National Women & Infants Health Programme

National Clinical Practice Guideline

Fertility – Investigation and Management in Secondary Care

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

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This Guideline aims to provide evidence-based recommendations for the care of women, men or couples presenting with infertility. To promote a standardised approach nationally across all maternity hospitals/units regarding the structure and organisation of care, including counselling and supportive care, investigation and management.
Description:
This National Clinical Practice Guideline establishes an evidence-based, nationally standardised framework for the investigation and management of infertility within secondary care in Ireland. It addresses service organisation, timely referral, couple-centred assessment and diagnostic evaluation of male and female factors. Recommendations encompass semen analysis, assessment of ovulation, ovarian reserve, pelvic anatomy and tubal patency, alongside appropriate medical, surgical and assisted reproductive interventions. It also embeds pre-conception counselling, psychosocial support, audit and implementation measures to promote equitable, safe and patient-centred fertility care.

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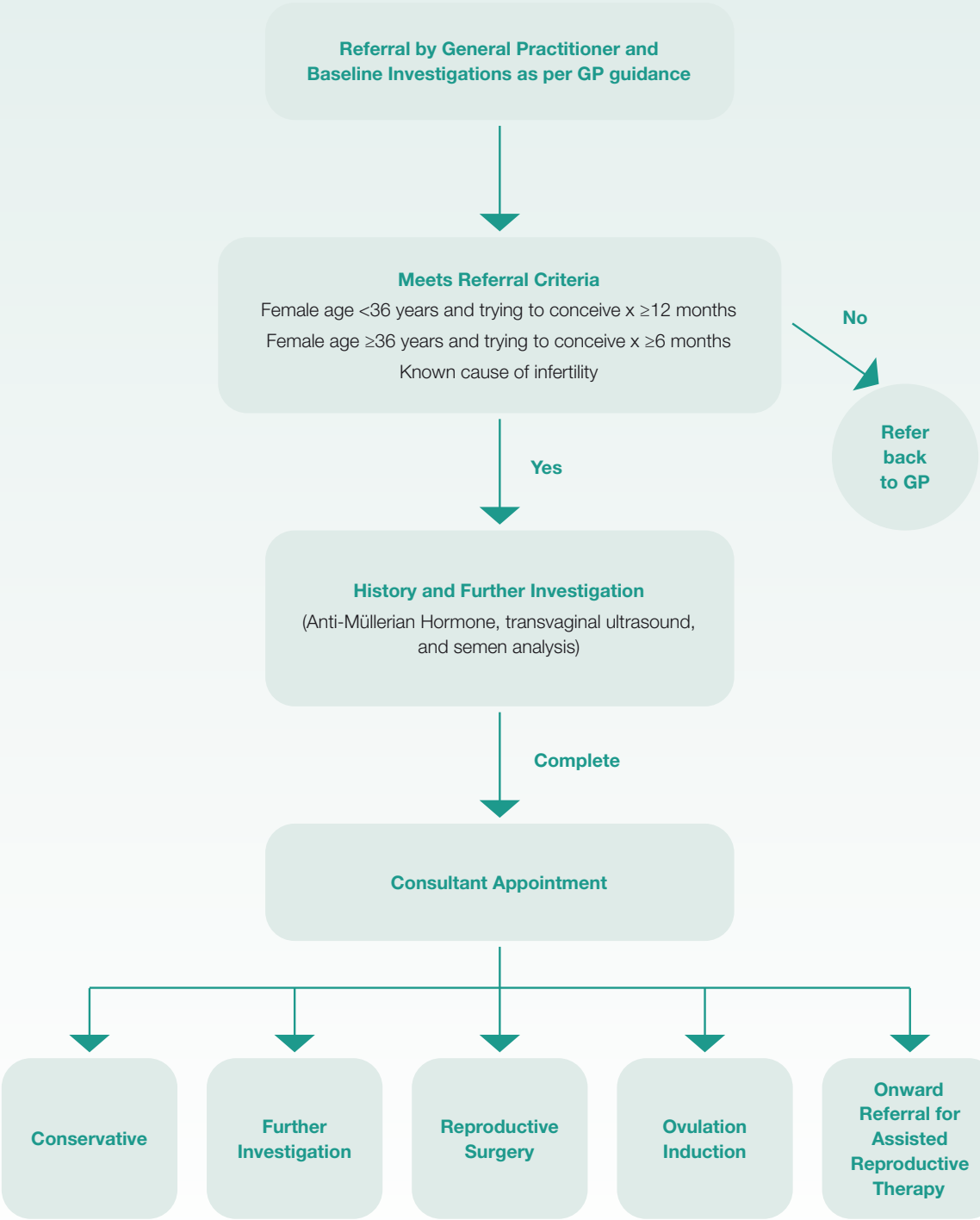
Algorithm

The Regional Fertility Hub Referral Pathway



Key Recommendations

No	Recommendation	Grade of recommendation*	Supporting Evidence**
Organisation of Fertility Care in Ireland			
How should the care of those with infertility be managed?			
1	Women/couples seeking a fertility consultation should initially be reviewed in a primary care setting, ideally by their General Practitioner (GP).	Best Practice	GDG
Investigation of Infertility			
When should infertility investigations be commenced?			
2	Couples should be seen together at all fertility consultations. A thorough history and examination focusing on reproductive history factors and assessment of pregnancy related risks should be undertaken at first assessment and updated as required.	Best Practice	GDG/NICE
3	Investigations should be offered to couples of reproductive age who have been trying to conceive for 12 months or longer with no underlying medical condition.	Grade 1A	GDG/NICE
4	Earlier referral to secondary or tertiary care should be considered after six months of trying to conceive if the female is 36 years of age or older or earlier if there is a known cause of infertility in either intending parent. Immediate referral should be considered if there is no possibility of conception without treatment.	Grade 1A	GDG/NICE
5	All couples planning a pregnancy should have a detailed medical history taken and lifestyle optimisation should be discussed. In women with a complex medical or psychiatric history, referral for pre-pregnancy counselling should be considered and initiated where appropriate.	Best Practice	GDG
6	All women planning to conceive and/or engaging with fertility services, should have their varicella status assessed as part of pre-conception counselling either by history or laboratory testing and those who are non-immune should be offered varicella vaccination where possible.	Best Practice	GDG/HSE

No	Recommendation	Grade of recommendation*	Supporting Evidence**
What initial investigations should be performed for men?			
7	All men should have an initial semen analysis performed and compared with World Health Organisation (WHO) reference values.	Best Practice	GDG/NICE/ ESHRE/WHO
What initial investigations should be performed for women?			
Ovulation			
8	In women with a regular menstrual cycle, tests to confirm ovulation are not routinely recommended.	Grade 1B	GDG/NICE
9	If confirmation of ovulation is required in women with regular menstrual cycle, this can be done with mid-luteal Progesterone, urinary Luteinizing Hormone (LH) kits or a transvaginal ultrasound.	Grade 1B	GDG/ESHRE
10	If ovulation cannot be confirmed, hormonal profile on Day 2-4 should be performed to include Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH) and Oestradiol.	Best Practice	GDG
Ovarian Reserve Testing			
11	Ovarian reserve should be quantified using either Antral Follicle Count (AFC) and/or Anti-Müllerian Hormone (AMH).	Best Practice	GDG/NICE
Ultrasound			
12	Baseline transvaginal pelvic ultrasound with a high frequency (5-8MHz) transducer should be ideally performed in the first 10 days of the cycle.	Grade 1A	GDG/NICE
Tubal Patency Testing			
13	Tubal patency should be performed with hysterosalpingogram (HSG) or Hysterosalpingo-Contrast-Sonography (HyCoSy) where no pelvic pathology is suspected.	Best Practice	GDG/NICE
Further Investigations			
14	It is reasonable to test thyroid stimulating hormone (TSH) in women presenting with infertility.	Grade 1B	GDG/ASRM

No	Recommendation	Grade of recommendation*	Supporting Evidence**
Treatment of Infertility			
What is the recommended treatment of couples with unexplained infertility?			
15	Ovulation induction should not be offered to women with regular menstrual cycles who have proven ovulation.	Best Practice	GDG/NICE
16	Ovulation induction for women with unexplained infertility who have proven ovulation is not recommended.	Best Practice	GDG/NICE
17	Intrauterine insemination (IUI) with ovarian stimulation should be considered first line treatment for couples with unexplained infertility.	Best Practice	GDG/ESHRE
What are the treatment options for women with ovulation disorders?			
18	Women with anovulatory polycystic ovary syndrome (PCOS) should be offered treatment with Letrozole as first line treatment.	Grade 1A	GDG/ ESHRE
19	At least two cycles of ovulation induction with oral agents should be tracked with ultrasound scanning.	Best Practice	GDG
20	If there is no ovulation despite initial therapy, gonadotropins may be considered +/- laparoscopic ovarian drilling.	Best Practice	GDG/ESHRE
21	Assisted reproduction may be required for refractory anovulatory PCOS.	Best Practice	GDG/ESHRE
22	Disorders of ovulation that are not secondary to PCOS, or associated with low Oestrogen will not respond to oral ovulation induction (OI) and should be managed with the appropriate form of ovulation induction – e.g. gonadotrophins or gonadotropin-releasing hormone (GnRH) pump.	Grade 1B	GDG/ ESHRE
Treatment of women with premature ovarian insufficiency			
23	Women with premature ovarian insufficiency should be referred to a dedicated multidisciplinary clinic.	Best Practice	GDG/ESHRE
24	Oocyte donation can be considered in women with premature ovarian insufficiency following specialist workup and counselling.	Best Practice	GDG/ESHRE
When should Intrauterine Insemination (IUI) be offered			
25	IUI should be offered to heterosexual couples with unexplained infertility, psychosexual disorders (e.g. vaginismus or dyspareunia) or cervical factor who meet defined eligibility criteria.	Best Practice	GDG/ ASRM

No	Recommendation	Grade of recommendation*	Supporting Evidence**
26	IUI should be offered to all couples/ women planning treatment with donor sperm who meet defined eligibility criteria.	Best Practice	GDG
27	IUI should be considered for heterosexual couples with; mild male factor, stage I/II endometriosis, mild tubal disease or for women with confirmed ovulation following ovulation induction.	Best Practice	GDG/ ASRM
28	IUI should only be considered in stimulated cycles.	Grade 1B	GDG/ ESHRE
29	All IUI cycles should be monitored with ultrasound tracking.	Best Practice	GDG
30	IUI should be scheduled approximately 24 hours after LH positive urine if performed, or between 0 to 36 hours following an ovulation trigger.	Grade 1A	GDG
When should referral to a tertiary care unit be considered?			
31	Referral to a tertiary fertility clinic should be considered for: women with very low ovarian reserve, 36 years of age or older, unexplained infertility, unsuccessful ovulation induction treatment and/or intrauterine insemination (IUI), donor gamete, fertility preservation and for severe male factor infertility.	Grade 1A	GDG
Patient Centred Supportive Care			
What information and supportive care should be provided to couples regarding mental health and infertility?			
32	All couples should be provided with information and access point for supportive care during their first contact with a fertility specialist including information on fertility counselling and support groups.	Best Practice	GDG/NICE

** GDG: refers to the evidence based on the literature review conducted by the Guideline Development Group
NICE: The National Institute for Health and Care Excellence
ESHRE: European Society of Human Reproduction and Embryology
ASRM: American Society for Reproductive Medicine

Chapter 1: Initiation

The National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) define clinical guidelines as systematically developed statements, based on a thorough evaluation of the evidence, to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances, across the entire clinical spectrum.[1]

1.1 Purpose

The purpose of this Guideline is to provide a comprehensive, evidence-based Guideline for the provision of secondary level fertility services within the Republic of Ireland.

1.2 Scope

Target Users

The Guideline is a resource for all primary, secondary and tertiary health and social care professionals who are involved in the care of women, men or couples with infertility. It may also be of interest and a valuable resource to women, men or couples with infertility, support and advocacy organisations and those involved in research.

Target Population

Women, men or couples presenting with infertility to secondary level care services in the Republic of Ireland.

1.3 Objective

To provide evidence-based recommendations for the care of women, men or couples presenting with infertility. To promote a standardised approach nationally across all maternity hospitals/units regarding the structure and organisation of care, including counselling and supportive care, investigation and management.

1.4 Guideline development process

The Guideline Developers agreed to undertake this work under the direction of the Guideline Programme Team (GPT). An Expert Advisory Group (EAG) was commissioned by the GPT. Their role was to critically review the Guideline prior to submission to the National Women and Infants Health Programme (NWIHP) for final approval.

See Appendix 1 for EAG membership and Appendix 2 for Guideline programme process.

1 National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) (2015) National quality assurance criteria for clinical guidelines. Version 2. Dublin: NCEC and HIQA. https://www.hiqa.ie/sites/default/files/2017-01/National-Quality-Assurance-Criteria.pdf

The Guideline Developers/writing group comprised:

- Dr Laurentina Schäler, Specialist Registrar Obstetrics and Gynaecology
- Dr Danielle O'Leary, General Practitioner with special interest in Women's Health, Sexual Health, and Family Planning.
- Ms Michelle Barry, Midwife Specialist, Fertility Hub at the National Maternity Hospital, Dublin.
- Dr David Crosby, Consultant Obstetrician and Gynaecologist, Subspecialist in Reproductive Medicine, Surgery & Genetics, Head of Department of Reproductive Medicine, National Maternity Hospital, Dublin. Assistant Clinical Professor, University College Dublin.

1.5 Stakeholder involvement

Stakeholders are people who have a common interest in improving health services. This includes persons that are responsible for delivering and those who receive services related to the clinical Guideline. The Expert Advisory Group has representatives from a broad range of professional backgrounds. This includes representatives from Patient Advocacy Ireland. Also included in the membership are professionals from the areas of obstetrics, midwifery and pharmacology.

The following additional stakeholders were consulted in regard to this Guideline.

- Dr Moya McMenamin. Consultant Obstetrician and Gynaecologist, Subspecialist in Reproductive Medicine, Cork University Maternity Hospital (CUMH)
- Dr Lucia Hartigan. Consultant Obstetrician and Gynaecologist, Subspecialist in Reproductive Medicine, University Hospital Limerick
- Dr David Fitzgerald. Chief Pharmacist, National Maternity Hospital, Dublin
- Dr Aisling Looney. Senior Clinical Fellow in Andrology, University College London Hospital
- Dr Lucy-Ann Behan. Consultant Endocrinologist, Tallaght University Hospital and The Coombe Hospital, Dublin.
- Dr Nikhil Purandare, Consultant Obstetrician and Gynaecologist, Subspecialist in Reproductive Medicine, University Hospital Galway.
- Dr Richard Duffy. Perinatal Psychiatrist. Rotunda Hospital.
- Ms. Alison Hickey. Senior Midwife. National Maternity Hospital

1.6 Disclosure of interests

Guideline developers and reviewers bring a range of experiences and perspectives to the work of the national Guideline Programme. It is likely that both Guideline developers and stakeholders/reviewers will have a variety of interests, arising from different contexts and activities done in a professional or personal capacity. These can include employment and other sources of income, speaking engagements, publications and research, and membership of professional or voluntary organisations. The involvement of individuals with relevant content expertise is essential for enhancing the value of Guideline recommendations, but these individuals may also have interests that can lead to conflicts of interest, as may peer reviewers, patient representatives and researchers.

All interests should be declared if, in the view of a reasonable person, they are relevant, or could be perceived to be relevant, to the work of the clinical practice guideline in question.[2] Declaring an interest does not mean there is a conflict of interest.

It is important that interests are openly declared so they can be appropriately managed. Conflicts of interest can bias recommendations and ultimately be harmful to women and the health system.

Disclosures of interests and appropriate management of conflicts of interest, when identified, are therefore essential to producing high-quality, credible health guidelines.[3]

The Guidelines International Network (GIN), a global network of Guideline developers that aims to promote best practices in the development of high-quality guidelines, developed a set of 9 principles to provide guidance on how financial and non-financial conflicts of interest should be both disclosed and managed. It is recommended that Guideline developers follow the GIN principles.[4]

For this National Clinical Practice Guideline, all Guideline developers are asked to complete a conflict of interest declaration form. The response to declared interests will be managed by the Guideline programme team, in accordance with GIN principles. Conflicts of interest may be reported in the published Guideline and declarations of interest can be made available.

1.7 Disclaimer

These guidelines have been prepared to promote and facilitate standardisation and consistency of good clinical practice, using a multidisciplinary approach. Information in this Guideline is current at the time of publication.

The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the Clinician in light of clinical data presented by the woman and the diagnostic and treatment options available.

Clinical material offered in this Guideline does not replace or remove clinical judgment or the professional care and duty necessary for each specific woman.

Clinical care carried out in accordance with this Guideline should be provided within the context of locally available resources and expertise.

2 NICE (2019) Policy on declaring and managing interests for NICE advisory committees https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf

3 Traversy G, Barnieh L, Akl EA, Allan GM, Brouwers M, Ganache I, Grundy Q, Guyatt GH, Kelsall D, Leng G, Moore A, Persaud N, Schünemann HJ, Straus S, Thombs BD, Rodin R, Tonelli M. CMAJ. 2021, 193(2):E49-E54. https://www.cmaj.ca/content/193/2/E49

4 Holger J. Schünemann, Lubna A. Al-Ansary, Frode Forland, *et al.*; for the Board of Trustees of the Guidelines International Network. Guidelines International Network: Principles for disclosure of interests and management of conflicts in guidelines. Ann Intern Med. 2015;163:548-553. https://www.acpjournals.org/doi/10.7326/m14-1885

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women/men/couples in an environment that is appropriate, and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- Advising women/men/couples of their choices and ensuring informed consent is obtained
- Providing care with professional scope of practice, meeting all legislative requirements and maintaining standards of professional conduct
- Applying standard precautions and additional precautions, as necessary, when delivering care
- Documenting all care in accordance with local and mandatory requirements.

1.8 Use of language

Within this guidance we use the terms 'woman' and 'women's health'. However, it is important to acknowledge that people who do not identify as cis-gender women are excluded from this descriptor, including people who identify as transgender, gender diverse and gender non-binary[5]. We also appreciate that there are risks to desexing language when describing female reproduction[6 7]. Services and delivery of care must be appropriate, inclusive and sensitive to the needs of people whose gender identity does not align with the sex they were assigned at birth. This includes training and education regarding diverse pathways to pregnancy and the use of practices which affirm the sexual and gender identities of all people using Obstetrics and Gynaecology services.

Language use is key to effectively communicate options, recommendations, and respectfully accept a woman's fully informed decision[8]. With this in mind, the use of birth is preferable to the term delivery in all circumstances and is used consistently where possible throughout the guidelines. It is acknowledged that in some circumstances (e.g., in the case of a medically indicated intervention or surgery) and in some contexts, substituting with the term delivery is considered appropriate and this term may be used instead.

5 Moseson H, Zazanis N, Goldberg E, *et al.* The Imperative for Transgender and Gender Nonbinary Inclusion. Obstet Gynecol. 2020;135(5):1059-1068. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7170432/

6 Brotto LA, Galea LAM. Gender inclusivity in women's health research. BJOG: An International Journal of Obstetrics & Gynaecology. https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.17231

7 Gribble KD, Bewley S, Bartick MC, *et al.* Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language. *Frontiers in Global Women's Health*. 2022;3. Accessed June 9, 2022. https://www.frontiersin.org/article/10.3389/fgwh.2022.818856

8 https://blogs.bmj.com/bmj/2018/02/08/humanising-birth-does-the-language-we-use-matter/

Chapter 2:
Clinical Practice Guideline

Background

Reproductive Endocrinology and Infertility is one of the most rapidly evolving medical specialties in modern medicine. Infertility is a major cause of psychological and social morbidity globally, affecting individuals, families and communities.

Societal changes have had a significant impact on the prevalence of infertility. Despite awareness regarding reduced fecundity rates with increasing female age, the average age of primiparous women in Ireland has risen from 27.4 years in 2000 to 31.1 years in 2018 [1]. Reasons reported in the literature for this increase in female age at time of conception include lack of 'readiness', relationship status, education and prolonged adolescence[2]. Other factors contributing to increased risk of both female and male infertility include obesity, smoking and recreational drug use, all of which are prevalent among the younger fertile population.

Rates of sexually transmitted infection (STI) have also increased, further contributing to infertility [3]. A US study concluded that in 2018, STI rates were highest among the 15 to 24 year age group, which is a critical age for fertility planning [4]. Nevertheless, alongside the increase in infertility rates, due to the above-mentioned factors, assisted human reproduction (AHR) has developed ways to try to ameliorate these problems with significant improvements in assisted reproductive technology, resulting in increased success rates[5]. Furthermore, following the introduction of vitrification to replace slow freezing as the method of cryopreservation of gametes, oocyte vitrification, embryo vitrification and oocyte donation have become much more successful, cost effective and readily available [6, 7]. Unfortunately, new AHR techniques do not always have the power to overcome the above-mentioned causes of infertility, thus prevention remains key.

Through societal advances and cultural changes, there is an increase in the number of families created outside the traditional male/female relationship [8]. In addition, assisted human reproduction (AHR) provides the opportunity for couples or singles who wish to fulfil their desire for parenthood to do so through gamete donation and/or surrogacy.

Prevalence of infertility

The global burden of infertility in the modern world is substantial and the evidence suggests it is increasing in prevalence. Research has confirmed an increase in the prevalence of both female and male infertility over the last 20 years, and when analysed based on age, infertility rates are found to be highest in the 35 to 39 year age group, independent of sociodemographic index [9]. Unexplained infertility and tubal factor infertility have been reported to be almost twice as high in women over the age of 35 years of age compared to those under 30 years of age [10]. Approximately 15% of couples of reproductive age will struggle to conceive naturally, with increased rates observed in certain populations such as those with increased female age, previous abdomino-pelvic surgeries or other medical co-morbidities [11, 12]

The World Health Organisation (WHO) estimates that, worldwide, approximately 48 million couples and 186 million individuals have infertility [13]. The European Society of Human Reproduction and Embryology (ESHRE) estimates that 25 million people are affected by infertility in the European Union [14].

In Ireland, there is no current database available on infertility rates. Recent research has highlighted the increased need for reliable data collection to improve understanding on the prevalence of infertility [12]. Infertility rates in Ireland are likely to be similar to that of other European countries where the lifetime infertility rate is reported to be 16.5% [12].

The social economic and legal impact of assisted reproductive therapy (ART)

Infertility is having an increasing adverse effect on people worldwide with growing numbers of individuals availing of assisted reproductive therapy (ART). Barriers in access to care include lack of infrastructure, trained personnel, and the high cost of treatment medication, however funding in Ireland has been secured to facilitate the first steps in a move towards a fully publicly funded fertility service.

The World Health Organisation (WHO) notes that laws and policies regulating third party reproduction and ART are critical to "ensure universal access without discrimination" and to "protect and promote the rights of all human parties involved" [1]. Legislation in ART is extremely complex, because it raises ethical questions about the status of a human embryo and the creation of families outside the traditional male/female relationship. This requires, in contrast to other medical fields, regulation by both state legal and medical guidelines.[2 3] The Human Fertilisation and Embryo Authority (HFEA) regulates research and clinical use of ART within the UK, but no such regulatory authority exists in Ireland.[4] While most countries practicing AHR have some legislation in place, this varies widely. Ireland is one of five European countries which currently lacks specific legislation on AHR and as a result was ranked 40th in the "European Atlas of Fertility Treatment Policies" [15]. This atlas scores 43 European countries based on the results of a European invitro fertilisation Monitoring (EIM) Consortium. At the time of writing, the Health (Assisted Human Reproduction) Bill 2022 is currently being debated before Dáil Éireann; the Bill addresses AHR treatments, posthumous use of gametes, surrogacy and counselling amongst other issues [16].

Fertility Hubs in Ireland

Six public Regional Fertility Hubs have been launched nationally[9] within the existing maternity networks i.e.

- Coombe Women & Infants University Hospital (CWIUH), Dublin
- Cork University Maternity Hospital (CUMH), Cork
- National Maternity Hospital (NMH), Dublin
- Rotunda Hospital, Dublin
- University Hospital Galway (UHG), Galway
- University Hospital Limerick (UHL), Limerick

9 https://www.hse.ie/eng/services/news/media/pressrel/hse-funded-fertility-treatment-services-to-start-in-september.html

These hubs offer a formalised, multidisciplinary service to those who are experiencing fertility issues. The aim of these hubs is to maximise outcome for women and their partners by providing a comprehensive assessment and management on-site and to minimise delays in access to fertility services. This model of care comprises three stages, starting in primary care, extending into secondary care (i.e. Regional Fertility Hubs) and then, if indicated, tertiary care (i.e. AHR). All six Regional Fertility Hubs will provide a consistent approach to service delivery. The Fertility Hub service can be accessed through a standardised referral form available through Healthlink.

Terminology and Definitions

Infertility is defined as a disease characterised by the failure to conceive a pregnancy within 12 months of regular, unprotected sexual intercourse or due to the inability to reproduce, either as an individual or with a partner [13, 17, 18,19].

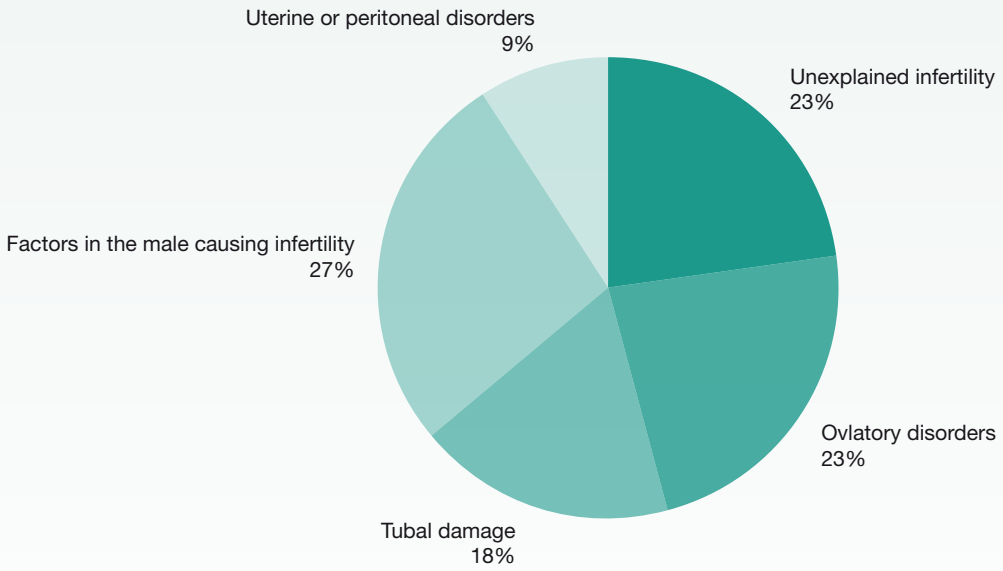
Infertility: Pathology and Aetiology

There are four basic conditions that are required for pregnancy:

1. Ovulation
2. Adequate sperm production and release
3. Successful transfer of sperm to meet the oocyte
4. Implantation of fertilised embryo.

Infertility can be caused by an issue during one or more of these steps. The main aetiologies of infertility in the developed world are outlined in Figure 1: these include gamete or embryo problems, uterine or endometrial defects and pelvic conditions such as tubal disease and/or endometriosis. It is estimated that approximately 40% of cases of infertility have a combined male and female factor [20] issues.

Figure 1: Causes of Infertility [21]



There are several epidemiological and modifiable lifestyle factors that are associated with infertility (Table 1). These are discussed in more detail in Section 2 of this Guideline. Additional infertility risk factors that will be discussed include ovulatory disorders, tubal factors, and pelvic inflammatory disease. For further information please refer to the Endometriosis: Clinical Practice Guideline for diagnosis and management in Ireland which is currently under development within the National Women and Infants Health Programme (due 2024).

Table 1: Factors associated with infertility

Epidemiological Risk Factors	Additional Risk Factors Female
Maternal and paternal age	Ovulation disorders
Tobacco use	Tubal and uterine surgery
Alcohol	Endometriosis
Illicit Drug Use	Pelvic Inflammatory Disease
Body Mass Index (BMI) <18.5 or ≥25kg/m^2	Other abdominal surgery

Female Factor Infertility

As outlined in Figure 1, female factor infertility encompasses ovulation disorders, tubal factors and uterine or peritoneal factors.

Ovulation Disorders

Ovulation disorders typically present with menstrual disturbance, oligomenorrhoea or amenorrhoea. The WHO categorises ovulation disorders into three groups [21]

Group I: Hypothalamic Pituitary Failure – 10%

- Includes hypothalamic amenorrhoea and hypogonadotropic hypogonadism
- Typically presents with amenorrhoea (primary or secondary)
- Characterised by low gonadotrophins and Oestrogen deficiency
- Often associated with low body mass index (<18.5kg/m^2) or excessive exercise.

Group II: Hypothalamic-Pituitary-Ovarian Dysfunction – 85%

- Normo-gonadotrophic, normo-oestrogenic anovulation
- Examples include polycystic ovary syndrome (PCOS) and hyperprolactinaemic amenorrhoea.

Group III: Ovarian Failure – 5%

- Characterised by hypergonadotropic and hypooestrogenic anovulation.

Table 2: Characteristics of World Health Organisation (WHO) classification of amenorrhoea/ anovulation [7,8,9]

	Group I	Group II	Group III
Oestrogen	↓	Normal	↓
FSH	↓	Normal	↑
Prolactin	Normal	Normal	
Example	Low body weight, excessive exercise, known pituitary disease, genetic cause	PCOS	Ovarian Failure

Tubal Factor

It is estimated that tubal factors are responsible for 18% of the causes of infertility in women [22]. Tubal blockage can occur in the proximal portion, the mid portion or the distal portion of the fallopian tube [10]. Tubal disease includes tubal obstruction and pelvic adhesions due to infection, endometriosis and previous surgery. The principal cause of tubal damage is infection. This is usually as a result of pelvic inflammatory disease with chlamydia trachomatis but may also be due to pelvic infection as a result of appendicitis, septic miscarriage, tuberculosis, and other intra-abdominal inflammatory disorders such as Crohn's disease.

Uterine or Peritoneal Factors

The uterus plays a significant role in conception, implantation and pregnancy maintenance. Uterine anomalies affecting fertility include adhesions, polyps, submucosal fibroids and septae. These can be found in 9 to 15% of women with fertility issues [11].

Male Factor Infertility

The causes of male factor infertility can be divided into [23 24]:

- Pre-testicular
- Extra-testicular
- Testicular
- Post-testicular.

Pre-testicular

Pre-testicular causes include extra-gonadal endocrine disorders that originate in the hypothalamus, pituitary, or adrenals which have an adverse effect on spermatogenesis. Typically, the luteinizing hormone (LH) and follicular stimulating hormone (FSH) will be low, with low testosterone (unless in steroid abuse).

Examples of pre-testicular causes of infertility include:

- Hypothalamic disorders
- Pituitary disorders

- Brain tumours
- Radiation or surgery to brain
- Exogenous testosterone or anabolic steroids.

Extra-testicular

This encompasses issues with spermatogenesis caused by conditions unrelated to the reproductive organs or exposures to particular drugs or substances. In extra-testicular causes, FSH and testosterone are usually normal (although testosterone can be lower in obese men who may have a higher Oestradiol level).

Examples of extra-testicular causes of infertility include:

- Severe illness (e.g., malignancy)
- Obesity
- Medications
- Excessive alcohol consumption
- Cigarette use
- Recreational drugs (e.g., marijuana).

Testicular

Testicular causes typically occur due to damage to, or poor function of, the testicles. The FSH is usually high with low or normal testosterone.

Examples of testicular causes of infertility include:

- Testicular torsion
- Undescended testes
- Genetic disorders
- Primary testicular failure
- Scrotal trauma
- Varicocele
- Epididymitis
- Chemotherapy/radiotherapy.

Post-testicular

This includes conditions that affect the transport of the sperm and can be caused by genital tract blockage, erectile dysfunction or inability to ejaculate.

Examples of post-testicular causes of infertility include:

- Infection
- Vasectomy
- Congenital bilateral abnormality/absence of vas deferens
- Ejaculatory duct obstruction

- Spinal cord injury
- Pelvic surgery or injury
- Severe hypospadias.

Table 3: Hormonal profiles of different clinical scenarios – Male Infertility [24]

	Follicle-stimulating hormone (FSH)	Luteinising hormone (LH)	Testosterone	Prolactin
Pre-Testicular				
• **Hypogonadotropic hypogonadism**	↓	↓	↓	Normal or ↑
• **Prolactinoma**	Normal or ↓	Normal or ↓	↓	↑
Extra-Testicular	Normal	Normal	Normal or ↓	Normal
Testicular				
• **Testicular failure**	↑	↑	↓	Normal
• **Abnormal spermatogenesis**	↑	↑	↓	Normal
Post-testicular	Normal	Normal	Normal	Normal

Section 1: Organisation of Fertility Care in Ireland

Clinical Question 2.1: **How should the care of those with infertility be managed?**

Evidence Statement

The recommendations made in this section are guided by the Model of Care for Infertility along with expert consensus from those working in the field [25]. The National Model of Care for Infertility plan comprises of three stages, starting in primary care i.e., General Practitioners (GPs) and extending into secondary care i.e., Regional Fertility Hubs and then, where necessary, tertiary care i.e., IVF, and other advanced assisted human reproduction (AHR) treatments, with women/couples being referred onwards through structured pathways.

Clinical Practice

Regional fertility hubs should offer a range of treatments and interventions, including relevant blood tests, semen analysis, assessment of tubal patency, hysteroscopy, laparoscopy, fertility-related surgeries, ovulation induction and follicle tracking.

There are currently three stages of care in the National Model of Care for Infertility.

- Primary care i.e., GPs: this should be the first point of contact for couples with fertility concerns.
- Secondary care i.e., Regional Fertility Hubs: following initial consultation and investigation in a primary care setting, couples may be referred to their Regional Fertility Hub.
- Tertiary care i.e., IVF and other advanced AHR: these services are offered through private fertility clinics in Ireland at present, with government plans to create a publicly funded service.

Recommendation

1. **Women/couples seeking a fertility consultation should initially be reviewed in a primary care setting, ideally by their general practitioner (GP).**

Section 2: Investigation of Infertility

Clinical Question 2.2: **When should infertility investigations be commenced?**

Evidence Statement

These recommendations are largely derived from expert consensus, specifically from the NICE guideline 'Fertility problems: assessment and treatment", and adapted to the Irish context[21]. Overall, it has been estimated that 80% of couples will achieve a pregnancy within 12 months of trying to conceive provided the female partner is less than 40 years of age, they do not use contraception and have regular sexual intercourse. A decline in female fertility rates is reported after the age of 30 years and this decline is more prominent after the age of 35 years [26 27]. An age related decline in male fertility also occurs as a result of a decline in sperm quality and fertilising capacity [28]. Research suggests that these changes in men occur at approximately 30 to 35 years of age [29, 30].

Primary Varicella Zoster Virus (VZV) infection in pregnancy is uncommon; it is estimated to complicate three in every 1000 pregnancies [31]. Nevertheless, varicella may cause severe disease in susceptible pregnant women, fetal death or congenital varicella syndrome, characterised by limb hypoplasia, cutaneous scarring, ocular and central nervous system (CNS) anomalies [32]. Over 90% of the antenatal population in the UK and Ireland are seropositive for VZV IgG antibody [33, 34]. Varicella vaccine is 92% (95% CI 88-95%) effective in preventing severe disease after two doses [35 10].

10 Drew RJ, Barry R, Houlihan E, Cahill Ú, Farhan M, Gavin P, Geisler M, Knowles S, Lynch J, Lynch M, Ryan G. National Clinical Practice Guideline: Varicella in pregnancy. National Women and Infants Health Programme and The Institute of Obstetricians and Gynaecologists. 2023

Clinical Practice

Women/couples trying to conceive should be seen together at all fertility consultations.

Fertility investigations and referral to secondary or tertiary care should be offered to couples of reproductive age who have been trying to conceive for 12 months with no known underlying medical condition.

Following initial investigations at primary care level, couples should be appropriately referred onto secondary care in regional fertility hubs, or where deemed appropriate, to a tertiary fertility unit (eg. those who will require IVF/ICSI and do not meet criteria for public funding).

Earlier referral should be considered if the female is 36 years of age or older or there are underlying medical conditions that may affect reproduction in either intending parent.

Women/couples should be given information that explains that over 80% of couples in the general population will conceive within 1 year if:

- the woman is aged under 40 years
- they do not use contraception and have regular vaginal intercourse.

Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%).

All couples planning a pregnancy should have a detailed medical history taken and lifestyle optimisation should be discussed. In women with a current or past complex medical or psychiatric history, referral for pre-pregnancy counselling should be considered and initiated where appropriate.

All women planning to conceive and/or engaging with fertility services, should have their varicella status assessed as part of pre-conception counselling either by history or laboratory testing and those who are non-immune to should be offered varicella vaccination where possible.

Recommendation

2. Couples should be seen together at all fertility consultations. A thorough history and examination focusing on reproductive history factors and assessment of pregnancy related risks should be undertaken at first assessment and updated as required.
3. Investigations should be offered to couples of reproductive age who have been trying to conceive for 12 months or longer with no underlying medical condition.
4. Earlier referral to secondary or tertiary care should be considered after six months of trying to conceive to secondary or tertiary care if the female is 36 years of age or older or earlier if there is a known cause of infertility in either intending parent. Immediate referral should be considered if there is no possibility of conception without treatment.
5. All couples planning a pregnancy should have a detailed medical history taken and lifestyle optimisation should be discussed. In women with a complex medical or psychiatric history, referral for pre-pregnancy counselling should be considered and initiated where appropriate.
6. All women planning to conceive and/or engaging with fertility services, should have their varicella status assessed as part of pre-conception counselling either by history or laboratory testing and those who are non-immune should be offered varicella vaccination where possible.

Clinical Question 2.3: **What epidemiological factors should be considered in couples presenting with fertility concerns?**

Evidence Statement

These recommendations are largely derived from expert consensus, specifically from the NICE guideline [21] and ESHRE guidelines [36] on unexplained infertility, and adapted to the Irish context.

Couples should be reassured that approximately 80% will achieve a pregnancy within 12 months of trying to conceive provided the female partner is less than 40 years, they do not use contraception and have regular sexual intercourse. Of those that do not conceive in the first year, approximately half will go on to do so within the second year [21].

Rates of conception do not alter dramatically between couples who engage in sexual intercourse daily or every second day during their fertile window [37]. Women should be advised that predicating ovulation using basal body temperature is not accurate and therefore not advised [21].

Conception rates decline with increase in female age. Studies show that fertility rates fall sharply after the age of 35 years in females. Fertility is decreased by approximately 50% among women in their late thirties compared with women in their early twenties [21].

Vitamin D and folic acid are advised in pregnancy. Folic acid taken three months prior to conception and up to 12 weeks of pregnancy has been shown to reduce the risk of neural tube defects by 50-70%[38]. Low levels of vitamin D been linked to pregnancy complications including pre-eclampsia, gestational diabetes, preterm birth and small for gestational age [39, 40]. Sufficient levels of vitamin D have also been shown to increase pregnancy and livebirth rates when taken periconceptually [41].

Research suggests that women with a body mass index (BMI) over 30 kg/m^2 can take longer to conceive when compared to women with a BMI between 18.5 and 30 kg/m^2 [42]. In ART, research has shown that obesity is associated with lower oocyte responsiveness to stimulation and impaired oocyte quality [43]. In pregnancy, obesity has been linked to increased risk of miscarriage and adverse maternal and fetal outcomes [44]. Evidence demonstrates that it is important clinicians advocate for the best possible treatment and care for women with obesity suffering with infertility and involve this cohort of women in decision making when it comes to treatment options. [45 46]. Weight loss programmes including specialist dietary and exercise advise can help with weight loss and improve pregnancy rates[47].

In females, excessive exercise can lead to amenorrhea and irregular ovulation. [48] However, in moderation, exercise can increase insulin sensitivity and improve ovarian function [49]. Increased levels of fitness and psychological wellbeing in women who are overweight has been shown to improve ovulation and pregnancy rates [48]. In men, sperm parameters including morphology, motility, count and concentration were found to be improved in those who engaged in exercise for one hour at least three times a week [50].

Smoking as little as two cigarettes a day has been associated with a reduction in fertility and has been shown to significantly reduce the success rates of fertility treatments [21].

In men, smoking has also been shown to reduce sperm count, concentration, semen volume and negatively affect DNA fragmentation. Men should be advised to stop smoking if trying to conceive [21, 51]. Studies on smoking in females have shown that smoking reduces fertility rates by increasing the thickness of the zona pellucida making sperm penetration more difficult [52].

Excessive alcohol consumption can contribute to infertility and have detrimental effects on the developing fetus. In men, excessive consumption can lead to increased Oestrogen and decreased testosterone levels [52], increased oxidative stress, and morphological changes within testicular tissue which negatively affect semen quality [21, 53]. The HSE recommends that those who are pregnant or trying to conceive avoid alcohol intake [54].

Furthermore, anabolic steroids, recreational drugs (e.g. Marijuana) and exogenous testosterone can have detrimental effects on spermatogenesis and their use should be avoided in women/couples wishing to conceive[55]. The use of Cannabis in Ireland has been estimated at approximately 1.2% of the population [56]. Cannabis is known to reduce sperm concentration and motility. By disrupting capacitation Cannabis can have a significant negative effect of fertility [57]

Caffeine is a commonly known stimulant that can affect the reproductive system. An intake of over 500mg per day (or 5 cups per day) has been reported to delay conception by interrupting fertilisation and implantation [49]. High levels of caffeine consumption in pregnancy are also known to be associated with increased pregnancy complications and stillbirth [58]. Evidence as to a safe amount of caffeine during pregnancy is conflicting but would suggest that 200mg a day is considered a moderate amount for those who are trying to conceive or are pregnant [49].

Men with obesity and the metabolic syndrome should also be advised that these diagnoses can have deleterious effects on spermatogenesis, and parameters can be improved with treatment of these conditions [59].

Studies suggest there is an increased rate of depressive symptoms and major depression with fertility assessment and treatment, but the direction of causality is unclear [41]. Some studies found that depressive symptoms may have a negative effect on the success rate of fertility treatment [43]. It should also be noted that fertility treatment may independently influence mood through hormonal effects of treatment (e.g. Oestrogen and Progesterone).

The association between infertility and mental health problems is well established yet the direction of the association has been harder to describe. Nevertheless, the impact of poorly controlled mental health conditions on the fetus is unambiguous and consequently proactive psychological assessment and interventions are an essential part of fertility treatment [60].

Clinical Practice

Initial Advice

Couples wishing to conceive are often faced with many sources of advice, however, it can be of varying quality and may be conflicting in content. It is, therefore, important that the information they are given at initial consultation is based on the best available evidence.

Consultations should follow a woman centred practice approach with adequate time given to address a couple's questions and concerns.

Couples should be reassured regarding the high rates of spontaneous conception within 12 months of trying to conceive in women under forty years who do not use contraception and have regular sexual intercourse [37]. They should also receive information and education on timing of sexual intercourse and ways to increase success rates of conception.

Female Age

Women should be informed that the chances of achieving a pregnancy fall sharply after the age of 35 years and that despite regular menstruation, by age 40 years, the quality of the oocyte is reduced, and chances of conception fall to below 30% per year.

Frequency and Timing of Intercourse

Couples should be informed that women are most fertile on the day of ovulation and the five days leading up to it. Ovulation usually occurs two weeks before menstruation. Couples trying to conceive should be advised that sexual intercourse every two to three days during the first half of their cycle can help optimise a chance of pregnancy.

Various non-invasive methods exist to time ovulation

- Cycle tracking
- LH or Ovulation kits
- Change in consistency of cervical mucus

If couples are having very frequent intercourse (i.e. three times or more per week), there is no need to predict ovulation.

Couples should be advised that there is no evidence that any particular sexual positions increase or decrease the chance of pregnancy and that it is not necessary to stay lying down or elevate the pelvis after intercourse.

Diet and Supplementation

Couples should be informed of the number of widely available preparations available for pregnant women which are suitable for pre-conception use. They should contain the daily requirements of 400mcg of Folic acid and 10mcg of vitamin D.

Body Mass Index (BMI)

Women should be informed that a BMI between 18.5 and 25kg/m^2 is associated with the best chance of conceiving. Couples trying to conceive should be advised that women and men with a BMI over 30kg/m^2, may take longer to conceive. Women who are not ovulating, or have no cycle at all, may find that restoring their weight to the optimal range can restore ovulation and correct disturbances in their menstrual cycle. Healthcare professionals should be mindful that women with a lower BMI may have an underlying eating disorder and should be referred to their general practitioner or a specialist in this area as required.

Due to the reduction in fertility and risks associated with pregnancy with BMI ≥30kg/m^2, it is advisable that BMI is reduced prior to fertility treatment, ideally between 18.5 and 30 kg/m^2.

Men should be advised of the negative effects that obesity and the metabolic syndrome can have on spermatogenesis. Men should also be advised that parameters can be improved with treatment of these conditions.

Exercise

Regular moderate exercise such as walking or swimming three times weekly for thirty minutes is advised.

Smoking

Women should be informed that smoking as little as two cigarettes a day has been associated with a reduction in fertility and has been shown to significantly reduce the success rates of fertility treatments. Additionally, passive smoking may affect a woman's chance of conception. Women who smoke should be offered referral to smoking cessation services by their general practitioner. Men should also be advised to stop smoking as it can negatively affect sperm parameters and therefore reduce conception rates.

Alcohol

Women should be counselled that excess alcohol consumption can affect female fertility, as well as harming the developing fetus. Women should be advised to drink no more than one or two units of alcohol, no more than one or two times per week and avoid any episode of intoxication when trying to conceive and avoid alcohol completely during pregnancy. Men should be informed that excessive alcohol consumption can negatively affect semen quality. Fertility hubs should be able to provide information on alcohol services if this emerges as a major factor.

Caffeine

Women who are trying to conceive should be advised to limit their caffeine consumption to no more than two cups of coffee or equivalent caffeinated drinks per day before and during pregnancy. High levels of caffeine consumption have been associated with decreased rates of fertility.

Mental Health

Couples having difficulty trying to conceive should be supported with their mental health and referred for specialist input where required. Women may experience stigma and effects on their self-esteem. This can have a significant impact on their relationship. GPs can play an important role in support and monitoring of this.

Comprehensive screening of anxiety and depression is a key part of fertility treatment. This, as well as where indicated, other mental health difficulties including psychosis, eating disorders and personality based difficulties should occur at multiple stops along the way. This needs to be done in a manner that is supportive and not communicated as a potential barrier to receiving treatment.

Results from a recent meta-analysis suggest that depression and anxiety can impact negatively on ART outcomes and medications used in ART can increase symptoms of depression and anxiety[61-63]. It is important to continue any psychotropic medications with a good perinatal safety profile throughout ART to prevent relapse or deterioration during a vulnerable period of immense physiological and psychological stress.

Women/couples may be referred to Specialist Perinatal Mental Health Services for preconception counselling.

Table 4: General advice that can be provided to couples who are trying to conceive.

	Female	Male
Regular Intercourse	Every 2-3 days optimises the chance of pregnancy	
Alcohol	1 or 2 units once or twice per week. Avoid intoxication	3 to 4 units per day unlikely to affect semen quality
Smoking	Likely to reduce fertility (including passive smoking)	Can reduce semen quality
Caffeinated Beverages	Limit to no more than two cups of coffee or equivalent caffeinated drinks per day	
Obesity (BMI ≥ 30kg/m^2)	Likely to take longer to conceive. If associated with anovulation, losing weight is likely to increase chance of conception	Likely to have reduced fertility
Low BMI (< 18.5kg/m^2)	And irregular menstruation/ amenorrhoea, advise to increase BMI	
Tight Underwear		Association with elevated scrotal temperature and semen quality
Occupation	Some occupations involve exposure to hazards that can reduce male or fertility	
Prescribed, OTC and recreational drug use	A number of prescriptions, over-the-counter and recreational drugs interfere with male and female fertility e.g. NSAIDs – can inhibit ovulation, Cimetidine and sulphasalazine	

	Female	Male
Folic Acid Supplementation	Recommend supplementation with folic acid (0.4mg per day) pre-conception and up to 12 weeks gestation. High dose folic acid (5mg) is indicated in: previous history of neural tube defect, diabetes, obesity, taking anti-epileptic medication.	
Vitamin D Supplementation	Recommend supplementation with Vitamin D (10mcg/400IU daily) [41]	
Mental Health	Proactive management of mental health conditions and support with stress management	

Clinical Question 2.4: **What initial investigations should be performed for men?**

Evidence Statement

These recommendations are largely derived from expert consensus, specifically from the NICE guidelines along with the WHO laboratory manual for the examination and processing of human sperm and adapted to the Irish context [21, 64].

A semen analysis provides information about the quantity and quality of semen and sperm it contains. It is the most important test in the assessment of the man, but it does not determine a man's fertility. It is very important to get an adequate sample to ensure it is representative. The results of a semen analysis should be compared with WHO reference values. The normal values as per the WHO are presented in Table 5 [65].

Following routine investigations, imaging can be considered to assess testicular volume and morphology and may also provide evidence for possible causes of reversible azoospermia[66].

Table 5 Semen Analysis – World Health Organisation reference values [67]

Volume	≥ 1.4 mL
Sperm concentration	≥ 15 million/mL
Total sperm count	≥ 39 million
Total motility	≥ 42%
Progressive motility	≥ 30%
Vitality	≥ 54%
Normal morphology	≥ 4%

Two to seven days of abstinence is recommended from sexual intercourse prior to sampling. Shorter periods may have a negative impact on sperm count, whereas longer periods can affect motility. Collection of the sample should be made directly into a sterile container and analysis should be performed within one hour.

Clinical Practice

Semen Analysis

- In men with results within normal range (i.e. normal count, motility and morphology), a single test is sufficient.
- In the case of an initial sample with results outside of the normal range, a further sample should be offered at a three-month interval to allow time for a further cycle of spermatozoa to be completed.
- In cases with severe oligospermia or azoospermia a repeat sample should be sent earlier.

Table 6. Definition of terms describing abnormal semen

Azoospermia	No sperm present
Oligospermia	< 15 million/mL
Severe Oligospermia	< 5 million/mL
Asthenozoospermia	Absent or low motility
Teratozoospermia	Excess of abnormal forms

Other male investigations

Other investigations that may be indicated and requested by a fertility specialist in conjunction with an andrologist include:

1. Gonadotropins

Severe abnormalities in semen analysis results warrants further investigation to determine if the defect is a result of a primary testicular cause or outflow obstruction. Gonadotropins are used to differentiate between the two as follows:

- Obstructive: normal FSH and normal testosterone
- Failure of spermatogenesis: increased FSH and normal testosterone
- Complete testicular failure: increased FSH and decreased testosterone
- Hypogonadotropic hypogonadism: decreased FSH & decreased testosterone

2. Genetic testing

A karyotype is indicated if severe oligospermia (< 5 million/mL) or azoospermia. The most common abnormality identified is Klinefelter Syndrome or a paternal balanced translocation. Y chromosome microdeletion studies and cystic fibrosis (CF) carrier screening should be performed if severe oligospermia (< 5 million/mL) or azoospermia is found/diagnosed.

3. Testicular imaging

A testicular ultrasound may be useful to assess for testicular tumours, microlithiasis and small varicoceles. A transrectal ultrasound (TRUS) and MRI can be useful to investigate ejaculatory duct obstruction.

4. Testicular biopsy

This can indicate if any sperm are available for Intracytoplasmic sperm injection (ICSI).

Recommendation

7. **All men should have an initial semen analysis performed and compared with WHO reference values.**

Clinical Question 2.5: **What initial investigations should be performed for women?**

Evidence Statement

These recommendations are largely derived from expert consensus, specifically from the NICE guidelines, American society of reproductive medicine (ASRM), along with the WHO laboratory manual for the examination and processing of human sperm, and the ESHRE guideline on fertility preservation, and adapted to the Irish context [21 65, 68-70]

Female age is the most significant predictor of fertility[69]. Ovarian reserve testing should be employed to supplement counselling based on female age and as a predictor of ovarian response to stimulation as part of ART. When assessing ovarian reserve, Anti-Müllerian Hormone (AMH) is considered to be more sensitive than FSH, LH, inhibin or Oestradiol in determining ovarian reserve [68]. Both antral follicle count (AFC) and AMH are the two recommended tests for ovarian reserve testing as they have low intercycle variability and are readily available in most units [68, 71].

It is important to note that ovulation reserve tests (ORTs):

- Do not predict reproductive potential among women with unproven fertility
- Do not predict reproductive potential among women with infertility
- Do not predict pregnancy and live birth after in IVF
- Do predict oocyte yield after controlled ovarian stimulation for IVF

Pelvic Ultrasound

Ultrasound is a cost effective, efficient and minimally invasive imaging tool used in the diagnosis of many conditions which contribute to infertility; endometriosis, uterine abnormalities, tubal and ovarian pathology. Pelvic ultrasound can also be used to assess ovarian reserve [27, 36, 72]. It is best performed in the follicular phase, prior to ovulation with a high frequency transducer[72].

2D ultrasound remains the primary tool of investigation. The addition of 3D ultrasound however allows coronal imaging of the uterus increasing the accuracy in the diagnosis of congenital uterine anomalies [36, 72-75]. A prospective cohort study demonstrated an increase in accuracy of diagnosis of congenital uterine anomalies to >95% when using 3D-US from 82.9% with expert 2D- US [73]. A further prospective study of women with suspected congenital Mullerian abnormalities showed increased sensitivity and specificity of 3D-US vs 2D-US (sensitivity 94.7% and specificity 75% vs. 30.2% and 78.1%)[74]

Tubal patency test

The investigation of choice for tubal patency testing is based on the woman's clinical history.

Recent studies including a systematic review and meta-analysis have shown Hysterosalpingogram to be a safe and cost effective test to investigate tubal patency where no underlying pelvic pathology is suspected. Sensitivity of HSG was reported at 0.70 (95% CI 0.66- 0.74) and specificity 0.78 (95% CI 0.75-0.80)[76 77].

HyCoSy can also be considered where available and has a high level of sensitivity and specificity similar to that of HSG (0.86 (95% CI 0.80-0.91) and 0.94 (95% CI 0.90-0.96)) [78]. Hycosy can be performed immediately following a pelvic ultrasound and does not expose the patient to radiation.

Anti Müllerian Hormone (AMH)

Anti-Müllerian Hormone (AMH) is a substance produced by granulosa cells in the developing ovarian follicles and is thought to reflect the size of the remaining egg supply or 'ovarian reserve' [25].

AMH is gonadotropin independent and inversely related to the female age. It is more sensitive than FSH, so it often declines before changes are seen in FSH. It shows minimal variation both within and between cycles. It can, therefore, be tested on any day of the menstrual cycle [22].

Elevated AMH is predictive of an increased response to controlled ovulation hyperstimulation in ART and more eggs retrieved, while a low AMH is predictive of poor ovarian response [26,27].

For women attempting natural conception, AMH correlates poorly with fecundity [28]. AMH does not provide information about egg quality. It is also important to note that those with low AMH levels can still conceive if ovulating. Table 7 outlines factors to consider with high and low AMH levels.

Table 7: The effects of high and low AMH levels

High AMH	Low AMH
PCOS	Low number of eggs
Increased risk of OHSS	Often need more stimulation for success
	More urgency to move to IVF
	May require egg donation if very low

Follicular Stimulating Hormone (FSH)

Follicular Stimulating Hormone (FSH) is produced by the anterior pituitary and it is involved in the production of mature eggs in the ovaries. FSH levels should be measured in the early follicular phase (day 2-4) of the menstrual cycle, in addition to an Oestradiol level. It is an indirect marker of ovarian

reserve based on the feedback inhibition of pituitary FSH secretion.

Young ovaries only require a small amount of FSH for stimulation to make them work effectively. As women age, the ovaries become more resistant to FSH and therefore the pituitary needs to produce more FSH in order to stimulate the ovaries. However, sometimes despite the high levels of FSH produced, the ovaries cannot produce eggs. This is seen in menopause. From a fertility point of view, an FSH > 10 IU/L should indicate concern.

An FSH concentration of over 10 IU/L has a high specificity for poor ovarian response to ovarian hyperstimulation in women undergoing ART but is poorly sensitive. Sensitivity is even poorer for predicting conception. FSH levels demonstrate significant intra- and inter-cycle variation [22-24].

Thyroid Function Tests (TFT)

Thyroid dysfunction is commonly seen in women of reproductive age and is a known contributor of infertility, miscarriage and adverse obstetric and fetal outcomes [33-35].

Overt hyperthyroidism is often diagnosed and treated early due to clinical symptoms leading patients to seek medical advice. The focus of thyroid function testing is therefore targeted at patients with subclinical hypothyroidism (SCH) which is often left undiagnosed.

Subclinical hypothyroidism is defined as raised levels of serum TSH, above the accepted laboratory reference range, accompanied by normal concentrations of circulating thyroid hormones (free T4 and free T3) [79]. There is currently insufficient evidence to suggest SCH as a single causative factor of infertility [79]. Multiple studies have however shown increased rates of SCH in patients with infertility [80-82]. Increased levels of TSH have also been noted in IVF patients with fertilisation failure linking TSH with oocyte physiology[79, 83].

Current available evidence suggests that it is reasonable to test TSH in infertile women attempting pregnancy [36]. If the TSH is elevated over the non-pregnant laboratory reference range (typically >4mIU/L), women should be treated with levothyroxine to maintain levels <2.5mIU/L. The guidance is less clear if the TSH levels are between 2.5 and 4mIU/L. In these cases, management options include either monitoring levels and treating when TSH >4mIU/L or treating with levothyroxine to maintain TSH <2.5mIU/L [84]

Clinical Practice

Ovarian Reserve Testing

Ovarian reserve testing should be performed by measuring

- Antral Follicle Count
- Anti-Mullerian Hormone.

Ovarian reserve testing is related to fertility potential and estimated response to ovarian stimulation. Therefore, women should be evaluated on an individual basis prior to performing ovarian reserve testing.

Ovulation

In women with a regular menstrual cycle, tests to confirm ovulation are not routinely recommended. If confirmation is required in women with regular menstrual cycle, this can be done with mid-luteal Progesterone, urinary LH kits or a transvaginal ultrasound. In women who present with irregular menstrual cycles, serum gonadotropins should be investigated FSH and LH.

Pelvic Imaging

All women presenting with infertility should have a baseline pelvic ultrasound performed with a high frequency (5-8MHz) transducer, ideally in the first ten days of their cycle. This should include review of

- Ovaries and antral follicle count (AFC)
- Uterus and endometrial thickness and pattern
- Adnexae.

Thyroid Function Tests (TFTs)

A baseline thryoid stimulating hormone (TSH) should be considered in all women presenting with infertility.

Tubal patency testing

Women who are considered to have no underlying pelvic pathology following pelvic ultrasound should have a hysterosalpingogram (HSG) performed as first line investigation for tubal patency. Alternatively, depending on availability and access, Hysterosalpingo-Contrast Sonography (HyCoSy) can be performed as sensitivity and specificity are similar to HSG.

In cases where pelvic pathology is suspected, consideration should be given to laparoscopy and dye, and this allows for pelvic assessment and treatment if required. If endometrial pathology is suspected on ultrasound or imaging, an outpatient or inpatient hysteroscopy could be performed to evaluate and treat as required.

Further investigations

Women seeking to conceive should also have the following investigations performed:

- Rubella status to allow for vaccination where necessary
- Cervical screening in accordance with the national cervical screening programme guidance
- Chlamydia screening

It is not recommended to investigate prolactin levels unless in cases of ovulation disorders, galactorrhoea or suspected pituitary tumour or they are on medication that may increase prolactin (e.g. antipsychotics).

Table 8: Female Investigations Overview

Regular cycle	Confirm Ovulation	Irregular cycle
AMH	Urinary LH kit/Mid-luteal Progesterone/TVUS	Day 2-4 FSH+ LH
TSH		
Pelvic USS (+ AFC)		
Tubal patency (HSG/HyCoSy)		

Recommendation

8. In women with a regular menstrual cycle, tests to confirm ovulation are not routinely recommended.
9. If confirmation of ovulation is required in women with regular menstrual cycle, this can be done with mid-luteal Progesterone, urinary LH kits or a transvaginal ultrasound.
10. If ovulation cannot be confirmed, hormonal profile on Day 2-4 should be performed to include follicular stimulating hormone (FSH), Luteinizing Hormone (LH) and Oestradiol.
11. Ovarian reserve should be quantified using either Antral Follicle Count (AFC) and/or Anti-Müllerian Hormone (AMH).
12. Baseline transvaginal pelvic ultrasound with a high frequency (5-8MHz) transducer should be ideally performed in the first 10 days of cycle.
13. Tubal patency should be performed with Hysterosalpingogram (HSG) or Hysterosalpingo-Contrast-Sonography (HyCoSy) where no pelvic pathology is suspected.
14. It is reasonable to test thyroid stimulating hormone (TSH) in women presenting with infertility.

Section 3: Treatment of Infertility

Clinical Question 2.6: **What is the recommended treatment of couples with unexplained infertility?**

Evidence Statement

These recommendations are largely derived from expert consensus, specifically from the ESHRE guideline, NICE guideline, WHO classification of ovulation disorders and the Practice Committee Guideline of the ASRM subject to minor wording changes when adapting to the Irish context [21, 85-87].

Ovulation induction (OI) agents such as clomifene citrate and letrozole should not be offered to women with unexplained infertility as they are not considered to lead to a higher pregnancy success rate when compared to expectant management [21, 85]

A randomised control trial (RCT) including 385 patients with unexplained infertility showed a higher cumulative birth rate with expectant management 16% (26/167) when compared to clomifene citrate with timed intercourse 13% (23/173) [88].

A three arm RCT compared expectant management to clomifene citrate with timed intercourse and intrauterine insemination (IUI) in a natural cycle. Although not powered to compare the two treatment arms to each other, treatment with IUI resulted in a higher live birth rate compared to clomiphene citrate and timed intercourse[88].

Evidence shows that IUI in natural cycles is not significantly more effective than expectant management. A systematic review and meta-analysis showed higher live birth rates in IUI with stimulated cycles than in IUI with natural cycles (OR 2.07, 95% CI 1.22-3.50, 4 RCT, 396 women)[89]. IUI should therefore only be considered in stimulated cycles with normal sperm/mild male factor infertility.

A systematic review and meta-analysis comparing success rates of stimulated IUI cycles with IVF has shown higher live birth rates in IVF cycles compared to stimulated IUI cycles (RR 1.54, 95% CI 1.04-2.28, 7 RCT, 1391 women) with no significant difference in multiple pregnancy rates or OHSS[90].

International guidance suggests that women with premature ovarian insufficiency (POI) should be referred to a service with expertise in this area for a complete workup [70]. Following workup and counselling oocyte donation can be considered.

Clinical Practice

Ovulation induction should not be offered to women with regular menstrual cycles who are ovulating. Ovarian stimulation with IUI is recommended over expectant management in couples with unexplained infertility.

Recommendation

15. **Ovulation induction alone should not be offered to women with regular menstrual cycles who have proven ovulation.**
16. **Ovulation induction for women with unexplained infertility who have proven ovulation is not recommended.**
17. **IUI with ovarian stimulation should be considered first line treatment for couples with unexplained infertility.**

Clinical Question 2.7: **What are the treatment options for women with ovulation disorders?**

Evidence Statement

Ovulation Induction (OI)

The evidence to support this recommendation is largely derived from expert consensus, specifically from the ESHRE guideline, NICE guideline, WHO classification of ovulation disorders and the Practice Committee Guideline of the ASRM subject to minor changes when adapting to the Irish context [21, 85-87].

Aromatase inhibitors such as letrozole and anastrozole are effective as ovulation-inducing agents in women with ovulation disorders in the absence of hypogonadotropic hypogonadism[91]. A meta-analysis comparing letrozole with clomifene citrate found that letrozole led to higher ovulation rate per woman; pregnancy rate per woman; and live birth rate per woman with no difference in multiple pregnancy and miscarriage rates per woman [92]. Women should be advised about the potential side effects of aromatase inhibitors, this should include the mental health side effects.

Multiple pregnancy rates with clomifene citrate have been reported as high as 10%. Although multiple pregnancy rates are lower with aromatase inhibitors, ultrasound tracking of follicular growth is still recommended to avoid multiple pregnancy [21, 93].

In women with anovulatory PCOS, metformin can be used alone or in combination with a further ovulation induction agent. Metformin alone has been shown to increase the live birth rate, pregnancy rate and ovulation rate in women with PCOS [94-96]. A systematic review demonstrated that metformin combined with clomifene citrate showed increased pregnancy, livebirth and ovulation rate when compared to metformin alone[96].

The evidence on the use of gonadotrophins for women with anovulatory PCOS who have been unsuccessful with other first line ovulation induction treatments remains unclear [92].

There is insufficient evidence to support laparoscopic ovarian surgery over treatment with letrozole [97-99]. A RCT showed no difference in live birth rate, pregnancy rate, ovulation rate per woman or miscarriage rate per pregnancy with laparoscopic ovarian surgery compared to gonadotropins however multiple pregnancy rates were lower with gonadotropin use [100].

For women with POI, egg donation is the most successful option and pregnancy rates are not greatly affected by the age of the recipient [70]. ESHRE guidance specific can be referred to for clinical and ethical considerations regarding premature ovarian insufficiency [70].

Clinical Practice

Cycle preparation

For women with amenorrhea where ovulation induction is planned, Progesterone can be commenced for 7-10days to induce a withdrawal bleed (e.g. Provera 10mg daily, Primolut-N 5 mg three times a day or Duphaston 10mg three times a day). Women commencing Progesterone should be advised only to do so following two weeks of protected sexual intercourse or abstinence and a negative home pregnancy test. Women should be advised about the potential side effects of Progesterone, in particular this should include the mental health side effects.

Where considerable or ongoing intermenstrual bleeding is noted, consideration must be given to further investigations prior to OI to out rule further pathology e.g. cervical or endometrial pathology.

Choice of medication

Medication	Dose	Dose Increase	Maximum Dose	Instructions
Letrozole	2.5-5mg OD	2.5mg OD	7.5mg OD	• Commenced on Day 2 to Day 6 for a total of 5 days. • Aim for 3-6 ovulatory cycles .
Clomifene Citrate	25-50mg OD	25mg OD	100mg OD	• Second line treatment. • Commenced on Day 2 to Day 6 for a total of 5 days. • Aim for 3-6 ovulatory cycles. • Higher rate of multiple pregnancy than Letrozole.
Metformin	500mg TDS or 850mg BD			• Not as effective as other OI agents. • Less risk of multiples and does not require ultrasound monitoring. • Monitored based on ovulatory cycles and can take up to 6 weeks.

- An ovulation trigger can be considered in OI cycles with oral agents.
- If there is no ovulation despite initial therapy, consider gonadotropins (Follicular Stimulating Hormone (FSH) +/- Luteinising Hormone (LH)) with an ovulation trigger. Consideration could be given to laparoscopic ovarian drilling for refractory anovulatory PCOS.
- Assisted reproduction may be required for refractory anovulatory PCOS.

Ultrasound tracking

- Baseline ultrasound is not required at cycle commencement for uncomplicated OI cycles.
- At least two cycles of ovulation induction with oral agents should be tracked with ultrasound scanning.
- All cycles of ovulation induction with FSH +/- LH should be tracked with ultrasound scanning.
- Ultrasound is recommended once between day seven to twelve to monitor follicular response initially and follow up decided upon on an individualised basis taking into account previous cycle history and size of the leading follicle. The endometrial thickness and pattern should be assessed at the same time.
- Follicular growth is approximately 1 to 1.5mm per day.
- Cancellation should be advised in cases of failure to respond (anovulation) or follicular overresponse (≥3 each average diameter ≥ 14 mm)
- In cases of cancellation due to overresponse, strict instructions regarding protected sexual intercourse until the next cycle must be given to couples in order to avoid complications. A cancellation agreement should be signed detailing that advice on abstinence and information on potential risks was discussed with the woman or couple.

Recommendation

18. Women with anovulatory polycystic ovary syndrome (PCOS) should be offered treatment with Letrozole as first line treatment.
19. At least two cycles of ovulation induction with oral agents should be tracked with ultrasound scanning.
20. If there is no ovulation despite initial therapy, gonadotropins may be considered +/- laparoscopic ovarian drilling.
21. Assisted reproduction may be required for refractory anovulatory PCOS.
22. Disorders of ovulation that are not secondary to PCOS, or associated with low Oestrogen will not respond to oral ovulation induction (OI) and should be managed with the appropriate form of ovulation induction – e.g. gonadotrophins or GnRH pump
23. Women with premature ovarian insufficiency should be referred to a dedicated multidisciplinary clinic.
24. Oocyte donation can be considered in women with premature ovarian insufficiency following specialist workup and counselling.

Clinical Question 2.8: **When should Intrauterine Insemination (IUI) be offered?**

Evidence Statement

The evidence to support this recommendation is largely derived from expert consensus, specifically from the ESHRE Guideline on Unexplained Infertility[36] and the Practice Committee Guideline of the ASRM subject to minor changes when adapting to the Irish context [21, 85].

Evidence shows that IUI in natural cycles is not significantly more effective that expectant management. A systematic review and meta-analysis showed higher live birth rates in IUI with stimulated cycles than in IUI with natural cycles (OR 2.07, 95% CI 1.22-3.50, 4 RCT, 396 women)[89]. IUI should therefore only be considered in stimulated cycles.

IUI can also be considered in cases of mild male factor infertility. Studies assessing male factor infertility and IUI success rates show significant increase in positive pregnancy rates following IUI based on total motile sperm count (TMSC). Increased positive IUI cycles were noted in men with a TMSC over 5-10 million [101-103].

Clinical Practice

IUI should be offered in the following circumstances:

- Cycles requiring donor sperm treatment (e.g., same sex female couples/ single women)
- Cycles requiring sperm preparation (e.g., sperm washing for infectious diseases)
- Where vaginal intercourse is not possible due to a physical or psychosexual cause
- Heterosexual couples with unexplained infertility
- Cervical factor infertility.

IUI should be considered in the following circumstances:

- Heterosexual couples with mild male factor infertility where the total motile sperm count is 5 million.
- Stage I/II endometriosis
- Mild tubal disease
- Ovulation induction women with confirmed ovulation on treatment and an additional fertility factor.

Ultrasound tracking

- All IUI cycles should be tracked with ultrasound scanning.
- Baseline ultrasound is not required at cycle commencement for uncomplicated IUI cycles.
- Ultrasound is recommended once between day seven to ten to monitor follicular response initially and follow up decided upon on an individualised basis taking into account previous cycle history size of the leading follicle. The endometrial thickness and pattern should be assessed at the same time.
- Follicular growth is approximately 1 to 1.5mm per day.
- Cancellation should be advised in cases of failure to respond (anovulation) or follicular over response (≥3 each average diameter ≥ 14 mm)
- In cases of cancellation due to overresponse, strict instructions regarding protected sexual intercourse until the next cycle must be given to couple in order to avoid complication and a cancellation agreement signed.
- Letrozole: Starting dose of 2.5-5mg with dose increases by 2.5mg to 7.5mg if inadequate response.
- Clomifene citrate: 25-50mg with dose increases by 25mg to a maximum of 100mgif inadequate response.
- Letrozole/Clomifene citrate is commenced on day two to day six for a total of 5 days.
- Ovulation trigger (e.g., Ovitrelle 250mcg or equivalent) should be given if at least one follicle >17 mm to help time IUI unless positive LH prior to same if performing LH kits.

Timing of IUI

IUI should be scheduled:

- approximately 24 hours after LH positive urine if performed
- between 0 and 36 hours following an ovulation trigger.

Recommendation

25. Intrauterine Insemination (IUI) should be offered to heterosexual couples with unexplained infertility, psychosexual disorders (e.g. vaginismus or dyspareunia) or cervical factor who meet defined eligibility criteria.
26. IUI should be offered to all couples/women planning treatment with donor sperm who meet defined eligibility criteria.
27. IUI should be considered for heterosexual couples with; mild male factor, stage I/II endometriosis, mild tubal disease or for women with confirmed ovulation following ovulation induction.
28. IUI should only be considered in stimulated cycles.
29. All IUI cycles should be monitored ultrasound tracking.
30. IUI should be scheduled approximately 24 hours after LH positive urine if performed or between 0 and 36 hours following an ovulation trigger.

Clinical Question 2.9: **When should referral to a tertiary care unit be considered?**

Irish tertiary fertility clinics offer a comprehensive array of treatments including IVF, ICSI, preimplantation genetic testing (PGT), donor treatments and fertility preservation. All fertility clinics in Ireland currently operate within the private sector, however the Model of Care for Infertility includes plans to make tertiary services available publicly.

Referral to a tertiary fertility clinic should be considered for the following:

- Abnormal semen analysis
- Diminished ovarian reserve
- Anovulatory disorders with failed OI/IUI
- Pelvic pathologies including moderate-severe endometriosis
- Donor gamete
- Fertility preservation
- Surrogacy
- Unexplained infertility

Recommendation

31. Referral to a tertiary fertility clinic should be considered for: women with very low ovarian reserve, 36 years of age or older, unexplained infertility, unsuccessful ovulation induction treatment and/or intrauterine insemination (IUI), donor gamete, fertility preservation and severe male factor infertility.

Section 4: Patient Centred Supportive Care

Clinical Question 2.10: **What information and supportive care should be provided to couples regarding mental health and infertility?**

Evidence Statement

The psychological impact of infertility is a major burden for many couples and their families. Infertility has been associated with increased rates of depression and anxiety and can lead to dysfunction in sexual relationships and identity problems [4, 5]. The effects of infertility can be long lasting and it is known that those who continue to desire a pregnancy three to five years following unsuccessful infertility treatment are more likely to suffer with increased rates of anxiety and depression when compared to those who managed to refocus their life-goals [6]. Even in the population that go on to achieve a successful pregnancy, increased anxiety levels are common following multiple ART cycles or stressful treatment phases [7].

Clinical Practice

Women/couples should be provided with written information on clinical and psychological aspects of infertility. Access to a specialist fertility nurse or counsellor should be available to provide support and further information for women/couples. Where required, women should be referred to their GP for psychological assessment and support and onward referral where warranted. In instances where psychotropic medication is being used, input from a psychiatrist with specialist expertise in this area is recommended.

Support Groups that may be of help include:

- Fertility Ireland
- National Infertility Support & Information Group (NISIG)
- The Human Fertilisation & Embryology Authority – UK
- The Endometriosis Society of Ireland
- https://pregnancyandinfantloss.ie/

Recommendation

32. **All couples should be provided with information and access point for supportive care during their first contact with a fertility specialist including information on fertility counselling and support groups.**

Chapter 3: Development Of Clinical Practice Guideline

3.1 Literature search strategy

A comprehensive literature review was undertaken which included national and international publications. PUBMED MEDLINE and Cochrane Library were searched using terms related to infertility including 'unexplained infertility', 'fertility investigations', 'reproductive endocrinology' and 'male infertility' between November 2022 and March 2023. Searches were limited to humans and English language articles. Date of publication was considered however no limit was set. Guidelines from other national and international professional bodies including the British Fertility Society, The European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine were also analysed.

3.2 Appraisal of evidence

Following a comprehensive literature review the quality, validity and relevance of the evidence gathered were critically appraised by the Guideline developers under the following headings:

- Study design
- Relevance of primary and secondary outcomes
- Consistency of results across studies
- Magnitude of benefit versus magnitude of harm
- Applicability to practice context

A number of evidence-based recommendations for Fertility: Investigation and Management were agreed upon. They have been adapted to reflect care in the Irish healthcare setting.

3.3 AGREE II process

While being developed, the Guideline was assessed using the AGREE II checklist (Appendix 3) as recommended by the Department of Health in the 'How to Develop a National Clinical Guideline: a manual for Guideline developers', 2019[11].

The purpose of AGREE II is to provide a framework to:

1. Assess the quality of guidelines;
2. Provide a methodological strategy for the development of guidelines; and
3. Inform what information and how information ought to be reported in guidelines

11 Department of Health (2019). How to develop a National Clinical Guideline. Available at: https://www.gov.ie/en/collection/cd41ac-clinical-effectiveness-resources-and-learning/

3.4 Literature review

Details of supportive evidence based literature for this Guideline are reported in chapter two.

A comprehensive review of guidelines was undertaken and appraisal of the selected guidelines was done by LS, DC, DOL and MB. A secondary review of the literature was also undertaken by LS, DC, DOL and MB and evidence was appraised according to study design, study sample size, methodology, primary and secondary outcomes as well as applicability and relevance.

In the Guideline, the evidence to support the association of various factors with infertility is provided. Updated evidence pertaining to individual investigations and treatments is presented in each section, alongside the adapted recommendations from the international guidance. However, to minimise overlap, not all original evidence supporting every recommendation for each investigation and treatment is presented here but is present within the guidelines of origin.

3.5 Grades of recommendation

GRADE offers a transparent and structured process for developing and presenting evidence summaries and for carrying out the steps involved in developing recommendations. While we acknowledge that for this particular work an extensive GRADE approach is not possible, we have used the suggested language set out in the GRADE table when making recommendations.[12] (Appendix 4)

3.6 Future research

An important outcome of the Guideline development process is in highlighting gaps in the evidence base.

Some suggested topics in this broad area include:

- RCT on Adjuvant therapies in IVF
- Risk of Congenital Anomalies with OI/IVF/ICSI
- Obstetric Outcomes in ART pregnancies in Ireland
- Long term cancer risks in ART conceived infants.

12 SMFM adopts GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for clinical guidelines. Society for Maternal-Fetal Medicine (SMFM), Chauhan SP, Blackwell SC. Am J Obstet Gynecol. 2013 Sep;209(3):163-5. doi: 10.1016/j.ajog.2013.07.012. PMID: 23978245 https://pubmed.ncbi.nlm.nih.gov/23978245/

Chapter 4: Governance and Approval

4.1 Formal governance arrangements

This Guideline was written by the Guideline Developers under the direction of the Guideline Programme Team. An Expert Advisory Group was formed to review the Guideline prior to submission for final approval with the National Women and Infants Health Programme. The roles and responsibilities of the members of each group and their process were clearly outlined and agreed.

4.2 Guideline development standards

This Guideline was developed by the Guideline Developer Group (GDG) within the overall template of the HSE National Framework[13] for developing Policies, Procedures, Protocols and Guidelines (2016) (Appendix 5) and under supervision of the Guideline Programme Team (GPT).

A review was conducted by a group of experts, specialists and advocates (the EAG) prior to approval by the Clinical Advisory Group (CAG) of the National Women and Infants Health Programme (NWIHP) with final sign off for publication by CAG Co-Chairs, the Clinical Director of NWIHP and the Chair of the IOG. See Appendix 6 for list of CAG members.

13 Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/use-of-improvement-methods/nationalframeworkdevelopingpolicies/

Chapter 5: Communication and Dissemination

A communication and dissemination plan for this Guideline has been developed by the GPT and endorsed by NWIHP.

Effective ongoing clear communication is essential in explaining why the Guideline is necessary and securing continued buy-in. It provides an opportunity to instil motivation within staff, helps overcome resistance to change and gives an opportunity for feedback[14].

The Clinical Guideline will be circulated and disseminated through the Guideline Programme Team as well as through the professional networks who participated in developing and reviewing the document.

Senior management within the maternity hospital/units are responsible for the appropriate dissemination of new and updated guidelines. Local hospital groups including Guideline committees are also instrumental in the circulation of new and updated Guidelines and promoting their use in the relevant clinical settings.

The HSE will make this Guideline available to all employees through standards networks as well as storing it in the online PPPG repository. Electronic versions available on the NWIHP https://www.hse.ie/eng/about/who/acute-hospitals-division/woman-infants/clinical-guidelines/ and RCPI websites https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology/ and other communication means can be used to maximise distribution. The NWIHP website will also provide a training webinar introducing each Guideline and where relevant a downloadable version of the recommended algorithm will be available.

14 Department of Health (2018). NCEC Implementation Guide and Toolkit. Available at: https://health.gov.ie/national-patient-safety-office/ncec/

Chapter 6: Implementation

6.1 Implementation plan

Implementation was considered at the beginning, and throughout the Guideline development process. The local multidisciplinary clinical team, senior executive and clinical management in each maternity and gynaecology unit are ultimately responsible for the appropriate structured adoption and implementation of the Guidelines within their area of responsibility. They must ensure that all relevant personnel under their supervision have read and understood the Guideline and monitor both its effectiveness and adoption.

Within each site, local multidisciplinary teams are responsible for the clinical implementation of Guideline recommendations and ensuring that their local clinical practices and processes reflect and are aligned with the Guideline recommendations.

In the case of this Guideline the following have been put in place to help facilitate the implementation of this Guideline.

- Quick Summary Document (QSD) for clinical staff (includes key recommendations, auditable standards, algorithms and recommended reading)
- Clinical Guideline mobile application
- Plain language summary

6.2 Education plans required to implement the Guideline

It is acknowledged that this Guideline should be complemented by ongoing education, training and assessment where required.

This Guideline education plan could include:

- Formal launch of the Guideline
- Presentation at local levels
- Use of summary documents and algorithms
- Awareness campaign through relevant media including websites attached to regional fertility hubs.

6.3 Barriers and facilitators

To ensure successful implementation of guidelines, it is first necessary to look at potential barriers and facilitators. Taking these into account when developing the implementation plan should improve levels of support from relevant users. (DOH 2018, 2019)

Barriers may be categorised as internal (specific to the Guideline itself) or external (specific to the clinical environment).

The Guideline Development Group has aimed to address any internal barriers during the development of this Guideline.

Potential external barriers include:

- Structural factors (e.g. budget or service redesign)
- Organisational factors (e.g. lack of facilities or equipment)
- Individual factors (e.g. knowledge, skills, training)
- Patient perceptions

In the case of this Guideline it will be necessary to examine possible barriers and consider implementation strategies to address them. By example, this may include discussion with relevant management groups with regards budgetary impact or providing training to the relevant staff.

Findings from the GDG highlight variation in practices nationally, with gynaecology and fertility clinics using a range of international guidelines, with some having adapted/adopted their own guidelines locally. The need to support champions (locally/regionally/nationally), provide resources (suitably trained staff, facilities, access to laboratories, timely access to genetic counselling), and highlight the evidence to support practice changes were identified facilitators and should be addressed as part of Guideline implementation.

6.4 Resources necessary to implement recommendations

The implementation of this Guideline should be undertaken as part of the quality improvement of each hospital. Hospitals should review existing service provision against this Guideline, identifying necessary resources required to implement the recommendations in this Guideline.

In the case of this Guideline, funding has been provided by government in setting up regional fertility hubs. These hubs however require staff recruitment and training. Consideration may also need to be given to increasing awareness and education of those in primary and secondary care regarding the referral pathway and criteria and initial investigations for fertility patients. An increase in publicly available andrology services nationally to facilitate male investigations is also required. Currently andrology services are predominantly within the remit of private fertility services and developing public services would require significant resources, including capital investment for laboratories and the recruitment of skilled staff.

Specialist mental health services will be needed to be developed with the fertility services. An expert by experience group will need to be developed to further enhance the services.

A further guideline which will discuss artificial reproductive treatment is planned to supplement this Guideline.

Chapter 7: Audit and Evaluation

7.1 Introduction to audit

It is important that both implementation of the Guideline and its influence on outcomes are audited to ensure that this Guideline positively impacts on the woman's care. Institutions and health professionals are encouraged to develop and undertake regular audits of Guideline implementation. Personnel tasked with the job of conducting the audit should be identified on receipt of the most recent version of the Guideline.

7.2 Auditable standards

Audit using the key recommendations as indicators should be undertaken to identify where improvements are required and to enable changes as necessary. Audit should also be undertaken to provide evidence of continuous quality improvement initiatives.

Auditable standards for this Guideline include:

1. Percentage of referrals seen within 6 months of GP referral
2. Spontaneous pregnancy rates following conservative management
3. Pregnancy success rates (Implantation and Clinical Pregnancy) as defined by ICMART for ovulation induction services
4. Pregnancy success rates (Implantation and Clinical Pregnancy) as defined by ICMART for IUI services
5. Percentage of couples referred onward for IVF and ICSI
6. Numbers of onward referrals to Urologist or Andrologist
7. Numbers of onward referrals for reproductive surgery
8. Spontaneous pregnancy rates following reproductive surgery

7.3 Evaluation

Evaluation is defined as a formal process to determine the extent to which the planned or desired outcomes of an intervention are achieved [15]. Implementation of this Guideline will be audited periodically at national level, with standards for this set by NWIHP. Evaluation of the auditable standards should also be undertaken locally by senior hospital clinical management to support implementation.

15 Health Information Quality Authority (2012). National Standards for Safer Better Healthcare [Internet]. Available from: https://www.hiqa.ie/reports-and-publications/standard/national-standards-safer-better-healthcare

Chapter 8: Revision Plan

8.1 Procedure for the update of the Guideline

It may be a requirement to amend, update or revise this Guideline as new evidence emerges. This Guideline will be reviewed at national level every three years, or earlier if circumstances require it, and updated accordingly.[16]

The Guideline Development Group will be asked to review the literature and recent evidence to determine if changes are to be made to the existing Guideline. If the Guideline Development Group are unavailable, the GPT along with the NWIHP senior management team will select a suitable expert to replace them.

If there are no amendments required to the Guideline following the revision date, the detail on the revision tracking box must still be updated which will be a new version number and date.

The recommendations set out in this Guideline remain valid until a review has been completed.

8.2 Method for amending the Guideline

As new evidence become available it is inevitable that Guideline recommendations will fall behind current evidence based clinical practice. It is essential that clinical guidelines are reviewed and updated with new evidence as it becomes available.

In order to request a review of this Guideline one of the following criteria must be met:

a) 3 years since the Guideline was published

b) 3 years since last review was conducted

c) Update required as a result of new evidence

Correspondence requesting a review of the Guideline be submitted to the National Women and Infants Health Programme. Any such requests should be dealt with in a timely manner.

16 Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

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Glossary
(for the Purpose of this Guideline)

AFC Antral Follicle Count
AHR Assisted human reproduction
AMH Anti-Müllerian Hormone
ART Assisted reproductive therapy
ASRM American society of reproductive medicine
BMI Body mass index
CF Cystic fibrosis
DNA Deoxyribonucleic acid
EIM European Invitro Fertilisation Monitoring
ESHRE The European Society of Human Reproduction and Embryology
FSH Follicular Stimulating Hormone
GPs General Practitioners
HSG Hysterosalpingogram
HyCoSy Hysterosalpingo-Contrast Sonography
ICMART International Committee for Monitoring Assisted Reproductive Technologies
ICSI Intracytoplasmic sperm injection
IUI Intrauterine insemination
IVF In vitro fertilisation
LH Luteinizing Hormone
MRI Magnetic resonance imaging
OI Ovulation induction
ORTs Ovulation reserve tests
PCOS Polycystic Ovary Syndrome
PGT Preimplantation Genetic Testing
POI Premature Ovarian Insufficiency
RCT Randomised control trial
STI Sexually transmitted infection
TFTs Thyroid function tests
TMSC Total motile sperm count
TRUS Transrectal ultrasound
TSH Thyroid stimulating hormone
USS Ultrasound scan
VZV Varicella Zoster Virus
WHO World Health Organisation

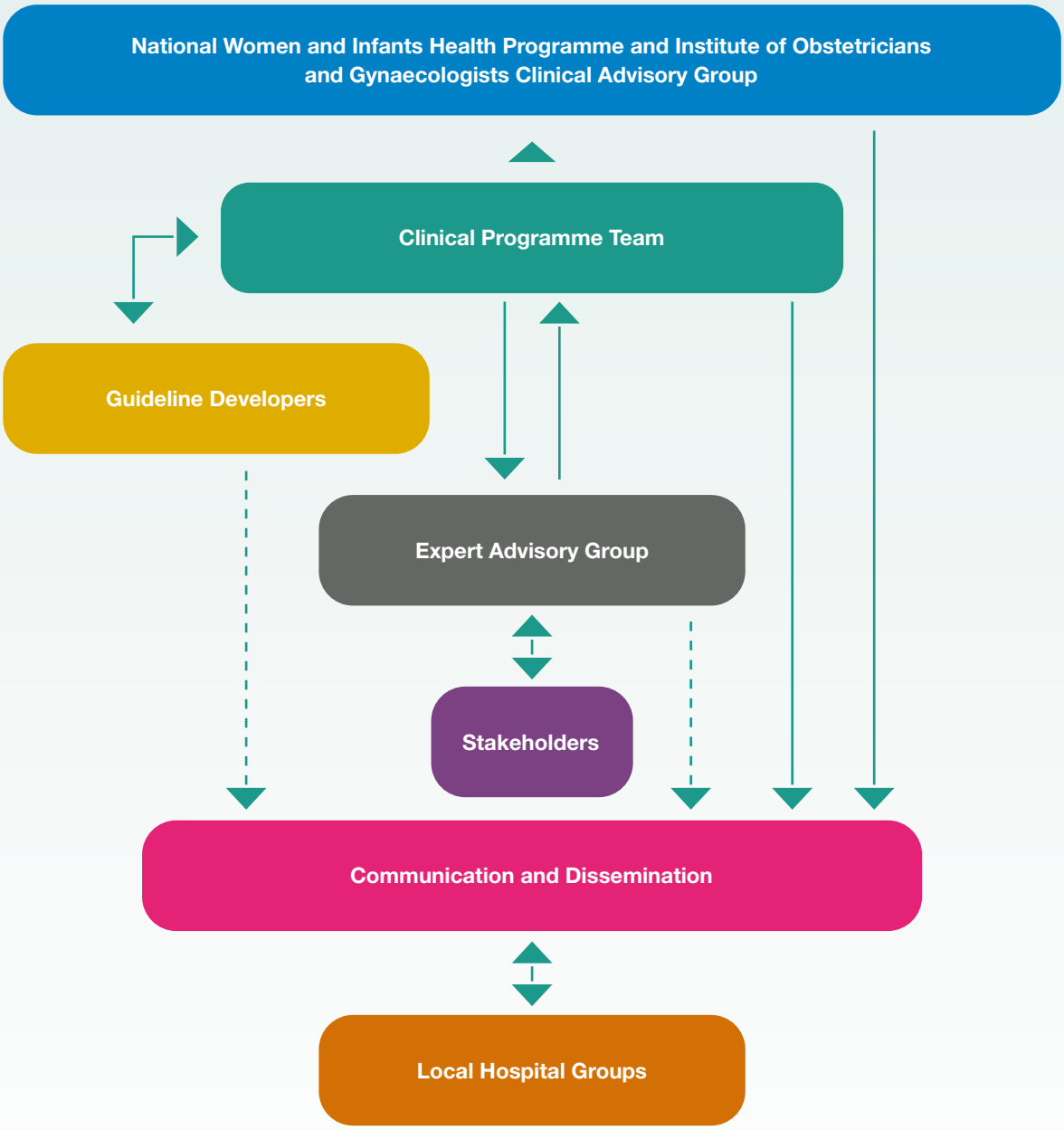
Appendix 1: Expert Advisory Group Members 2021-

Attendee	Profession	Location (2021)
Dr Fergus McCarthy	Consultant Obstetrician, Gynaecologist, Senior Lecturer and Maternal-Fetal Medicine Sub-specialist	Cork University Maternity Hospital, University College Cork
Dr Mairead Butler	Consultant Obstetrician and Gynaecologist	University Hospital Waterford
Prof Declan Keane	Professor of Obstetrics and Gynaecology	National Maternity Hospital Dublin, Royal College of Surgeons in Ireland
Dr Katherine Astbury	Consultant Obstetrician and Gynaecologist Gynaecology Oncology Sub-specialist	University Hospital Galway
Dr Sarah Petch	Specialist Registrar, Obstetrics and Gynaecology	National Maternity Hospital Dublin
Dr Orla Donohoe	Specialist Registrar, Obstetrics and Gynaecology	Sligo University Hospital
Prof John Murphy	Consultant Neonatologist and Clinical Lead for the National Clinical Programme for Paediatrics and Neonatology	National Women and Infants Health Programme
Ms Siobhan Canny	Group Director of Midwifery	Saolta University Health Care Group
Ms Fiona Hanrahan	Director of Midwifery and Nursing	Rotunda Hospital Dublin
Ms Margaret Quigley	National Lead for Midwifery	Office of Nursing and Midwifery Services Director
Prof Valerie Smith	Professor of Midwifery	School of Nursing and Midwifery, Trinity College Dublin
Ms Triona Cowman	Director of the Centre for Midwifery Education	Centre for Midwifery Education, Coombe Women and Infants University Hospital
Ms Janet Murphy	Advanced Midwifery Practitioner	University Hospital Waterford
Dr Ciara McCarthy	General Practitioner and ICGP Women's Health Lead	Irish College of General Practitioners

Attendee	Profession	Location (2021)
Mr Fergal O' Shaughnessy And Dr Brian Cleary *(Shared nomination)*	Senior Pharmacist, Honorary Lecturer And Chief Pharmacist, Honorary Clinical Associate Professor and Medications Lead, Maternal and Newborn Clinical Management System	Rotunda Hospital Dublin Royal College of Surgeons in Ireland
Ms Marie Finn	Medical Social Work Counsellor	Saolta University Health Care Group
Ms Marie Culliton	Scientific Lead	National Clinical Programme for Pathology
Ms Marita Hennessy	Post-Doctoral Researcher	Pregnancy Loss Research Group, INFANT Centre, University College Cork
Ms Niamh Connolly-Coyne And Ms Mandy Daly *(Shared nomination)*	Board of Directors	Irish Neonatal Health Alliance
Ms Caroline Joyce	Principal Clinical Biochemist PhD Candidate	Cork University Hospital University College Cork
Dr Richard Duffy	Consultant Perinatal Psychiatrist	Rotunda Hospital Dublin
Ms Clare Farrell	Physiotherapy Manager	Coombe Women and Infants University Hospital
Ms Fiona Dunlevy And Ms Sinéad Curran *(Shared nomination)*	Dietician Manager	Coombe Women and Infants University Hospital National Maternity Hospital
Dr Nicholas Barrett	Lead for Obstetric Anaesthesiology services	Limerick University Hospital
Dr Brendan Fitzgerald	Consultant Perinatal Pathologist	Cork University Hospital
Dr Niamh Conlon	Consultant Histopathologist	Cork University Hospital
Ms Georgina Cruise	Service Manager	Patient Advocacy Ireland

Appendix 2: Guideline Programme Process

Guideline Programme Process



Appendix 3: Agree II Checklist[17]

AGREE Reporting Checklist 2016

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☐ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☐ Target(s) (e.g., patient population, society)	
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☐ Target population ☐ Intervention(s) or exposure(s) ☐ Comparisons (if appropriate) ☐ Outcome(s) ☐ Health care setting or context	
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☐ Target population, sex and age ☐ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/ rating the evidence and individuals involved in formulating the final recommendations.*	☐ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☐ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☐ A description of the member's role in the guideline development group	

17 AGREE Reporting Checklist is available on the AGREE Enterprise website, a free and open access resource to support the practice guideline field (www.agreetrust.org).

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☐ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☐ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☐ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☐ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☐ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☐ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix)	
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☐ Target population (patient, public, etc.) characteristics ☐ Study design ☐ Comparisons (if relevant) ☐ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
9. STRENGTHS AND LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☐ Study design(s) included in body of evidence ☐ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☐ Appropriateness/relevance of primary and secondary outcomes considered ☐ Consistency of results across studies ☐ Direction of results across studies ☐ Magnitude of benefit versus magnitude of harm ☐ Applicability to practice context	
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☐ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☐ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ Recommendations reflect considerations of both benefits and harms/side effects/risks	
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☐ How the guideline development group linked and used the evidence to inform recommendations ☐ Link between each recommendation and key evidence (text description and/or reference list) ☐ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☐ A statement that the guideline will be updated ☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☐ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☐ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☐ Description of management options ☐ Population or clinical situation most appropriate to each option	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☐ Specific recommendations grouped together in one section	
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☐ Types of facilitators and barriers that were considered ☐ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☐ How the information influenced the guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☐ Additional materials to support the implementation of the guideline in practice. For example: ☐ Guideline summary documents ☐ Links to check lists, algorithms ☐ Links to how-to manuals ☐ Solutions linked to barrier analysis (see Item 18) ☐ Tools to capitalize on guideline facilitators (see Item 18) ☐ Outcome of pilot test and lessons learned	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☐ Criteria to assess guideline implementation or adherence to recommendations ☐ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the guideline	
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☐ Types of competing interests considered ☐ Methods by which potential competing interests were sought ☐ A description of the competing interests ☐ How the competing interests influenced the guideline process and development of recommendations	

From: Brouwers MC, Kerkvliet K, Spithoff K, on behalf of the AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ 2016;352:i1152. doi: 10.1136/bmj.i1152.

For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at http://www.agreetrust.org.

Appendix 4: Grade of Recommendations[18]

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
1A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk	Strong recommendations can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present	We strongly recommend… We recommend that …should be performed/ administered… We recommend that …. is indicated/ beneficial/ effective…

18 SMFM adopts GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for clinical guidelines. Society for Maternal-Fetal Medicine (SMFM), Chauhan SP, Blackwell SC. Am J Obstet Gynecol. 2013 Sep;209(3):163-5. https://pubmed.ncbi.nlm.nih.gov/23978245/

1B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate	Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present	We recommend… We recommend that … should be performed/ administered… We recommend that … is (usually) indicated/ beneficial/ effective…
1C. Strong recommendation, low-quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality	We recommend… We recommend that … should be performed/ administered… We recommend that … Is (maybe) indicated/ beneficial/ effective…
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk	Weak recommendation: best action may differ depending on circumstances or patients or societal values	We suggest… We suggest that… may/might be reasonable...

2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances	We suggest… We suggest that … may/might be reasonable...
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain	Very weak recommendation: other alternatives may be equally reasonable	We suggest … is an option We suggest that … may/might be reasonable.
Best practice	A recommendation that is sufficiently obvious that the desirable effects outweigh undesirable effects, despite the absence of direct evidence, such that the grading of evidence is unnecessary			We recommend… We recommend that … should be performed/ administered… We recommend that… Is usually) indicated/ beneficial/effective

Appendix 5: **Policies, Procedures, Protocols and Guidelines Checklist**

The PPPG Checklists were developed to assist staff to meet standards when developing Clinical PPPGs.

Standards for developing clinical PPPG	
Stage 1 Initiation	**Checklist**
The decision making approach relating to the type of PPPG guidance required (policy, procedure, protocol, guideline), coverage of the PPPG (national, regional, local) and applicable settings are described.	☐
Synergies/co-operations are maximised across departments/organisations (Hospitals/ Hospital Groups/Community Healthcare Organisations (CHO)/National Ambulance Service (NAS)), to avoid duplication and to optimise value for money and use of staff time and expertise.	☐
The scope of the PPPG is clearly described, specifying what is included and what lies outside the scope of the PPPG.	☐
The target users and the population/patient group to whom the PPPG is meant to apply are specifically described.	☐
The views and preferences of the target population have been sought and taken into consideration (as required).	☐
The overall objective(s) of the PPPGs are specifically described.	☐
The potential for improved health is described (e.g. clinical effectiveness, patient safety, quality improvement, health outcomes, quality of life, quality of care).	☐
Stakeholder identification and involvement: The PPPG Development Group includes individuals from all relevant stakeholders, staff and professional groups.	☐
Conflict of interest statements from all members of the PPPG Development Group are documented, with a description of mitigating actions if relevant.	☐
The PPPG is informed by the identified needs and priorities of service users and stakeholders.	☐
There is service user/lay representation on PPPG Development Group (as required).	☐
Information and support is available for staff on the development of evidence-based clinical practice guidance.	☐

Stage 2 Development	**Checklist**
The clinical question(s) covered by the PPPG are specifically described.	☐
Systematic methods used to search for evidence are documented (for PPPGs which are adapted/adopted from international guidance, their methodology is appraised and documented).	☐
Critical appraisal/analysis of evidence using validated tools is documented (the strengths, limitations and methodological quality of the body of evidence are clearly described).	☐
The health benefits, side effects and risks have been considered and documented in formulating the PPPG.	☐
There is an explicit link between the PPPG and the supporting evidence.	☐
PPPG guidance/recommendations are specific and unambiguous.	☐
The potential resource implications of developing and implementing the PPPG are Identified e.g. equipment, education/training, staff time and research.	☐
There is collaboration across all stakeholders in the planning and implementation phases to optimise patient flow and integrated care.	☐
Budget impact is documented (resources required).	☐
Education and training is provided for staff on the development and implementation of evidence-based clinical practice guidance (as appropriate).	☐
Three additional standards are applicable for a small number of more complex PPPGs: Cost effectiveness analysis is documented. A systematic literature review has been undertaken. Health Technology Assessment (HTA) has been undertaken.	☐
Stage 3 Governance and Approval	**Checklist**
Formal governance arrangements for PPPGs at local, regional and national level are established and documented.	☐
The PPPG has been reviewed by independent experts prior to publication (as required).	☐
Copyright and permissions are sought and documented.	☐
Stage 4 Communication and Dissemination	**Checklist**
A communication plan is developed to ensure effective communication and collaboration with all stakeholders throughout all stages.	☐
Plan and procedure for dissemination of the PPPG is described.	☐
The PPPG is easily accessible by all users e.g. PPPG repository.	☐

Stage 5 Implementation	**Checklist**
Written implementation plan is provided with timelines, identification of responsible persons/ units and integration into service planning process.	☐
Barriers and facilitators for implementation are identified, and aligned with implementation levers.	☐
Education and training is provided for staff on the development and implementation of evidence- based PPPG (as required).	☐
There is collaboration across all stakeholders in the planning and implementation phases to optimise patient flow and integrated care.	☐
Stage 6 Monitoring, Audit, Evaluation	**Checklist**
Process for monitoring and continuous improvement is documented.	☐
Audit criteria and audit process/plan are specified.	☐
Process for evaluation of implementation and (clinical) effectiveness is specified.	☐
Stage 7 Revision/Update	**Checklist**
Documented process for revisions/updating and review, including timeframe is provided.	☐
Documented process for version control is provided.	☐

To view in full refer to website: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

Appendix 6: NWIHP/IOG CAG Membership 2023

Dr Cliona Murphy (Chair). Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Director, National Women and Infants Health Programme.

Dr Sam Coulter-Smith. Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Chair, Institute of Obstetricians and Gynaecologists.

Angela Dunne. Director of Midwifery, National Women and Infants Health Programme.

Kilian McGrane. Director, National Women and Infants Health Programme.

Dr Peter McKenna. Clinical Lead, Obstetric Event Support Team, National Women and Infants Health Programme.

Prof John Murphy. Clinical Lead Neonatology, National Women and Infants Health Programme.

Prof Maeve Eogan. Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Clinical Lead, Sexual Assault Treatment Units, National Women and Infants Health Programme.

Dr Aoife Mullaly. Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Lead, Termination of Pregnancy Services, National Women and Infants Health Programme.

Prof Keelin O'Donoghue. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Lead, National Guidelines, National Women and Infants Health Programme.

Prof Nóirín Russell. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, Cervical Check.

Prof Richard Greene. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, National Perinatal Epidemiology Centre, University College Cork.

Prof John Morrison. Consultant Obstetrician and Gynaecologist, University Hospital Galway. Clinical Director, Saolta Maternity Directorate.

Dr Suzanne O'Sullivan. Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Director of Education and Training, Obstetrics and Gynaecology, Institute of Obstetricians and Gynaecologists.

Prof John Higgins. Cork University Maternity Hospital, Consultant Obstetrician and Gynaecologist, Clinical Director, Ireland South Women and Infants Directorate.

Dr Mendinaro Imcha. Clinical Director, Consultant Obstetrician and Gynaecologist, University Maternity Hospital Limerick.

Prof Shane Higgins. Master, Consultant Obstetrician and Gynaecologist, National Maternity Hospital.

Prof Mike O'Connell. Master, Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital.

Dr Brian Cleary. Chief Pharmacist, Rotunda Hospital. Medications Lead, Maternal and Newborn Clinical Management System Project.

Prof Seán Daly. Master, Consultant Obstetrician and Gynaecologist, Rotunda Hospital.

Ms Clare Thompson. Consultant Gynaecological Oncologist, The Mater, Dublin.

Dr Vicky O'Dwyer. Consultant Obstetrician and Director of Gynaecology, Rotunda Hospital.