Committee, €8000). Speakers fees (Gedeon Richter, €2000).
Robert Rebar	Homer Stryker School of Medicine, Western Michigan University, Kalamazoo, USA	Employment (Lecturer WMU; editorial honorariums [NEJM Journal Watch Editor]) US$ 2500, honorarium (Contraception Journal deputy editor), US$ 3000. Honorarium (Associate editor Obs Gyn Clinical Alert), US$ 1600); consulting (BSMB for several clinical trials (Myovant; US$ 6000) up to 2020.
Richard Reindollar	Geisel School of Medicine, Dartmouth, New Hampshire, USA	No interest declared.
Roberta Rizzo	University of Ferrara, Ferrara, Italy	No interest declared.
Rita Sembuya	Joyce Fertility Support Centre, Kampala, Uganda	No interest declared.
Gamal Serour	Al Azhar University, Cairo, Egypt	No interest declared.
Basil Tarlatzis	Aristotle University of Thessaloniki, Thessaloniki, Greece	Consulting; non-monetary support valued at >US$ 1000; research support for unrestricted research grants (Merk Serono) and Travel grants (MSD), honorariums (IBSA; Ferring - company sponsored speakers bureau); Advisory board (Ovascience).
Carla Tatone	University of L'Aquila, L'Aquila, Italy	No interest declared.
Lan N. Vuong	University of Medicine and Pharmacy, Ho Chi Minh City, Viet Nam	Research support/grants (2018–2020), valued at US$ 49 478 (Ferring). Non-monetary support valued at over US$ 1000 (Merck, for public education workshops). Speaker fees from Ferring (two conferences per year valued at US$ 500-1700), MSD (US$ 500–700), Merck (US$ 500–700) and ARD (US$ 3000). Travel support (including meeting registration fees) from Ferring, MSD and Merck.
Marie Lena Windt De Beer	Tygerberg Academic Hospital, Stellenbosch University, Cape Town, South Africa	No interest declared.
Cong Yali	Health Science Centre, Peking University, Beijing, China	No interests declared.

[a] The following GDG members contributed to the initial part of the guideline but later stepped down: **Lars Björndahl** (Karolinska Institutet, Stockholm, Sweden), **Roy Farquharson** (Liverpool Women's NHS Foundation Trust, Liverpool, United Kingdom), **Anna Krawczack** (Fertility Europe [Pan-European organisation representing patients' associations], Evere, Belgium), **Kersti Lundin** (Sahlgrenska University Hospital, Gothenburg, Sweden) and **Rebecca Sokol** (Keck School of Medicine, University of Southern California, Los Angeles, USA).

[b] The published interests exclude declared income from employment with public, regulatory, non-profit or nongovernmental organizations, academic institutions or universities, or public hospitals.

Annex 5. Summary of declared interests from members of the ERG

ERG member[a]	Affiliation	Nature of declared interest
David Adamson	The International Committee Monitoring Assisted Reproductive Technologies, Saratoga, United States of America (USA)	Consultant manuscript author fees over US$ 1000 (Organon), 2024. Conference speaker fees (ESHRE) US$ 5000 annually ongoing); Founder and CEO (ARC Fertility).
Amal Benbella	Reproductive Health Hospital, IbnSina University Hospital, Rabat, Morocco	No interest declared.
Márcia Mendonça Carneiro	Department of Obstetrics and Gynecology, Federal University of Minas Gerais, Minas Gerais, Brazil	Travel grants and honorariums for speaker fees and lectures (Ferring, Organon, Johnson and Johnson, Boehringer), with a total amount of less than US$ 10 000 in the last 4 years; ongoing lectures, 2024.
Julia Chain	Human Fertilization and Embryology Authority, London, United Kingdom of Great Britain and Northern Ireland	No interests declared.
Ivonne J. Diaz Yamal	Department of Gynecology and Obstetrics, Central Military Hospital, Bogota, Colombia	No interests declared.
Bart C.J.M. Fauser	Reproductive Medicine, University Medical Center Utrecht, Utrecht, the Netherlands	Consultant (Ferring, Celmatix, Univfy ReproNovo Vortex Imaging) amounts not disclosed; all current. Member of DSMB (Myovant), current; Co-chair (COGI) amounts not disclosed, current. Author fees (UpToDate) amount not disclosed, current.
Muntaha Gharaibeh	Department of Maternal & Child Health, Jordan University of Science and Technology, Irbid, Jordan	No interests declared.
Grigoris F. Grimbizis	Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Thessaloniki, Greece	No interests declared.

ERG member[a]	Affiliation	Nature of declared interest
Joyce Harper	Institute for Women's Health, University College London, London, United Kingdom	Paid talks (Gedeon Richter), £4000, ceased; conference speaker fees (Cook IVF), £2000, ceased; manuscript author fees (Ferring) £2000; ceased.
Márcia C. Inhorn	Department of Anthropology, Yale University, New Haven, USA	No interests declared.
Mohan S. Kamath	Department of Reproductive Medicine and Surgery, Christian Medical College, Vellore, Tamil Nadu, India	Research grants support via CMC Vellore (ICMR) (US$ 110 000 for whole project, ongoing 2023–2026). Journal editorial honorarium (€3000 paid to employer annually; ongoing 2023–2025). Several unpaid honorary editorial positions (ESHRE journals, ISAR journals and Cochrane Gynaecology and Fertility groups); all ongoing.
Tamar Khomasuridze	Eastern Europe and Central Asia Regional Office, United Nations Population Fund (UNFPA), Istanbul, Türkiye	No interests declared.
Neena Malhotra	Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India	Research grant support (Ferring Pharmaceuticals) for a multicentre randomized controlled trial assessing the efficacy and safety of follitropin delta versus follitropin alfa (GONAL-F) in controlled ovarian stimulation for ART; no personal income received, grant provided solely to conduct IVF for individuals.
Edgar Mocanu	Department of Obstetrics and Gynaecology, RCSI University of Medicine and Health Sciences, Dublin, Ireland	Scientific/research adviser fees (Cryos) €4000 per year, ceased. Conference travel and accommodation support (Merck) value not declared, ceased. President (IFFS) income not declared; current.
Ben W. Mol	Department of Obstetrics and Gynaecology, Monash University, Melbourne, Australia	Consultant fees (Merck KGaA, Organon and Norgine); amounts not disclosed, all current. Research grant (NHMRC); amount not disclosed, current. Travel grants (Merck KGaA); amount not disclosed, current. Stock Options (ObsEva); amounts not declared; current.
Olarik Musigavong	Chaophya Abhaibhubejhr Hospital, Prachin Buri, Thailand	No interests declared.
Zozo Nene	Department of Obstetrics & Gynaecology University of Pretoria, Pretoria, South Africa	ESHRE Conference sponsorship 2024 (Ferring Pharmaceuticals), 2024; travel and accommodation only.

ERG member[a]	Affiliation	Nature of declared interest
Robert J. Norman	Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia	Consultancy fees (an IVF unit in Hanoi, Viet Nam, with no ownership of the IVF unit itself, minor income declared, ongoing).
Sasha Ottey	PCOS Challenge: The National Polycystic Ovary Syndrome Association, Atlanta, USA	Non-monetary support (Androgen Excess and PCOS Society, Jones Foundation Infertility Counselors Conference [JFICC], Fertility Empowerment International Conference [FEI]). Conference travel costs (AE-PCOS annual meeting) 2023; (FEI), 2024; and (JFICC), 2024.
Ameet Patki	Indian Society for Assisted Reproduction, Mumbai, India	No interests declared.
Jie Qiao	Peking University Health Science Center, Peking University Third Hospital, Beijing, China	No interests declared.
Promise E. Sefogah	Department of Obstetrics & Gynaecology, University of Ghana Medical School, Accra, Ghana	Research grant and Research Fellowship Training Grant (Fogarty International Center, Northern Pacific Global Health), US$ 10 000; 2023.
Trinh The Son	Military Institute of Clinical Embryology and Histology, Hanoi, Viet Nam	No interests declared.
Oleg Tishkevich	Centre of Assisted Reproduction, Minsk, Belarus	Acting Chairman of the Board (Belarusian Medical Society for Human Reproduction, 2021–2024), current. No other declared interest.
Karla Torres	Centre for Reproductive Rights, Geneva, Switzerland	No interests declared.
Sheryl Van der Poel	International Health Consultant, Geneva, Switzerland	Travel reimbursements (Carrot Fertility, USA); several flights and/or hotel, no current travel. Stock options (Carrot Fertility, USA), US$ 4500, current; Stock options (Bea Fertility, United Kingdom), US$ 365, current. Adviser (Fertility Basics, USA), unpaid, current.
Mónica Vazquez-Levin	Institute of Biology and Experimental Medicine –National Scientific and Technical Research Council, (IBYME–CONICET), Buenos Aires, Argentina	Consultant fees related to Spanish translation of WHO Semen Manual sixth edition (WHO); current.

ERG member[a]	Affiliation	Nature of declared interest
Maria P. Velez	Division of Reproductive Endocrinology and Infertility, McGill University, Montreal, Canada	No interests declared.
Nathalie Vermeulen	European Society of Human Reproduction and Embryology, Strombeek-Bever, Belgium	No interests declared.
Mohamed Youssef	Department of Obstetrics and Gynaecology, Cairo University, Cairo, Egypt	No interests declared.

[a] Several ERG members declared current income from employment, including those working with public, regulatory, non-profit and nongovernmental organizations, academic institutions and universities, or public hospitals; these are not included above.

Annex 6. Components of female medical history and physical examination[1]

Personal information

Full name			
Date of birth		**Age**	
Address			
Contact information (phone, email)			
Occupation			
Marital or relationship status			

Relevant dates for evaluation

	Date		Month		Year	
Date of history taking						

	Date		Month		Year	
Date of birth of male partner						

	Date		Month		Year	
Date of birth of female partner						

[1] Form developed for a standardized investigation, diagnosis and management of the infertile female

Infertility history

Infertility	☐ Primary ☐ Secondary
Duration of infertility infertility/attempting to achieve pregnancy	_____ years
If secondary, months since last pregnancy	_____ months
Previous investigation(s) and/or treatments for infertility	☐ No ☐ Yes *If yes, please specify:*_____
Previous pregnancy	☐ Current partner ☐ Another partner
Previous miscarriage	☐ Current partner ☐ Another partner
Treatments/evaluations of the *male* partner	*Please specify:*_____

1. Sexual history

Sexual activity and practices

Frequency of sexual activity	☐ Regular ☐ Irregular ☐ Rarely
Timing of intercourse	☐ Spontaneous ☐ Around ovulation
Pain during intercourse (dyspareunia)	☐ Yes ☐ No
Presence of sexual anxiety	☐ Yes ☐ No
Stress	☐ Yes ☐ No
Psychological barriers to sexual function	☐ Yes ☐ No
Use of sexual performance enhancers or lubricants	☐ Yes ☐ No
Prolonged abstinence	☐ Yes ☐ No *If yes, please specify duration:* _____ days _____ months
Perceived quality of sexual activity	☐ Normal ☐ Inadequate
Previous or current sexual dysfunction	☐ Yes ☐ No

2. Menstrual history

Age at menarche	_____ years old

Cycle characteristics

Length of cycle	_____ days	☐ Regular	☐ Irregular
Duration of bleeding	_____ days		
Flow	☐ Light	☐ Moderate	☐ Heavy
Dysmenorrhea (painful periods)	☐ Yes	☐ No	
Severity	_____ /10		
Intermenstrual spotting	☐ Yes	☐ No	

3. Obstetric history

Total number of pregnancies	_____
Number of live births	_____
Number of miscarriages	_____
Number of stillbirths	_____
Number of ectopic pregnancies	_____
Termination of pregnancy	☐ Yes ☐ No *If yes how many:*_____
History of complications during pregnancy (e.g. preeclampsia, gestational diabetes)	*Specify:*_____

4. Contraceptive history

Previous contraceptive methods used	*Specify:* _____
Type	*Specify:* _____
Duration of use	Date of cessation: *specify:* _____
Use of emergency contraception	☐ Yes ☐ No

5. Childhood and development history

Pubertal development	Age at onset of puberty: _____
Sexual development	☐ Normal ☐ Delayed
History of ovarian or uterine abnormality	☐ Yes ☐ No
Treatment for ovarian or uterine abnormality	☐ Medical ☐ Surgical
Congenital anomaly	☐ Yes ☐ No *If yes, please specify:* _____

Vaginal anomalies	☐ Yes ☐ No *If yes, please specify:* _____
Pathology possibly causing ovarian or uterine damage	
Pelvic inflammatory disease (PID)	☐ Yes ☐ No
Endometriosis	☐ Yes ☐ No
Polycystic ovarian syndrome (PCOS)	☐ Yes ☐ No
Ovarian torsion	☐ Yes ☐ No ☐ Left ☐ Right
Surgery on reproductive organs	☐ Yes ☐ No *If yes, please specify:* _____

6. Medical history

a. History of disease	☐ None
	☐ Diabetes ☐ Hypertension ☐ Thyroid disorders ☐ Autoimmune diseases ☐ Neurologic disease ☐ Fibrocystic of the pancreas ☐ Chronic respiratory tract disease ☐ Tuberculosis (or exposure) ☐ Uterine fibroids ☐ Ovarian cysts ☐ Other, *please specify:* _____
b. History of infection	☐ None
High fever in past 6 months	☐ Yes ☐ No
Urinary infection	☐ Yes ☐ No
Sexually transmitted disease (STI)	☐ Yes ☐ No ☐ Syphilis ☐ Gonorrhoea ☐ Chlamydia ☐ HPV (human papillomavirus) ☐ Trichomoniasis ☐ Herpes simplex virus (HSV) ☐ Cervicitis ☐ Other, *specify:* _____
c. History of surgery	☐ None
Retroperitoneal and/or pelvic surgery	☐ Hysterectomy ☐ Oophorectomy ☐ Salpingectomy ☐ Myomectomy (fibroid removal) ☐ Pelvic adhesion surgery
Inguinal or perineal surgery	☐ Inguinal hernia repair ☐ Cyst removal (e.g. ovarian or pelvic cysts) ☐ Endometriosis surgery ☐ Laparoscopy (diagnostic or therapeutic) ☐ Tubal ligation ☐ Tubal ligation reversal

Bariatric, bladder, or prostate surgery	☐ Bariatric surgery ☐ Uterine reconstruction	☐ Transvaginal or abdominal bladder surgery
Cranial surgery	☐ Pituitary surgery	
Spinal surgery	☐ Spinal cord surgery	
Urethral and genital reconstruction	☐ Vaginal reconstruction	☐ Urethral surgery
Sympathetic nervous system surgery	☐ Sympathectomy ☐ Other, *please specify:* _____	

d. Occupational history

Current occupation	*Specify:* _____
Duration	___ years _____ months
Work Environment	☐ Indoors ☐ Outdoors
Exposure to	☐ extreme temperatures ☐ noise ☐ poor ventilation
Exposure to chemicals	☐ solvents ☐ heavy metals ☐ toxic substances at work *If yes, specify the substances:*_____
Exposure to radiation	☐ Yes ☐ No *If yes, specify the source/type:* _____ *If yes, specify if doses were above recommended occupational levels* ☐ Yes ☐ No
e. History of gonadotoxic medication	☐ ß-blockers ☐ Finasteride ☐ Opioids ☐ Chemotherapy ☐ Calcium blockers ☐ Serotonin reuptake inhibitors ☐ Anabolic steroids
Prescription medications	☐ Immunosuppressants (e.g. glucocorticoids, calcineurin inhibitors) ☐ Anti-epileptic drugs (AEDs) ☐ Serotonin reuptake inhibitors (SSRIs) ☐ Thiazide ☐ Other, *specify:* _____ ☐ Cimetidine ☐ Allopurinol ☐ Sulfasalazine ☐ Colchicine ☐ Nitrofurantoin

f. Lifestyle History

Physical activity	☐ Regular	☐ Irregular	☐ Rarely
Diet	☐ Balanced ☐ Vegan ☐ Processed	☐ High-protein ☐ Keto ☐ *Please specify:* _____	☐ Vegetarian ☐ Mediterranean

Smoking or use of tobacco products including electronic cigarette?	☐ Yes ☐ No
Number of cigarettes	Per day: _____ Number of years smoking: _____
Consumption of alcohol	☐ Yes ☐ No *If yes, how often:* ☐ Regular ☐ Irregular ☐ Rarely How much? ____(units/week)
Use recreational drugs?	☐ Yes ☐ No *If yes, which ones (specify):* _____ Frequency ☐ Regular ☐ Irregular ☐ Rarely
Recent stressors or changes in life	☐ Yes ☐ No *If yes, specify:* _____

g. Family history

Infertility in the family	☐ Yes ☐ No
Genetic or hereditary conditions	☐ Cystic fibrosis ☐ Kartagener syndrome ☐ Endometriosis ☐ PCOS ☐ Other, *specify:* _____
Family history of early menopause	☐ Yes ☐ No
Endocrine diseases	☐ Yes ☐ No *If yes, specify:* _____

7. General physical examination

Height (cm) | | | | BMI | |

Weight (kg) | | | | Blood pressure (mmHG) | | | | | |

General physical examination	☐ Normal ☐ Abnormal *If abnormal specify:* _____
Signs of virilization	☐ Yes ☐ No *If yes, specify:* _____
Signs of hypoestrogenism	☐ Yes ☐ No *If yes, specify:* _____
Signs of hyperandrogenism	☐ Yes ☐ No *If yes, specify:* _____

Skin changes	☐ Yes ☐ No *If yes, specify:* _____
Thyroid examination	☐ Normal ☐ Enlarged thyroid (goiter) ☐ Thyroid nodules

8. Gynecological examination

External genitalia (vulva)	☐ Normal ☐ Scars ☐ Lacerations ☐ Other, *specify:* _____	
Vagina	☐ Normal ☐ Atrophic (dryness, thinning) ☐ Narrowed ☐ Abnormal discharge. *If present, specify:* _____	
Cervix	☐ Normal ☐ Ectropion (cervical eversion) ☐ Cervical scars ☐ Other, *specify:* _____	
Uterus	☐ Normal ☐ Enlarged ☐ Fibroids (size and location) ☐ Retroverted ☐ Anomalies, *specify:* _____	
Ovaries	☐ Normal ☐ Polycystic (PCO) ☐ Enlarged ☐ Tender ☐ Cystic lesions, *specify size and type:* _____	
Fallopian tubes	☐ Patency (confirmed by _____) ☐ Blocked (if known) ☐ Abnormalities, *specify:* _____	
Pelvic examination	Tenderness:	☐ Yes ☐ No If yes specify location: _____
	Thickened uterus:	☐ Yes ☐ No
	Cystic or mass lesions:	☐ Yes ☐ No *If yes specify size:* _____ *Specify location:* _____
	Palpable adnexal masses:	☐ Yes ☐ No *If yes specify location:* _____
	Other:	*Specify:* _____
Rectal examination (if performed)	☐ Normal ☐ Tender ☐ Masses ☐ Abnormal ☐ Soft swelling ☐ Hard swelling ☐ Other, *specify:* _____	

9. Additional information

_____

_____

_____

Annex 7. Components of male medical history and physical examination[1]

Personal information

Full name			
Date of birth		**Age**	
Address			
Contact information (phone, email)			
Occupation			
Marital or relationship status			

Relevant dates for evaluation

	Date		Month		Year	
Date of history taking						

	Date		Month		Year	
Date of birth of male partner						

	Date		Month		Year	
Date of birth of female partner						

[1] Adapted from the *WHO manual for the standardized investigation, diagnosis and management of the infertile male.*

Infertility history

Infertility	☐ Primary ☐ Secondary
Duration of infertility/attempting to achieve pregnancy	_____ years
If secondary, months since last impregnation	_____ months
Previous investigation (s) and/or treatments for infertility	☐ No ☐ Yes *If yes, please specify:* _____
Contraceptive methods used	*Please specify:* _____ *Duration of contraception use:* _____
Previous pregnancy	☐ Current partner ☐ Another partner
Previous miscarriage	☐ Current partner ☐ Another partner
Treatments/evaluations of the *female* partner	*Please specify:* _____

1. Sexual history

Sexual activity and practices

Frequency of sexual activity	☐ Regular ☐ Irregular ☐ Rarely
Timing of intercourse	☐ Spontaneous ☐ Around ovulation
Erectile dysfunction	☐ Yes ☐ No ☐ Normal ☐ Inadequate
Ejaculatory dysfunction	☐ Yes ☐ No
Pain during intercourse	☐ Yes ☐ No
Presence of sexual anxiety	☐ Yes ☐ No
Stress	☐ Yes ☐ No
Psychological barriers to sexual function	☐ Yes ☐ No
Use of sexual performance enhancers or lubricants	☐ Yes ☐ No
Prolonged abstinence	☐ Yes ☐ No *If yes, please specify duration:* _____ days _____ months
Perceived quality of sexual activity	☐ Normal ☐ Inadequate
Previous or current sexual dysfunction	☐ Yes ☐ No

2. Childhood and development history

Pubertal development	Age at onset of puberty: _____

Sexual development	☐ Normal	☐ Delayed
History of undescended testicle	☐ Yes ☐ Left	☐ No ☐ Right
Treatment of undescended testicle	☐ Yes ☐ Medical	☐ No ☐ Surgical
Epispadia	☐ Yes	☐ No
Hypospadia	☐ Yes	☐ No
Pathology possibly causing testicular damage	☐ Yes **Injury** **Torsion** **Orchitis:** mumps **Orchitis:** other	☐ No ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right ☐ Left ☐ Right

3. Medical history

a. History of disease	☐ None
	☐ Diabetes ☐ Hypertension ☐ Thyroid disorders ☐ Autoimmune diseases ☐ Neurologic disease ☐ Fibrocystic of the pancreas ☐ Chronic respiratory tract disease ☐ Tuberculosis (or exposure) ☐ Other, *please specify:* _____
b. History of infection	☐ None
High fever in past 6 months	☐ Yes ☐ No
Urinary infection	☐ Yes ☐ No
Epididymitis	☐ Yes ☐ No *If yes, specify:* _____ ☐ Left ☐ Right
Orchitis	☐ Yes ☐ No *If yes, specify:* _____ ☐ Left ☐ Right
Sexually transmitted disease (STI)	☐ Yes ☐ No ☐ Syphilis ☐ Gonorrhoea ☐ Chlamydia ☐ Other, *specify:* _____
Treatment for STIs	☐ Yes ☐ No *If yes, specify treatment:* _____
Symptoms of current infection	☐ Yes ☐ No ☐ Discharge ☐ Testicular pain ☐ Fever ☐ Other, *specify:* _____

c. History of surgery	☐ None	
Retroperitoneal and/or pelvic surgery	☐ Prostate	☐ Bladder neck
Inguinal, scrotal or perineal surgery	☐ Herniorraphy ☐ Inguinal hernia repair ☐ Hydrocele ☐ Vasectomy ☐ Epididymal cyst removal	☐ Orchiectomy ☐ Varicocele repair ☐ Testicular surgery ☐ Vasectomy reversal
Sperm retrieval	☐ PESA ☐ MESA ☐ Electroejaculation	☐ TESE ☐ Penile vibratory stimulation
Bariatric, bladder, or prostate surgery	☐ Bariatric surgery	☐ Transurethral resection of the prostate (TURP)
Cranial surgery	☐ Pituitary surgery	
Spinal surgery	☐ Spinal cord surgery	
Urethral and genital reconstruction	☐ Hypospadias repair	☐ Urethral structures surgery
Hernia treatment	☐ Yes ☐ No	
Sympathetic nervous system surgery	☐ Sympathectomy ☐ Other, *please specify:* _____	
d. Occupational history		
Current occupation	*Specify:* _____	
Duration	_____ years _____ months	
Work environment	☐ Indoors ☐ Outdoors	
Exposure to	☐ Extreme temperatures ☐ Poor ventilation	☐ Noise
Exposure to chemicals	☐ Solvents ☐ Heavy metals ☐ Toxic substances at work *If yes, specify the substances:* _____	
Exposure to radiation	☐ Yes ☐ No *If yes, specify the source/type:* _____ *If yes, specify if doses were above recommended occupational levels* ☐ Yes ☐ No	

e. History of gonadotoxic medication	☐ ß-blockers ☐ Finasteride ☐ Opioids ☐ Chemotherapy	☐ Calcium blockers ☐ Serotonin reuptake inhibitors ☐ Anabolic steroids
Prescription medications	☐ Immunosuppressants (e.g. glucocorticoids, calcineurin inhibitors) ☐ Anti-epileptic drugs (AEDs) ☐ Selective serotonin reuptake inhibitors (SSRIs) ☐ Thiazide ☐ Other, *specify:* _____	☐ Cimetidine ☐ Allopurinol ☐ Sulfasalazine ☐ Colchicine ☐ Nitrofurantoin
f. Lifestyle History		
Physical activity	☐ Regular ☐ Irregular ☐ Rarely	
Diet	☐ Balanced ☐ High-protein ☐ Vegetarian ☐ Vegan ☐ Keto ☐ Mediterranean ☐ Processed ☐ *Please specify:* _____	
Smoking or use of tobacco products including electronic cigarette?	☐ Yes ☐ No	
Number of cigarettes	Per day: _____	Number of years smoking: _____
Consumption of alcohol	☐ Yes ☐ No *If yes, how often:* ☐ Regular ☐ Irregular ☐ Rarely How much? ____(units/week)	
Use recreational drugs?	☐ Yes ☐ No *If yes, which ones (specify):* _____ Frequency: ☐ Regular ☐ Irregular ☐ Rarely	
Recent stressors or changes in life	☐ Yes ☐ No *If yes, specify:* _____	
g. Family history		
Infertility in the family	☐ Yes ☐ No	
Genetic or hereditary conditions	☐ Cystic fibrosis ☐ Kartagener syndrome ☐ Varicocele ☐ Other, *specify:* _____	
Endocrine diseases	☐ Yes ☐ No *If yes, specify:* _____	

4. General physical examination

Height (cm) | | | | BMI | |

Weight (kg) | | | | Blood pressure (mmHg) | | | | | |

General physical examination	☐ Normal	Abnormal	☐ Hypoandrogenism ☐ Hyperandrogenism
Signs of virilization	☐ Normal	Abnormal	☐ Testicular enlargement ☐ Other, *specify:* _____

5. Uro-genital examination

Penis	☐ Normal ☐ Plaques ☐ Other, *specify:* _____	☐ Scars ☐ Epispadias	☐ Hypospadias ☐ Curvature
Testes			Side: Left - Right
Palpable in the scrotum	☐ Both palpable	☐ Abnormal	L ☐ R ☐
Palpable in inguinal region	☐ Both palpable	☐ Abnormal	L ☐ R ☐
	☐ Both palpable	☐ Thickened	L ☐ R ☐
		☐ Cystic/Nodule	L ☐ R ☐
		☐ Tender	L ☐ R ☐
Volume (ml)	Left: _____	Right: _____	
Device used for measurement	☐ Prader orchidometer ☐ Pachymeter ☐ Other		
Epididymis	☐ Both normal	☐ Thickened	L ☐ R ☐
		☐ Cystic	L ☐ R ☐
		☐ Tender	L ☐ R ☐
Vas deferens	☐ Both normal	☐ Non palpable	L ☐ R ☐
		☐ Thickened	L ☐ R ☐
Spermatic cord/Scrotum	☐ Normal	☐ Hydrocele	L ☐ R ☐
		☐ Hernia	L ☐ R ☐
Varicocele	☐ Normal	☐ Grade III	L ☐ R ☐
		☐ Grade II	L ☐ R ☐
		☐ Grade I	L ☐ R ☐
		☐ Subclinical	L ☐ R ☐
Inguinal examination	☐ Normal	☐ Lymphadenopaty	L ☐ R ☐

Scrotal skin	☐ Normal	☐ Infectious scars	L ☐ R ☐
		☐ Surgical scars	L ☐ R ☐
Rectal examination			
Prostate	☐ Normal	☐ Soft swelling	☐ Tender
		☐ Hard swelling	☐ Other
		☐ Palpable	☐ Abnormal
Seminal vesicles	☐ Normal	☐ Soft swelling	☐ Tender
		☐ Hard swelling	☐ Other
		☐ Palpable	☐ Abnormal

6. Additional information

For further information, please contact:

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Switzerland

Email: srhcfc@who.int
Website: https://www.who.int/health-topics/infertility
www.who.int