National Women & Infants Health Programme

National Clinical Practice Guideline

In Vitro Fertilisation (IVF) and Intracytoplasmic Sperm Injection (ICSI)

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

Guideline Development Group

Dr Sarah Petch, Specialist Registrar in Obstetrics and Gynaecology, Clinical and Research Fellow

Dr Laura O'Byrne, Specialist Registrar in Obstetrics and Gynaecology

Dr Lucia Hartigan, Consultant Obstetrician and Gynaecologist and Specialist in Reproductive Medicine and Surgery

Dr Bogdan Alexandru Muresan, Consultant Obstetrician and Gynaecologist

Dr Julie Keneally, PhD, Specialist Programme Manager and Senior Embryologist

Dr Cliona Murphy, Consultant Obstetrician and Gynaecologist

Dr Moya McMenamin, Consultant Obstetrician and Gynaecologist

Guideline Programme Team

Prof Keelin O'Donoghue (Clinical Lead)

Ms Nicolai Murphy (Programme Manager)

Approved by

The National Women and Infants Health Programme (NWIHP) and the Institute of Obstetricians and Gynaecologists (IOG) Clinical Advisory Group (CAG)

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Table of Contents

Key Recommendations

Number	Recommendation	Grade of evidence
Section 1: Indications for ART		
1	We recommend taking a detailed clinical history from all people embarking on fertility treatment. Medical and mental health co-morbidities, including body mass index, should be optimised prior to embarking on treatment.	Best Practice
2	We recommend that men should have a recent semen analysis (within 12 months of treatment).	Best Practice
3	We recommend that referral to a urologist with specialist training in andrology/ male infertility should be considered in the following indications: • Azoospermia • Severe oligospermia • Urological symptoms • Treatable or modifiable factor contributing to infertility	Best Practice
4	We do not recommend routine sperm DNA fragmentation testing prior to in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment.	2B
5	We suggest that women should have testing of ovarian reserve in the form of an anti-müllerian hormone (AMH) level and/or antral follicle count (AFC), to predict ovarian response.	2B
6	We suggest that a baseline ultrasound scan may be performed to ensure that ovaries are quiescent and that the endometrial thickness is <5mm prior to starting stimulation. Pregnancy must be out ruled prior to starting stimulation.	2C
7	We strongly recommend that IVF should be offered as a first line for complete tubal infertility.	1A
8	We recommend that IVF should be offered first line for couples with unexplained infertility when the woman is aged over 38 years.	1C
9	We suggest that IVF be offered for the following indications: • Mild tubal/partial tubal infertility • Endometriosis with infertility • Following previous unsuccessful treatment (ovulation induction or intrauterine insemination)	1B

Number	Recommendation	Grade of evidence
10	We recommend that individual/couple preferences should be considered when recommending IVF/ICSI treatment.	Best Practice
11	We strongly recommend that ICSI should be performed as the fertilisation technique for male factor infertility.	1A
12	We recommend that ICSI is performed when a previous IVF cycle resulted in failed fertilisation or suboptimal fertilisation.	1B
13	We recommend that ICSI is the fertilisation technique of choice for thawed oocytes.	1C
14	We recommend that ICSI should be used as a fertilisation technique for preimplantation genetic testing (PGT) for monogenic disorders (PGT-M) and structural rearrangements (PGT-SR). Conventional IVF is feasible for PGT for aneuploidy (PGT-A).	1B
Section 2: IVF/ICSI treatment in practice		
15	We strongly recommend that for women who are predicted to have a high ovarian response, a GnRH antagonist protocol should be used for controlled ovarian hyperstimulation (COH).	1A
16	We recommend that for women who are predicted to have a low ovarian response, a GnRH agonist protocol is a reasonable first line choice for COH, the GnRH antagonist protocol may also be used.	1B
17	We recommend that all clinics providing IVF/ICSI have their own standard operating procedure (SOP) providing evidence-based guidelines for prescribing medications for ovarian stimulation, taking into account availability of medications.	Best Practice
18	We suggest that pre-treatment with oestrogen or progesterone may be used for scheduling purposes as it does not appear to negatively affect outcomes.	2B
19	We do not recommend pre-treatment with the combined oral contraceptive pill (COCP) if a fresh embryo transfer is planned.	1B
20	We recommend monitoring with pelvic ultrasound, ideally transvaginal, during COH to measure: • Ovarian response (follicular growth) • Endometrial thickness	1B
21	We do not recommend monitoring with serum oestradiol in addition to pelvic ultrasound as it has not been shown to reduce the risk of ovarian hyperstimulation syndrome (OHSS).	1B
22	We suggest that endometrial thickness should ideally be >7mm before embryo transfer.	2B

Number	Recommendation	Grade of evidence
23	We recommend that an oocyte maturation trigger should be given 36-38 hours prior to egg collection.	1B
24	We recommend that the decision on when to trigger should be individualised, usually when lead follicles have reached 16-22mm size.	Best Practice
25	We recommend that if a fresh embryo transfer is planned, a HCG trigger is given, either alone or combined with a GnRH agonist trigger.	1A
26	We suggest that a dual trigger (hCG and GnRH agonist) may be considered in women who have predicted or previous low ovarian response in a GnRH antagonist cycle.	2B
27	We recommend that in GnRH antagonist cycles, where there is a high risk of OHSS, a GnRH agonist trigger may be given, along with a 'freeze all' approach as this reduces the risk of OHSS.	1B
28	We strongly recommend that progesterone is given for luteal phase support following oocyte retrieval (OCR) when a fresh embryo transfer is planned.	1A
29	We recommend that progesterone support is initiated after OCR (from that evening up to 3 days post-OCR) and continued until at least the date of pregnancy testing.	1C
30	We recommend that all non-oral routes of administration of progesterone appear to be efficacious and the decision on the route of administration should be decided upon based on clinician and the woman's preferences.	1B
31	We recommend embryo cryopreservation to individuals/couples that have surplus embryos suitable to freeze following a fresh embryo transfer.	1C
32	We suggest that the endometrial thickness should ideally be >7mm prior to a frozen embryo transfer (FET).	2B
33	We recommend that the protocol for endometrial preparation should be individualised, taking into consideration the regularity of the woman's cycle, previous treatment if any and her personal preferences.	Best practice
34	We recommend that all women should have an assessment of risk factors for OHSS and other complications of IVF.	Best Practice
35	We suggest that cabergoline 0.5mg/day for 5-7 days may be prescribed to women at high risk of OHSS.	2C
36	We strongly recommend that the antagonist protocol should be used in women at high risk of OHSS.	1A
37	We recommend venous thromboembolism prophylaxis for women who develop OHSS.	1B

Number	Recommendation	Grade of evidence
38	We suggest that antibiotics may be considered at OCR in women who are at increased risk of infection.	2B
39	We recommend that the decision to cancel an IVF/ICSI should be addressed on a case-by-case basis, considering the age and ovarian reserve of the woman, previous response to stimulation and the wishes of the individual/ couple.	Best Practice
40	We suggest that cycle cancellation may be considered when the response to COH is less than expected for the woman's age/ovarian reserve.	Best Practice
41	We suggest that cycle cancellation may be considered when there is a high risk of OHSS based on a high number of follicles, and the woman's clinical condition.	Best Practice
42	We suggest that cycle cancellation should be considered if another medical or social issue arises during stimulation that would make proceeding with treatment unsafe or unacceptable to the woman.	Best Practice
43	We do not recommend the transfer of more than 2 embryos under any circumstances.	1C
44	We recommend that elective single embryo transfer (eSET) should be the standard procedure whenever more than one good quality embryo is available. Double embryo transfer (DET) may be considered in selected circumstances.	1B
45	We recommend that medical risk factors should be considered before a DET due to the higher rates of maternal, fetal, and neonatal complications with multiple pregnancy.	Best Practice
46	We recommend that when a DET is considered, the individual/couple should be provided with clear information about the risks associated with multiple pregnancy.	Best Practice
Section 3: AHR standards of practice		
47	We recommend that any site in Ireland which carries out AHR procedures must be authorised by the HPRA and practice should follow guidance from the Health Products Regulatory Authority (HPRA).	Best Practice

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

This Guideline follows on from the National Clinical Practice Guideline on Fertility Investigation and Management, published in 2023[1].

The purpose of the current Guideline was to develop and provide an overview of evidence-based guidance for the provision of In Vitro Fertilisation (IVF) and Intracytoplasmic Sperm Injection (ICSI).

Assisted Human Reproduction (AHR) may include treatments other than IVF or ICSI. Fertility preservation, donor assisted conception, surrogacy, ovulation induction (OI), intrauterine insemination (IUI), reciprocal IVF and 'add ons' to IVF treatment are outside of the scope of this Guideline.

1.2 Scope

Target Users

The Guideline is intended as a resource for healthcare providers working in general practice, obstetrics and gynaecology, and fertility services. This includes healthcare staff, doctors, advanced midwifery practitioner[2], midwives, nurses, embryologists, health and social care professionals involved in the care of people with subfertility undergoing IVF/ICSI.

Target Population

This Guideline aims to give an overview of IVF/ICSI treatment. The target population for this guideline are people with subfertility undergoing IVF/ICSI. People who attend fertility clinics in Ireland include heterosexual couples with infertility who may wish to conceive with their own gametes or donor gametes, same sex couples, people who wish to become parents using a surrogate and people who wish to preserve their fertility for numerous reasons. In September 2023, publicly funded IVF/ICSI was made available to couples who meet specific access criteria which will be outlined in the Introduction under 'Access to Assisted Human Reproduction'. Currently public funding is only available to heterosexual couples using their own gametes to conceive. Single people, same sex couples, those using donor gametes or those wishing to preserve their fertility are not eligible for public funding of AHR.

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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://assets.hse.ie/media/documents/hse-national-framework-for-developing-pppgs-2016.pdf

2 Nursing and Midwifery Board of Ireland (NMBI) (2018) Advanced Practice (Midwifery) Standards and Requirements. Dublin.

Objective

To provide evidence-based recommendations for the care of people undergoing IVF/ICSI as well as promoting a standardised approach nationally across all fertility clinics.

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.

The Guideline Development Group was as follows:

- *Dr Sarah Petch, Specialist Registrar in Obstetrics and Gynaecology, Clinical and Research Fellow, Merrion Fertility Clinic, National Maternity Hospital*
- *Dr Laura O'Byrne, Specialist Registrar in Obstetrics and Gynaecology, Cork University Maternity Hospital*
- *Dr Lucia Hartigan, Consultant Obstetrician and Gynaecologist and Specialist in Reproductive Medicine and Surgery, University Maternity Hospital Limerick*
- *Dr Bogdan Alexandru Muresan, Consultant Obstetrician and Gynaecologist, Coombe Women and Infants Hospital*
- *Dr Julie Keneally, PhD, Specialist Programme Manager and Senior Embryologist, Cork University Maternity Hospital*
- *Dr Cliona Murphy, Consultant Obstetrician and Gynaecologist, Coombe Women and Infants Hospital*
- *Dr Moya McMenamin, Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital.*

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 Guideline Development Group was made up a specialist registrar and consultants in obstetrics and gynaecology, fertility specialists and fellows and an embryologist.

The following additional stakeholders were consulted regarding this Guideline:

- *Dr Maebh Horan, Consultant Obstetrician and Gynaecologist and Specialist in Reproductive Medicine and Surgery, National Maternity Hospital and Merrion Fertility Clinic*
- *Dr David Crosby, Consultant Obstetrician and Gynaecologist, Head of Department of Reproductive Medicine, National Maternity Hospital, Clinical Director Merrion Fertility Clinic*
- *Dr Aisling Looney, Consultant Urologist and Specialist in Andrology, St Vincent's University Hospital*
- *Dr Aoife Campbell, PhD, Senior Embryologist and Innovation Manager, Merrion Fertility Clinic*
- *Ms Eilleen Barrett, Senior Fertility Clinical Nurse Specialist, Merrion Fertility Clinic*
- *Ms Eilis McCarthy, Candidate Advanced Midwife Practitioner in Assisted Human Reproduction, Cork University Maternity Hospital*

In addition Ms Caitríona Fitzpatrick, Head of Programmes and Services and Chairperson of The National Infertility Support and Information Group (NISIG) along with other members of NISIG reviewed the guideline and provided feedback. NISIG is a registered charity and a support and advocacy group for people experiencing infertility.

The Expert Advisory Group (EAG) has representatives from Obstetrics and Gynaecology, General Practice, Anaesthetics, Midwifery, Nursing and Pharmacy.

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[3]. 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[4].

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[5].

For this National Clinical Practice Guideline, all Guideline developers were 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 are reported in the published Guideline and declarations of interest can be made available.

3 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

4 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. DOI: 10.1503/cmaj.200651 https://www.cmaj.ca/content/193/2/E49

5 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. doi:10.7326/M14-1885. https://www.acpjournals.org/doi/10.7326/m14-1885

Guideline Developer Group

Dr Sarah Petch is a Specialist Registrar in Obstetrics and Gynaecology. She is currently undertaking a clinical and research fellowship in Reproductive Medicine and Surgery at Merrion Fertility Clinic, a not-for-profit fertility clinic (July 2023-July 2025). Her research MD, through University College Dublin, is self-funded.

Dr Laura O'Byrne is a Specialist Registrar in Obstetrics and Gynaecology. She is currently employed by Cork University Maternity Hospital (CUMH) and its academic partner, University College Cork (UCC). She has an interest in fertility and is a PhD candidate in UCC. Her PhD was funded by the National Perinatal Epidemiology Centre (NPEC) and the Health Research Board (HRB).

Dr Lucia Hartigan is a Consultant Obstetrician and Gynaecologist working in University Maternity Hospital Limerick and Nenagh Fertility Hub. She is the clinical lead for fertility and reproductive medicine for UL Hospitals Group. She completed a clinical and research fellowship in Merrion Fertility Clinic, Dublin.

Dr Bogdan Alexandru Muresan is a consultant Obstetrician and Gynaecologist at the Coombe Hospital, where he completed a clinical fertility fellowship in fertility. He is a fertility consultant at Repromed Ireland from May 2024 to present. He is also Support Advisory Consultant at Thérapie Fertility LTD from August 2023 to present.

Dr Julie Kenneally is employed by Cork University Maternity Hospital (CUMH) and its academic partner, University College Cork (UCC). At the time of the Guideline developers' first meeting, she was employed by the Waterstone Clinic, a private fertility treatment provider in Ireland. She has no economic interest in any fertility clinic nor any links to pharma.

Dr Cliona Murphy is a Consultant Obstetrician and Gynaecologist and is employed by the Coombe Hospital and the Health Service Executive (HSE). She has a small private practice in general gynaecology and performs initial work up for infertility for private patients, as appropriate. She has no pecuniary interest in any IVF business. She has no links to pharma.

Dr Moya McMenamin is a Consultant Obstetrician and Gynaecologist with a specialist interest in Reproductive Medicine and Surgery in Cork University Maternity Hospital (CUMH). She is currently the clinical lead for the Cork Regional Fertility Hub located at CUMH. She previously worked in Waterstone Clinic (March 2015-September 2018), and completed an MD through University College Dublin whilst working in Merrion Fertility Clinic from July 2010-July 2012.

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.

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

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- Advising women of their choices and ensure informed consent is obtained
- Provide 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[6]. While there has been a trend to remove the word 'woman/women' and use 'gender neutral' language in policy and practice in relation to women's reproductive health and wellbeing, there is no evidence base to inform this change[7]. We also appreciate that there are risks to desexing language when describing female reproduction[8 9].

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. Finally, all those using maternal and reproductive health care and services should receive individualised, respectful care including use of the gender nouns and pronouns they prefer[7].

Language use is key to effectively communicate options, recommendations, and respectfully accept a woman's fully informed decision[10]. 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.

6 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/

7 Council of Deans of Health. Midwifery Network position paper: use of sexed language. May 2023. https://www.councilofdeans.org.uk/2024/02/midwifery-network-position-paper-use-of-sexed-language/

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

9 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

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

1.9 Adopting a trauma-informed approach to maternity care

Many women accessing maternity services may have experienced historical or current trauma prior to, or during pregnancy - including emotional, physical, sexual abuse, rape and torture. The perinatal period (pregnancy, birth and the postpartum) can be a time when previous trauma is triggered[11] . Maternity care procedures which may seem routine and 'non-invasive' to healthcare professionals (HCPs), e.g., abdominal palpation or providing breastfeeding support can be triggering for some women with a history of trauma, as can intimate procedures such as vaginal examinations[12].

Trauma-informed care (TIC) is a developing approach to healthcare which recognises the importance of psychological safety, and the need to prevent or resist re-traumatisation of individuals[13]. It is based on 4 key principles (known as the 4Rs): (1) realisation of trauma; (2) recognition of trauma; (3) responding to trauma and (4) resisting re-traumatisation[14],. A trauma-informed approach to maternity care means that all staff in an organisation have an understanding of the impact of trauma on individuals, families and organisations[15]. While a universal approach is yet to be agreed, within clinical practice and research, many organisations recognise the need to move towards becoming trauma-informed in the provision of maternity care15, [16]. Such an approach requires commitment, investment and transformation within maternity services.

In simple terms, HCPs should recognise the impact of women's previous or current history of trauma (whether disclosed or not) and adopt a universally sensitive approach to care provision that recognises the impact of trauma on service users and HCPs. Examples of this include ensuring clear communication and consent is sought before any procedures/interventions, ensuring women are provided with dignity and respect at all times.

11 Horsche A., Garthus-Niegel S., Ayers S, Chandra P., Hartmann K., Caisbuch E., Lalor J (2024). Childbirth-related posttraumatic stress disorder: definition, risk factors, pathophysiology, diagnosis, prevention, and treatment. Am J Obstet Gynecol. 2024 Mar;230(3S): S1116-S1127. doi: 10.1016/j.ajog.2023.09.089

12 Montgomery E. Feeling safe: a metasynthesis of the maternity care needs of women who were sexually abused in childhood. Birth 40:88–95. Birth. 2013 Jun;40(2):88-95. doi: 10.1111/birt.12043

13 Vogel TM, Coffin E. (2021). Trauma-informed care on labor and delivery. Anesthesiol Clin. 2021 Dec;39(4):779-791. doi: 10.1016/j.anclin.2021.08.007

14 SAMHSA's concept of trauma and guidance for a trauma-informed approach Rockville. October 2014. https://library.samhsa.gov/product/samhsas-concept-trauma-and-guidance-trauma-informed-approach/sma14-4884

15 Law C, Wolfenden L, Sperlich M, Taylor J. A (2021). Good practice guide to support implementation of trauma-informed care in the perinatal period. The centre for early child development (Blackpool, UK) commissioned by NHS England and NHS Improvement in 2021. https://www.england.nhs.uk/publication/a-good-practice-guide-to-support-implementation-of-trauma-informed-care-in-the-perinatal-period/

16 Ayers, S., Horsch, A., Garthus-Niegel, S., Nieuwenhuijze, M., Bogaerts, A., Hartmann, K., Karlsdottir, S. I., Oosterman, M., Tecirli, G., Turner, J. D., Lalor, J., & COST Action CA18211 (2024). Traumatic birth and childbirth-related post-traumatic stress disorder: International expert consensus recommendations for practice, policy, and research. Women and birth : journal of the Australian College of Midwives, 37(2), 362–367. https://doi.org/10.1016/j.wombi.2023.11.006

Chapter 2: Clinical Practice Guideline

Definitions

The following definitions are used in this Guideline:

Assisted Human Reproduction (AHR): All treatment of procedures that involve the handling of gametes and embryos for the purposes of establishing a pregnancy[2].

Assisted Reproductive Technology (ART): The technologies employed in pursuit of AHR[2].

Advanced maternal age (AMA): There is no international consensus on the definition of advanced maternal age. It is known that fertility declines sharply after the age of 35 years [3]. The ESHRE International Glossary on Infertility and Fertility Care defines AMA as age >40years[4]. For the purpose of this guideline, AMA is defined as >40years.

Advanced reproductive age (ARA): Recently, societies such as ESHRE have moved towards using the term advanced reproductive age to acknowledge that both male and female age play a role in fertility[3]. As for AMA, there is no consensus on the definition of advanced paternal age but male age >40 years has a less pronounced but important impact on fertility treatment[3].

Severe male factor infertility: As in the National Clinical Practice Guideline on Fertility Investigation and Management, severe male factor infertility is defined as oligospermia with a sperm concentration of <5million sperm per ml of ejaculate[1].

Other Guidelines

Recommendations relevant to this Guideline can also be found in other national guidelines:

- National Clinical Practice Guideline: Fertility – Investigation and Management in Secondary Care[1]
- National Clinical Practice Guideline: Recurrent Miscarriage[5]
- National Clinical Practice Guideline: Assessment and Management of Endometriosis[17]

The European Society for Human Reproduction and Embryology (ESHRE) provides training and accreditation for reproductive medicine and surgery specialists, nurses and midwives and clinical embryologists. In addition, ESHRE provides evidence based guidelines and good practice recommendations which have informed this Guideline:

- ESHRE Guideline on Unexplained Infertility[6]
- ESHRE Guideline on Ovarian Stimulation for IVF/ICSI[7]
- ESHRE Guideline on the number of embryos to transfer during IVF/ICSI[8]

17 DeMaio, A, McTiernan, A, Durand O' Connor A, Reidy F, O' Neill, A. National Clinical Practice Guideline: Assessment and Management of Endometriosis. National Women and Infants Health Programme and The Institute of Obstetricians and Gynaecologists. March 2025

In addition, the following UK guidelines are relevant to this Guideline:

- **RCOG Green-top Guideline No. 5: The Management of Ovarian Hyperstimulation Syndrome**[9]
- **European Association of Urology (EAU) Guidelines on Sexual and Reproductive Health**[10]

Introduction

Background on infertility

Infertility is defined by the World Health Organisation (WHO) as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse[11]. The prevalence of infertility is increasing worldwide. One in six heterosexual couples will experience difficulty conceiving and the estimated lifetime prevalence of infertility globally is 17.5% [12].

It is recommended to carry out investigations for the cause of infertility when a couple have been trying to conceive (TTC) for 12 months when the woman is under 35 years old, or after 6 months of TTC when the woman is aged over 35 years or when there is a known condition that may affect fertility for either member of the couple [1]. Appropriate investigations and referral pathways are discussed in more detail in the National Clinical Practice Guideline on Fertility Investigation and Management in Secondary Care. There, it is recommended that basic investigations for subfertility include semen analysis for the male partner, tests of ovulation and ovarian reserve for the female partner and consideration of tubal patency testing [1].

History of ART and Legal Framework in Ireland

In 1978, the first human was born through the ground-breaking method of In vitro fertilisation (IVF), marking a pivotal moment in reproductive technology [13]. Since this milestone, our understanding of the medical science behind IVF has significantly progressed, leading to the emergence of innovative technologies in this field. There have been over 8 million babies born because of IVF technologies to date [14].

Reflecting the increased prevalence of subfertility and the advancements in technology, the number of people using assisted reproductive technology (ART) to conceive is growing globally. The number of treatment cycles recorded per annum in Ireland went from 7,589 in 2009 to 9,878 in 2020 [2]. The true number of people in Ireland using AHR services is higher as many people travel to access fertility services abroad for financial or legislative reasons[2]. Until recently, there was a lack of clear legislation on fertility treatment in Ireland which caused challenges for people accessing fertility services and clinicians.

At the time of writing this guideline donor gametes are not included in publicly provided AHR services in Ireland. However, many people in Ireland use donor gametes to conceive[2]. In 2020, the *Children and Family Relationships Act (CFRA) 2015* was passed, which aimed to address legal issues surrounding donor assisted conception [15]. This legislation provides legal recognition to children born through donor assisted reproductive technologies and outlined the rights and responsibilities of parents. In accordance with CFRA 2015, the use of donated gametes and embryos is permitted in Ireland through directed donation (donation is designated for a recipient) or identifiable donation (unknown but identifiable donor). Therefore, gamete donation in Ireland is non-anonymous and donor conceived children may access the details of their donor once they reach the age of eighteen. The CFRA aims to reform family law in a way that is inclusive of, and sensitive to, the reality of contemporary family life in Ireland. Surrogacy is not covered by this legislation.

The *Health (Assisted Human Reproduction) Act* 2024 has just been enacted and will provide a regulatory framework for various assisted reproduction procedures and practices[16]. This new legislation will regulate the provision of human reproductive treatment and seeks to address issues such as donor assisted conception, surrogacy, and the rights of children born through AHR.

The Health Products Regulatory Authority (HPRA) is the competent authority (CA) in Ireland for the purpose of implementing European Union (EU) and National legislation relating to Human Tissues and Cells. Units providing AHR services fall under the Tissues Establishment (TE) classification according to this legislation.

Success rates of IVF/ICSI

Advancements in technologies in IVF/ICSI has led to improved success rates over the past few decades[17]. Female age is the single largest determinant of success in IVF/ICSI treatment with reduced likelihood of success as women age[18].

When interpreting reported success rates, it is important to carefully consider what data is being presented. Outcomes of assisted reproduction treatment can be reported as:

Positive Pregnancy Test – 2-3 week stage

Clinical Pregnancy – 8-12 week stage, visible by ultrasound scan

Live Birth – 9 months (full term) or earlier (premature)

Clinics may report these outcomes as rates per cycle started, per egg collection or per embryo transfer. When an individual/couple are planning to have IVF/ICSI treatment, their clinician should give them advice on their prognosis for a successful outcome, taking into account factors such as female age, cause of infertility, duration TTC and the presence of comorbidities which may impact on treatment. Some clinicians may use validated prediction tools to help them calculate the chance of pregnancy for an individual/couple[19].

Access to Assisted Reproductive Technology

Access to ART, including IVF remains highly inequitable. Huge disparities exist between the availability and quality of fertility services, and those in developing countries or from a lower socioeconomic class have the least access to services [20]. Globally the estimated need for IVF is estimated at 1,500 cycles per million population per year [21].

Until September 2023, there was no public provision of fertility treatment (IVF) in Ireland. IVF was provided exclusively through private clinics. Limited public funding is now available but with strict access criteria (below).

Eligibility criteria for people accessing publicly-funded IVF, ICSI and IUI treatment (2024):[22] From gov.ie, accessed on January 2025

- Individuals must be ordinarily resident in the State and referred through their GP (a woman cannot self-refer) to their local Regional Fertility Hub. There are 6 Regional Fertility Hubs nationally: Cork University Maternity Hospital, Galway University Hospital, Nenagh Hospital Tipperary, Coombe Women and Infants' Hospital, Rotunda Hospital, National Maternity Hospital
- Eligible couples must have no living children from the existing relationship and include at least one partner with no living child.

- Access to publicly funded AHR treatment is available for those individuals who have previously undertaken a maximum of one previous IVF cycle and where all embryos created as part of that cycle have been used.
- A couple/individual will not be eligible for publicly funded AHR treatment if either partner/individual has had voluntary sterilisation.
- To ensure the welfare of any children resulting from AHR treatment, an assessment will be carried out, based primarily upon a self-declaration form.
- There shall not be more than two intending parents of a child born as a result of AHR treatment and, they shall be in a relationship for at least one year.
- The intending birth mother should be a maximum age of 40 years plus 364 days at time of referral to Hub, while the maximum referring age for males is 59 years plus 364 days*.
- The BMI of an intending birth mother must be within the range of 18.5 kg/m^2 – 30.0 kg/m^2**.

Guidance regarding lifestyle: From gov.ie, accessed on January 2025

- Alcohol: Intending birth mother should have no more than one or two standard alcoholic drinks once or twice per week. Males should have no more than three to four standard alcoholic drinks per day, ideally 10 standard drinks or less over a week.
- Smoking: All intending parents should be non-smoking for at least three months.
- Recreational/illegal drugs: All intending parents should be non-users of recreational drugs for at least three months.

* **Regional Fertility Hubs:** Cork University Maternity Hospital, Galway University Hospital, Nenagh Hospital Tipperary, Coombe Women and Infants' Hospital, Rotunda Hospital, National Maternity Hospital
** Women may be referred to the fertility hubs for investigations up to the age of 42 years.
*** Women with a BMI between 18.5-35kg/m^2 may be referred to the fertility hubs for investigations.

Section 1 – Indications for ART

Clinical Question 2.1: What are the clinical factors that need to be measured prior to starting an IVF cycle?

Evidence Statement

Optimising co-morbidities

Pre-existing medical conditions, mental health conditions, medications and health related behavioural factors for both male and female partners can impact on the success of fertility treatment. Taking a detailed history from all individuals/couples is of huge importance. The goal of fertility treatment is for a woman to become pregnant, and so the risks of pregnancy for each individual woman should be considered. The 2022 MBRRACE report identified that 56% of women who died in pregnancy and up to six weeks post-pregnancy in 2019-2021 had a pre-existing medical condition, and 4% of women who died had conceived as a result of assisted conception [23]. Thus, it is important that co-morbidities have been optimally managed prior to embarking on fertility treatment. We recommend consulting physicians from relevant specialities and maternal medicine colleagues for pre-conceptual counselling if required.

At the time of writing this Guideline, access to public funding of ART in Ireland is only available to couples if the woman's body mass index (BMI) is between 18.5-30kg/m^2. Both obesity (BMI >30kg/m^2) and being underweight (BMI <18.5kg/m^2) can have a negative impact on IVF outcomes [24, 25]. A large meta-analysis of 18 cohort studies and over 975,000 IVF cycles demonstrated that maternal obesity is associated with lower live birth rates and an increased risk of adverse outcomes in IVF, and this is more pronounced when the BMI is >35kg/m^2 [26]. Maternal obesity also carries an increased risk of miscarriage, congenital anomaly, gestational diabetes, hypertensive disorders of pregnancy, Caesarean birth, and postpartum hemorrhage [27]. The current criteria for public funding do not include BMI criteria for male partners, however it is known that paternal obesity has a negative impact on ART outcomes [28].

BMI as a criterion for funding for fertility treatment has been widely debated as it is a crude measure of well-being. Weight loss prior to fertility treatment has not been shown to significantly improve outcomes and BMI alone does not impact fertility as significantly as age [29, 30]. However, weight loss does improve the chances of natural conception in women with obesity and reduces the risk of maternal, fetal and neonatal complications in pregnancy [31]. Ideally, both partners should be supported to optimise their general health, including BMI, prior to embarking on fertility treatment.

Baseline investigations for the female partner

Prediction of ovarian response, using ovarian reserve testing, allows clinicians to personalise treatment and select the most appropriate protocol and dose of gonadotropins to prescribe. It can also be useful for counselling individuals/couples about their likelihood of success and/or complications [7]. Several methods of ovarian reserve testing have been studied including female age, body mass index (BMI), antral follicle count (AFC), anti-müllerian hormone (AMH), basal follicle stimulating hormone (FSH), oestradiol and inhibin B. Whilst advancing female age is associated with reduced likelihood of success with IVF [18], age alone is not sufficient to predict ovarian response [7]. Oestradiol and BMI are not accurate markers of ovarian response and basal FSH and inhibin B are not sufficiently reliable [7]. Two large individual patient data (IPD) meta-analyses looked at age, AFC, AMH and FSH as predictors of low ovarian response (5705 women) and high ovarian response (4786 women) [32, 33]. Both AFC and AMH were shown to be reliable markers of ovarian response. In general the AFC and AMH levels will be similar in the same woman measured at the same time, however there may be discordance in AFC and AMH in approximately 1 in 5 women [34]. There is debate in the literature on which is superior, AMH or AFC. A global survey of 796 IVF clinics in 96 countries found that in practice, many clinics use both AMH and AFC to measure ovarian reserve, however AMH is used as a first line test by 60% and felt to perform better than AFC as a test for ovarian reserve (51% for AMH vs 40% for AFC) [35]. In practice, it is reasonable to use either AMH or AFC or both to predict ovarian response.

It is essential that pregnancy is ruled out prior to starting controlled ovarian hyperstimulation (COH). Many clinics perform a 'baseline scan' prior to commencing COH is to detect ovarian cysts or endometrial pathology which may impact on IVF success or require further investigation. The benefit of the baseline scan on success of IVF is debated however and many call for a more streamlined approach to ovarian stimulation[36]. If a baseline scan is performed, it should be performed by an adequately trained practitioner with an interest in fertility. The scan is performed early in the menstrual cycle (day 2-5) or following an induced bleed. Ideally ovaries should be 'quiescent', with no follicles >10mm in size and the endometrium should be thin (<5mm).

Simple or functional ovarian cysts, particularly those >20mm, produce estradiol (E2) which may have an endocrine effect and disrupt folliculogenesis. The impact of these cysts is controversial. Some authors argue that cysts have no impact on COH [37], whilst others reported that the presence of baseline ovarian cysts were associated with worse IVF outcomes[38]. The optimal management of simple cysts prior to COH is unclear. Conservative management, management with the combined oral contraceptive pill or GnRH agonist or cyst aspiration (transvaginal approach) are options. A 2014 Cochrane Review found

insufficient evidence that cyst aspiration prior to COH influences rates of live birth, clinical pregnancy, number of follicles recruited, or number of oocytes collected in women with a functional ovarian cyst. If functional cysts are discovered on the baseline scan, the management should be individualised, taking into consideration the woman's preferences.

The baseline scan may detect other ovarian pathology which may require referral to other colleagues. Relevant guidelines on the management of ovarian cysts in premenopausal women should be consulted [39].

Ultrasound scan may also identify endometrial pathology such polyps or submucosal fibroids, which are found in up to 15% of women with fertility issues [40]. A hysteroscopy may be performed to further investigate or treat submucosal fibroids or polyps prior to commencing IVF [41, 42]. There is no consensus on whether endometrial polyps, particularly small polyps, should be removed prior to IVF treatment[43].

Baseline investigations for the male partner

Semen analysis should be performed and analysed according to the WHO criteria, as outlined in the National Clinical Guideline on Fertility Investigations and Management [1]. Semen parameters documented in the 6th edition of World Health Organization Laboratory Manual for Examination and Processing of Human Semen (WHO, 2021) defines parameters affecting fertility in men[44]:

- Oligozoospermia: a sperm concentration <16x10 ^{6}/ml and with a total number of sperm in the ejaculate <39x10 ^{6})
- Asthenozoospermia: <42% total motility and/or <30% progressive motility
- Teratozoospermia: <4% normal forms.

The man should have a recent (within 12 months) semen analysis before embarking on treatment. A repeat semen analysis may be considered if there have been significant changes to health related behaviours, such as smoking cessation, whilst awaiting treatment. Generally, if the semen analysis is normal IVF used as the fertilisation method, and if there is male factor subfertility ICSI is performed. This will be discussed further in Clinical Questions 2.2 and 2.3.

The National Clinical Practice Guideline on Fertility Investigations and Management in Secondary Care suggests that men with azoospermia (no sperm in the ejaculate) or severe oligospermia (<5x10 ^{6}/ml) should have further investigations including serum testosterone, follicle stimulating hormone (FSH), karyotype, Y chromosome microdeletion studies and cystic fibrosis (CF) carrier screening and testicular ultrasound[1].

In line with urology/andrology guidelines, men with infertility should be referred to a specialist urologist/ andrologist for the following indications:

- Azoospermia
- Severe oligospermia
- The presence of an ongoing potentially treatable factor contributing to male infertility
- Urological symptoms such as testicular pain/swelling.

However, fertility treatment should not be delayed whilst awaiting urology referral, particularly if the man's partner is of advanced maternal age or has low ovarian reserve. In cases of repeated azoospermia, surgical sperm retrieval may be possible. Men should be referred to a urologist with experience in performing micro TESE in line with international best practice urology guidelines [10, 45].

Evidence exploring the relationship between Sperm DNA Fragmentation (SDF) and ART outcomes is conflicting [46-50]. Further work is required to provide evidence confirming ICSI as beneficial in the management of elevated SDF. The GDG currently do not recommend routine testing of SDF.

If it is anticipated that the man may have difficulty providing a sample on the day of egg collection, sperm may be produced in advance and frozen.

Clinical Practice

Individuals planning an ART cycle with their own gametes should undergo several clinical evaluations prior to commencing treatment.

A detailed history should be obtained from all people and the advice of other specialists should be sought, if necessary, prior to commencing treatment.

The female partner's ovarian reserve should be assessed with an AMH level, AFC or both. The female partner should have a baseline ultrasound scan to ensure that she is suitable to start controlled ovarian stimulation.

The male partner should have a semen analysis performed within 9 months of treatment.

Recommendations

1. **We recommend taking a detailed clinical history from all people embarking on fertility treatment. Medical and mental health co-morbidities, including body mass index, should be optimised prior to embarking on treatment.**
2. **We recommend that men should have a recent semen analysis (within 12 months of treatment).**
3. **We recommend that referral to a urologist with specialist training in andrology/male infertility should be considered in the following indications:**
    - **Azoospermia**
    - **Severe oligospermia**
    - **Urological symptoms**
    - **Treatable or modifiable factor contributing to infertility**
4. **We do not recommend routine sperm DNA fragmentation testing prior to IVF/ICSI treatment.**
5. **We suggest that women should have testing of ovarian reserve in the form of an AMH level and/or AFC, to predict ovarian response.**
6. **We suggest that a baseline ultrasound scan may be performed to ensure that ovaries are quiescent and that the endometrial thickness is <5mm prior to starting stimulation. Pregnancy must be out ruled prior to starting stimulation.**

Clinical Question 2.2: What are the clinical indications for IVF?

Evidence Statement

Standard IVF involves the introduction of sperm to a petri dish with oocyte(s) to facilitate fertilisation. To do so they must swim to the oocyte and penetrate the zona pelucida so that one sperm can enter the oocyte and fertilise it. This is the fertilisation technique that should be used when semen analysis parameters are favourable. Intracytoplasmic sperm injection (ICSI) is the recommended fertilisation technique in cases of male factor infertility. This is discussed in more detail in Clinical Question 2.3.

Compared with a non-assisted conception, IVF carries additional risks including the possibility of ovarian hyperstimulation syndrome (OHSS), adverse drug reactions to stimulation medications, venous thromboembolism (VTE), procedural risks of oocyte retrieval (OCR) and an increased risk of multiple pregnancy [51]. Thus, the decision to recommend IVF must be considered and appropriate. Individuals/couples should be given adequate information on the risks, benefits, and alternatives to IVF treatment to help them make an informed decision, with a focus on shared decision making.

The timeframe on when it is appropriate to recommend IVF treatment will differ depending on the clinical scenario and should be individualised, considering age, in particular the age of the woman, the length of time TTC and the cause of infertility.

IVF was originally used as a treatment for complete tubal infertility, as it bypasses the blocked fallopian tubes as eggs are retrieved directly from the ovary, fertilised in the laboratory and the embryo is inserted directly into the uterus [13]. If tubal patency testing reveals severe tubal infertility (bilateral tubal blockage), this is an absolute indication for IVF and treatment should not be delayed.

According to the National Guideline – Fertility Investigations and Management in Secondary Care ovulation induction (OI) may be an appropriate first line treatment in women with irregular cycles who are not spontaneously ovulating. In a younger couple with unexplained infertility who have been TTC for >1year, stimulated IUI should be offered as first line treatment [1]. The National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) recommend that IVF should not be offered to a couple with unexplained infertility until they have been TTC for at least 2 years [45]. The guideline also does not recommend IUI over expectant management for couples with unexplained infertility. The justification for this is that 50% of those who do not conceive in the first year will do so after a further year of TTC and they quote a cumulative pregnancy rate of 90% in 2 years where the female partner is aged under 40 years [45]. The European Society for Human Reproduction and Embryology (ESHRE) Guideline on Unexplained Infertility (UI) advises more individual recommendations for 'active treatment' for UI [6]. The ESHRE guideline recommends stimulated IUI first line for couples with unexplained infertility and a good prognosis, and states that 'the decision to use IVF is individualised by characteristics such as age, duration of infertility, previous treatment and previous pregnancy'[6].

IUI is less invasive and expensive than IVF treatment, however it is also less likely to be successful, particularly in older women. A systematic review and meta-analysis including eight randomised control trials (RCTs) comparing stimulated IUI to IVF in couples with unexplained infertility, found that IVF was significantly more likely to result in a live birth, with no difference in multiple pregnancy or OHSS (RR 1.53, 95% CI 1.01-2.32, P < 0.00001) [52]. In women aged ≥38 years, LBR was significantly higher after IVF treatment compared with IUI (RR 2.15, 95% CI 1.16-4.00, 1 RCT, 154 women) [52, 53]. In women >38 years, IVF should be considered first line, irrespective of the cause of infertility [51]. Couples with unexplained infertility may therefore wish to proceed directly to IVF treatment, particularly if they have been TTC for >1 year.

IVF may be offered following unsuccessful cycles of IUI or OI (3-6 cycles). Other indications for IVF include mild tubal disease, endometriosis, or mild male factor subfertility.

Conventional IVF should not be proposed in the presence of severe sperm abnormalities, or after fertilisation failure or low fertilisation in previous attempts.

Clinical Practice

To access IVF treatment people will need to be referred to a fertility clinic, either via the one of the 6 National Fertility Hubs, or privately via their GP or a self-referral. The decision to proceed with IVF treatment should be made by the person/couple after receiving adequate information about the treatment, the likelihood of success, risks of treatment and alternatives to treatment.

Infertility and its treatment can cause psychological distress and may negatively impact mental health and relationships. Counselling should be offered before, during and after investigation and treatment, irrespective of the outcomes.

Recommendations

7. **We strongly recommend that IVF should be offered first line for complete tubal infertility.**
8. **We recommend that IVF should be offered first line for couples with unexplained infertility when the woman is aged over 38 years.**
9. **We suggest that IVF be offered for the following indications:**
    - **Mild tubal/partial tubal infertility**
    - **Endometriosis with infertility**
    - **Following previous unsuccessful treatment (OI or IUI)**
10. **We recommend that individual/couple preferences should be considered when recommending IVF/ICSI treatment.**

Clinical Question 2.3: What are the clinical indications for ICSI?

Introduction

Intracytoplasmic sperm injection (ICSI) involves using micromanipulation so that a single spermatozoon is selected, immobilised, and injected into a mature oocyte. This technique was introduced in 1992, to overcome poor/failed fertilisation with conventional IVF and to address male factor infertility [54, 55]. ICSI is now considered a routine ART technique, though some indications for its use are debated.

Globally, the rate of ICSI compared to conventional IVF has increased, disproportionate to the rate of male infertility. According to the American Society for Reproductive Medicine (ASRM) committee opinion report 2020, the rate of ICSI increased from 36.4% of cycles in 1996 to 76.2% in 2012 [56]. A similar trend has been observed in Europe with two thirds of cycles using ICSI as the fertilisation technique [57].

The hope was that this fertilisation technique could overcome issues of poor fertilisation and unexplained infertility in the absence of abnormal parameters on semen analysis. However, it has since been demonstrated that ICSI does not improve reproductive outcomes in couples with non-male factor infertility [58]. The trend towards an increased use of ICSI has been the topic of much debate recently. A 2020 committee opinion published by the ARSM have advocated a more selective use of ICSI [56]. ICSI is not indicated for routine use. The clinical decision to offer ICSI rather than conventional IVF should be evidence-based.

Evidence Statement

ICSI is the accepted fertilisation method for male factor infertility.

The male partner should have a semen analysis performed for diagnostic purposes to determine if conventional IVF or ICSI is the most appropriate insemination procedure (as discussed in Clinical Question 2.1).

As previously discussed, in azoospermic men, it may be possible to retrieve live sperm via surgical retrieval, following which ICSI may be performed. The cut off values for semen analysis used as a threshold for ICSI are debated. Some argue that ICSI should be performed for all forms of male factor infertility, including low morphology alone (i.e. normal concentration, count and motility) [59, 60]. One retrospective cohort study from China including 375 number of cycles found that a morphology <4% was significantly associated with poorer normal fertilisation rates[61]. Others argue that ICSI should only be used for 'severe' male factor infertility, though no international consensus exists on the definition of severe male factor. One Chinese multicentre RCT compared IVF vs ICSI in couples where there was non-severe male factor, which they defined as semen concentration of 5-15×10 ^{6}/mL or sperm with a progressive motility 10%-32%. They randomised 2387 couples and found that ICSI did not improve LBR compared with conventional IVF[62]. Recruitment for a similar RCT in Denmark is on-going [63].

Some laboratories may recommend that IVF is reasonable in cases of low morphology only if the semen sample prepares well in the lab. Each laboratory in clinics providing IVF/ICSI should define a threshold for ICSI for male factor subfertility and follow standard operating procedures (SOPs).

ICSI for failed or poor fertilisation

Instances of total fertilisation failure following conventional IVF are indicative of a high chance of future failed fertilisation in subsequent IVF cycles [64]. According to the Vienna Consensus, an ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine, 2017, ICSI should be the fertilisation method used in future cycles where there has been total fertilisation failure or poor fertilisation following a conventional IVF cycle (<25% normal fertilisation of inseminated oocytes) [65]. A 2001 RCT comparing IVF with ICSI (435 treatment cycles) found that the frequency of total fertilisation failure with ICSI is lower than with conventional IVF (2% vs 5% per cycle). However, the same study found that the pregnancy rate was higher in the IVF group than the ICSI group (33% vs 26%) [66].

Rescue ICSI (mature oocytes that failed to fertilise following conventional IVF are subsequently injected with sperm via ICSI) should not be practised due to the risk of polyspermy. Conventional IVF cycles cannot establish the origin of or prevent polyploidy. However, using ICSI subsequent to a previous conventional IVF cycle which resulted in a high incidence of polyploidy zygotes may minimise the risk of reoccurrence through polyspermy[67, 68]. It should be discussed that if triploidy occurred through oocyte-derived meiotic failure, ICSI cannot correct the problem, and the phenomenon may repeat in subsequent cycles.

Other indications for ICSI

ICSI is the chosen fertilisation technique for the fertilisation of thawed oocytes. When oocytes are cryopreserved, the cumulus layer is removed which disrupts oocyte-sperm functions that impact fertilisation, e.g. capacitation of spermatozoa [69]. ICSI is associated with significantly better fertilisation rates when compared with IVF using thawed cryopreserved oocytes [70].

ICSI was previously recommended as the optimum fertilisation technique when pre-implantation genetic testing (PGT) is performed [71]. PGT involves taking a biopsy of embryos and performing genetic testing either to screen for a specific genetic disease and select unaffected embryos for transfer (PGT for monogenic disorders – PGT-M, or PGT for structural rearrangements – PGT-SR) or to screen for aneuploidy – PGT-A. The rationale for using ICSI over conventional IVF in these cases is to ensure monospermic fertilisation and to eliminate the potential for contamination with extraneous spermatozoa which could impact on the results. A retrospective study comparing fertilisation techniques in PGT-A identified a trend towards a higher rate of mosaicism in IVF (25.9%) versus ICSI (20.9%), though this was not statistically significant [72]. A retrospective analysis of 641 couples with non-male factor subfertility undergoing PGT-A cycles compared conventional IVF (cIVF) with ICSI. They found low rates of parental contamination with cIVF for PGT-A cycles and concluded that cIVF is feasible for PGT-A cycles [73] The fear of contamination seems to be less of a concern with newer technologies[74]. The ASRM recommend using ICSI for PGT in cycles where contamination with extraneous sperm will impact on the accuracy of the results [56].

Risks of ICSI

Oocyte degeneration following injection is an immediate risk which may be a consequence of injection technique or may reflect oocyte quality and resilience to the ICSI procedure itself. The ESHRE Special Interest Group of Embryology and Alpha Scientists in Reproductive Medicine, suggested an oocyte degeneration rate of no greater than 10%[75].

Further risks associated with ICSI include inherited male infertility in ICSI conceived offspring. It is well recognised that male factor infertility may have a genetic component [76]. Therefore, in cases of severe oligozoospermia (<5-15×10 ^{6}/mL) genetic testing for karyotyping, Y chromosome microdeletions and Cystic Fibrosis screening should be combined with appropriate counselling to manage men with oligozoospermia or azoospermia (no sperm in the ejaculate).

ICSI may be associated with an increased risk of congenital anomalies compared with conventional IVF. A recently published report from the Committee on Nordic ART and Safety (CoNARTaS) database comprising more than 86,000 children conceived using ART, and 4 million controls has found the risk of major malformations in ICSI significantly higher than in IVF[77]. Results showed a background rate of major malformations of 4.2%. Six percent of children conceived with fresh ICSI and 4.9% conceived with cryo ICSI had a major malformation. This compared with 5.3% of children born from fresh IVF (adjusted OR 1.07 ICSI vs IVF; OR 1.28 ICSI vs no medical assistance; and OR 1.11 fresh ICSI vs cryo ICSI) [77].

Furthermore, a retrospective study using data from the Canadian Assisted Reproduction Technologies Registry, studying over 80,000 cycles found that the use of ICSI for non-male factor infertility is associated with a higher risk of pregnancy complications including pre-term birth, intrauterine grown restriction, gestational diabetes and pregnancy induced hypertension [78].

Clinical Practice

It should be possible for the prescribing doctor to provide a treatment plan dictating ICSI as the fertilisation method in advance of most ICSI treatment cycles. Repeat semen analysis for diagnostic purposes will determine most cases that require ICSI treatment for male factor infertility based on sperm concentration, motility, and morphology. In these instances, a recommendation for ICSI will be made by the laboratory team based on the sperm parameters which in turn will be discussed with the couple during a consultation appointment.

There are specific scenarios whereby ICSI treatment may be recommended in the absence of male factor infertility. Treatment plans should be individualised considering previous conventional IVF/ICSI treatment fertilisation rates and prospective treatment cycle types (e.g. oocyte thaw and fertilisation).

In PGT cycles ICSI should be used when there is a concern that paternal contamination may impact the accuracy of results (PGT-M and PGT-SR). In the absence of male factor infertility or other indications, conventional IVF is feasible for PGT-A.

While the treatment plan provides a guide to the clinical and laboratory teams for a prospective treatment cycle, the plan may be altered during treatment to improve outcome, e.g. convert a conventional IVF cycle to ICSI in instances where a semen sample does not prepare well. Semen sample quality varies as it is a biological sample. Therefore, all couples should be counselled on ICSI as it may be recommended to convert a planned IVF cycle to ICSI on the day of OCR.

Recommendations

11. **We strongly recommend that ICSI should be performed as the fertilisation technique for male factor infertility.**
12. **We recommend that ICSI is performed when a previous IVF cycle resulted in failed fertilisation or suboptimal fertilisation.**
13. **We recommend that ICSI is the fertilisation technique of choice for thawed oocytes.**
14. **We recommend that ICSI should be used as a fertilisation technique for PGT-M and PGT-SR. Conventional IVF is feasible for PGT-A.**

Section 2 – IVF/ICSI treatment in practice

Introduction

A 'cycle' or 'round' of IVF/ICSI encompass several steps (listed below).

The type of medications used in pre-treatment and ovarian stimulation should be individualised and a treatment plan should be devised by physicians taking into consideration the woman's expected response to stimulation, response to previous stimulation, if applicable, and individual/couple preferences.

The duration of a cycle will depend on the stimulation protocol used and the woman's response to stimulation. Whether IVF or ICSI are used as a fertilisation method, the rest of the treatment cycle is the same and thus, for the remainder of the guideline 'IVF' will be the term used.

Steps involved in an IVF/ICSI cycle:

1. Baseline ultrasound scan
2. Pre-treatment medication
3. Controlled ovarian hyperstimulation (COH)
4. Monitoring during stimulation
5. Oocyte maturation trigger
6. Oocyte retrieval (OCR)
7. Production of sperm sample/thawing donor sperm
8. Fertilisation and embryo development in the laboratory
9. Embryo transfer
10. Pregnancy testing

Controlled ovarian hyperstimulation (COH) involves injection with gonadotropins for approximately 10-14 days. Protocols for stimulation will be discussed in more detail in Clinical Question 2.4.

Ovarian response refers to the number of ovarian follicles seen on ultrasound and/or the number of oocytes retrieved. Previously ovarian response was described as poor, normal or excessive [79]. This language can be triggering for individuals undergoing IVF treatment thus the terms low, normal, and high ovarian response are preferred [80]. There is no universally accepted definition for ovarian response, but The European Society of Human Reproduction and Embryology (ESHRE) guideline on ovarian stimulation for IVF/ICSI suggests the following definition be used [7]:

- **Low ovarian response**

  a diminished response to conventional ovarian stimulation.

  ≤ 3 follicles on day of oocyte maturation trigger and/or ≤ 3 oocytes collected.

- **High ovarian response**

  an exaggerated response to conventional ovarian stimulation.

  > 18 follicles ≥11 mm in size on day of trigger and/or 18 oocytes collected.

  This poses an increased risk of OHSS.

The definition of low ovarian reserve is based on the 'Bologna criteria' which was an ESHRE consensus statement published in 2011 in which poor ovarian response (POR) was described [79]. Whilst there has been some criticism of the Bologna criteria, including for the use of the word 'poor' to describe response, this was a practical attempt to identify a reproducible way of identifying women who are likely to have a lower response to ovarian stimulation [81]. The above definition of high ovarian response is based on a retrospective analysis of data from 3 trials, comprising over 2,400 women. Analysis showed that women with ≥19 follicles ≥11mm on the day of trigger are at higher risk of moderate to severe OHSS [82]. Clinical tools which can be used to predict ovarian response will be discussed below and strategies which can be used to prevent OHSS will be discussed in a later section.

Clinical Question 2.4: What stimulation protocol should be used in IVF?

Evidence Statement

The number of oocytes collected is associated with IVF success, the cumulative live birth rate (CBLR) increases with increasing number of oocytes retrieved [83, 84]. However, a greater quantity of oocytes does not mean greater quality, and beyond a certain threshold the LBR appears to plateau. This is particularly evident in women with polycystic ovarian syndrome (PCOS), the oocyte yield is often high but the oocyte quality may not be higher [85]. A large analysis of over 400,000 IVF cycles found that the optimum oocyte yield to achieve a live birth is approximately 15 eggs, above 15 eggs, the live birth rate (LBR) plateaus, and more than 20 eggs is associated with a lower LBR [84].

There are many gonadotropin preparations available, all contain follicle stimulating hormone (FSH), either highly purified urinary (HP u-FSH) or recombinant (rFSH) and some preparations contain luteinising hormone (LH). There is much discussion in the literature on the optimal stimulation medication and a detailed discussion of this is beyond the scope of this guideline which aims to give an overview of all steps of an IVF cycle. We recommend referring to the ESHRE Guideline on Controlled Ovarian Stimulation for a more detailed discussion of the various medications used for COH [7].

Conventional stimulation consists of a dose of 150-225 IU of FSH [7]. There is no agreed maximum dose of FSH, however evidence from a Cochrane meta-analysis of 5 randomised control trials (RCTs) showed no significant improvement in number of oocytes retrieved at doses higher than 300IU daily, even in low responders. Furthermore, there is an increased risk of OHSS with higher doses [86]. Addition of recombinant human luteinizing hormone(r-LH) to recombinant follicle stimulating hormone (r-FSH) to ovarian stimulation protocols has been shown to improve implantation rates and clinical pregnancy rates in women who are aged over 35 years or who are 'low-responders' to FSH alone[87, 88]. The addition of LH does not appear to be of benefit in an unselected population [89].

There are two basic protocols for COH – the GnRH agonist and GnRH agonist protocols. Overall, GnRH antagonist and GnRH agonist protocols have similar success rates. A 2016 Cochrane Review found that there was no difference in the live birth rate (LBR) between GnRH antagonist vs GnRH agonist protocol but that the GnRH antagonist protocol was associated with a reduced risk of OHSS [90, 91].

Pre-treatment

A 2017 Cochrane review, including analysis of 29 RCTs, summarised the evidence for pre-treatment vs no pre-treatment [92].

- Oestrogen pre-treatment resulted in a significant increase in the number of oocytes retrieved, compared to no pre-treatment in GnRH antagonist cycles, however there was no increase in clinical pregnancy rate, ongoing pregnancy rate or LBR.
- Progesterone pre-treatment, compared with no pre-treatment, did not result in a higher LBR in GnRH antagonist cycles and there was insufficient evidence to determine whether there was a difference in GnRH antagonist cycles.
- Pre-treatment with the COCP was found to be associated with a lower LBR and no difference in OHSS rate compared with no pre-treatment in GnRH antagonist cycles.

A more recent RCT, published in 2018, compared oestrogen pre-treatment with COCP pre-treatment and no pre-treatment showed no difference in clinical pregnancy rate (CPR) with the COCP. There was a higher CPR in the oestrogen pre-treatment group but this was not statistically significant [93].

Clinical Practice

COH involves daily injections with gonadotropins, these are generally self-administered by the woman. The woman's response to ovarian stimulation is monitored with ultrasound scans. Generally, approximately 10-12 days of stimulation is required. It is important to strike a balance between stimulating the ovaries sufficiently to retrieve oocytes and avoiding over-stimulating them and causing ovarian hyperstimulation syndrome (OHSS).

Based on the available evidence, we suggest aiming to collect 10-15 eggs in women with anticipated normal or high ovarian response.

Ovarian Response is predicted according to the definition used in the ESHRE guideline on ovarian stimulation for IVF/ICSI [7]:

Low ovarian response

- a diminished response to conventional ovarian stimulation.
- ≤ 3 follicles on day of oocyte maturation trigger and/or ≤ 3 oocytes collected.

High ovarian response

- an exaggerated response to conventional ovarian stimulation.
- > 18 follicles ≥11 mm in size on day of trigger and/or 18 oocytes collected.
- This poses an increased risk of OHSS.

Women with a low AMH or AFC often have a predicted low ovarian response and women with PCOS and a high AMH and AFC often have a predicted high ovarian response.

When a woman is undergoing COH with gonadotropins, it is important to prevent a premature surge in LH, to ensure that ovulation does not occur. This is achieved by either blocking or down-regulating gonadotropin releasing hormone.

There are two basic stimulation protocols for LH suppression used in IVF/ICSI:

1. GnRH antagonist
2. GnRH agonist (down regulation)

GnRH Antagonist protocol

GnRH antagonists competitively block GnRH receptors, resulting in rapid suppression of LH and FSH secretion by the pituitary gland. GnRH antagonists are introduced after COH with gonadotropins has begun, either on day 6 of stimulation (fixed start) or when the lead follicle is >14mm (flexible start).

GnRH Agonist protocol

In the physiological state, there is pulsatile secretion of GnRH from the hypothalamus, leading to secretion of FSH and LH from the pituitary gland. Administration of exogenous GnRH leads to a short period of gonadotropin hypersecretion, followed by gonadotropin suppression due to pituitary desensitisation. GnRH agonists are administered prior to commencing COH, either as a nasal spray or injection.

Pre-treatment with oestrogen, progesterone, or the combined oral contraceptive pill (COCP) is commonly used. Pre-treatment therapies aim to suppress or to reduce LH and/or FSH secretion prior to gonadotropin stimulation in IVF cycles. It can also be useful for scheduling purposes, allowing clinics to plan IVF cycles. The COCP should ideally not be used in cycles where a fresh embryo transfer is planned. The COCP may still be used in cases where no fresh embryo transfer is planned, for example PGT cycles.

There are many stimulation medications available. A detailed discussion of all these medications is beyond the scope of this guideline. Clinics providing IVF/ICSI should have their own standard operating procedure (SOP) providing guidance on medications to prescribe in specific clinical scenarios (for example in women at high risk of OHSS or women with low ovarian reserve). Clinics should liaise with their local pharmacy unit regarding availability of medications as this will dictate which medications may be prescribed.

The protocol and dose should be individualised, considering the woman's age, predicted ovarian response, response to any prior treatment and the woman's preferences.

Recommendations

15. We strongly recommend that for women who are predicted to have a high ovarian response, a GnRH antagonist protocol should be used for controlled ovarian hyperstimulation (COH).
16. We recommend that for women who are predicted to have a low ovarian response, a GnRH agonist protocol is a reasonable first line choice for COH, the GnRH antagonist protocol may also be used.
17. We recommend that all clinics providing IVF/ICSI have their own standard operating procedure (SOP) providing evidence-based guidelines for prescribing medications for ovarian stimulation, taking into account availability of medications.
18. We suggest that pre-treatment with oestrogen or progesterone may be used for scheduling purposes as it does not appear to negatively affect outcomes.
19. We do not recommend pre-treatment with the combined oral contraceptive pill (COCP) if a fresh embryo transfer is planned.

Clinical Question 2.5: How should an IVF cycle be monitored?

Evidence Statement

Ultrasound and serum hormone level monitoring

Monitoring of COH for IVF/ICSI cycles is important to identify and mitigate the risk of OHSS whilst also achieving a sufficient ovarian and endometrial response to stimulation necessary for successful treatment.

Generally, monitoring during COH has involved a combination of transvaginal ultrasonography (TVUS) and serum oestradiol level assessments. However, there is ongoing debate regarding the necessity of utilising both methods at the same time.

There is an association between higher serum oestradiol levels and OHSS but high quality studies have failed to show that monitoring of oestradiol levels prevents OHSS[94]. A systematic review and meta-analysis conducted in 2014, examining the monitoring techniques for ovarian stimulation in IVF/ICSI, compared ultrasound monitoring alone versus a combination of ultrasound and serum oestradiol levels across 6 RCTs (781 women) found that combining serum oestradiol measurements and ultrasound during stimulation did not show a significant decrease in the likelihood of OHSS, nor did it significantly improve the number of retrieved oocytes or CPR[95].

Monitoring of endometrial thickness during COH

The endometrium plays a crucial role in human reproduction. Its primary function is to provide an ideal environment for embryo implantation and development.

An endometrial thickness (EMT) of >7mm is desirable prior to embryo transfer and a thin endometrium has been shown to be associated with reduced likelihood of success in IVF treatment. A systematic review and meta-analysis from 2014, including over 10,000 women undergoing IVF cycles found that the probability of clinical pregnancy for an EMT <7 mm was significantly lower compared with cases with EMT > 7 mm [23.3% versus 48.1%, OR 0.42 (95% CI 0.27-0.67)] [96]. A more recent systematic review and meta-analysis investigating the association between endometrial thickness and live birth rate (LBR) in fresh IVF cycles reported that women with a thin endometrium (EMT < 7 mm) had a significantly lower LBR compared to women with EMT >7 mm (OR 0.47; 95% CI 0.37-0.61) [97]. The same review found that a thick endometrium (EMT >14mm) was not associated with a decreased chance of pregnancy. The prevalence of a thin endometrium (EMT <7mm) in women undergoing IVF treatment varies between studies, between 2.5%-5.5% [96, 98].

Clinical Practice

Women should be monitored by their fertility clinic whilst undergoing COH. Pelvic ultrasound, ideally transvaginal (if this is acceptable to the woman) should be used to monitor follicular response to COH and to measure endometrial thickness. Ultrasound scans should be reviewed by the clinical team daily. The number of scans required or frequency of ultrasound monitoring will depend on the individual woman's response to COH. The duration of COH varies but is typically 10-12 days. All women should be given contact details for the clinic and out-of-hours emergency services if required.

Recommendations

20. We recommend monitoring with pelvic ultrasound, ideally transvaginal, during COH to measure:
    - Ovarian response (follicular growth)
    - Endometrial thickness
21. We do not recommend monitoring with serum oestradiol in addition to pelvic ultrasound as it has not been shown to reduce OHSS risk.
22. We suggest that endometrial thickness should ideally be >7mm before embryo transfer.

Clinical Question 2.6: When and how should triggering occur?

Evidence Statement

How to trigger

In the physiologic state, oocyte maturation occurs just prior to ovulation and involves the release of the oocyte from meiotic arrest, under the influence of LH, and is essential for fertilisation [99]. In IVF cycles, triggering aims to ensure that oocytes retrieved at egg collection are mature and capable of fertilisation. The oocyte maturation trigger is usually initiated by a single injection of human chorionic gonadotropin (hCG), with doses ranging between 5,000 to 10,000 IU [100]. hCG is similar in its biologic activity to LH, but it has a longer half-life [101]. In GnRH antagonist cycles, oocyte maturation may also be triggered by the administration of a bolus injection of a GnRH agonist. This more closely mimics the natural increase of endogenous LH and FSH, thus making it more physiological. The use of a GnRH agonist trigger is associated with a lower risk of OHSS [102]. If a GnRH agonist trigger is given alone, fresh embryo transfer cannot take place without hCG and thus a 'freeze all' (where all suitable embryos are cryopreserved) approach should be adopted.

A combination of hCG and a GnRH agonist may be used to trigger in GnRH antagonist cycles. This is known as a 'dual trigger'. The ESHRE guideline does not recommend dual triggering for predicted normal responders [7]. However, a more recently published systematic review and meta-analysis including 4 RCTs and 2 prospective cohort studies comparing hCG trigger with dual trigger, found a statistically significantly higher number of ooctyes retrieved (SMD=0.24, 95% CI=0.01, 0.74) and live birth rate (OR=2.05, 95%CI=1.48, 2.84) in the dual trigger group [103]. A dual trigger should be considered in GnRH antagonist cycles, particularly in women with a predicted low ovarian response as it has been shown to be associated with a higher oocyte yield and LBR [104].

When to trigger

Timing of final oocyte maturation is a crucial moment in the IVF treatment cycle. The administration of the trigger is carefully timed to align the OCR procedure with the peak moment of egg maturity. If OCR happens too soon after triggering, less mature oocytes will be available for retrieval, if OCR is too late after the trigger injection ovulation can occur. A recently published systematic review and meta-analysis of 12 studies, including four RCTs, compared a short (≤36 hr) vs long (36-38 hr) interval between hCG trigger and OCR. Oocyte maturation rates, fertilisation rates and high quality embryo rates were similar between the two groups. The clinical pregnancy rate was significantly higher in the long interval group (OR, 0.66; 95% CI 0.45-0.95; I^2=35.4%) but miscarriage and LBR were similar between the two groups [105].

Criteria used for inducing the final egg maturation differ significantly between studies. In most studies, hCG is administered when ≥3 follicles ≥17 mm are present on ultrasound [106]. In a RCT involving 190 participants, the timing for trigger injection was set according to the size of the leading follicle – either 18 mm or 22 mm. The findings revealed that the live birth rate (LBR) did not significantly differ whether the trigger was applied at a follicle size of 22 mm, 35% LBR (34/97 women) or at 18 mm, 23% LBR (21/93 women) (RR 1.6 (0.98-2.47) [107]. Nonetheless, the study noted a higher incidence of ongoing pregnancies in the group with the 22 mm follicle size at trigger (38%) compared to the 18 mm cohort (24%) (RR 1.6, 95% CI: 1.03-2.5). In addition, the number of oocytes retrieved was significantly greater in the 22mm group (11.7 ±5.7) compared with the 18mm group(9.7 ±4.1) [107] A systematic review and meta-analysis of seven RCTs examined the implications of delaying the final stage of oocyte maturation by either 24 or 48 hours. The research found no notable difference in the LBR (3 RCTs, RR 1.14, 0.46-2.83, 354 women) or rate of ongoing pregnancies per oocyte retrieval (4 RCTs, RR 0.97, 95% CI 0.54-1.74, 743 women) when comparing the administration of early vs late hCG [108]. However, the group that received the later hCG treatment had a significantly higher number of oocytes collected (4 RCTs, MD 1.2, 95% CI 1.11-1.30, 743 women) [108].

Observational studies have shown an association between higher serum oestradiol levels and a greater yield of mature oocytes [109]. However, no interventional studies have been done to support the use of serum oestradiol as a threshold for triggering. Serum oestradiol levels should not be used to determine the timing of the oocyte maturation trigger.

The authors of the ESHRE guideline on Ovarian Stimulation concluded that the decision on timing of triggering should be individualised considering follicle in relation to follicle size, duration of stimulation, organisational factors, and patient burden[7].

Clinical Practice

The choice of the trigger should be clearly stated in the treatment plan. The hCG trigger is the 'gold standard' trigger and required if the intention is to proceed with fresh embryo transfer. In women where there is a high risk of OHSS (for example women with PCOS and a high AMH), the use of a GnRH antagonist protocol with GnRH agonist trigger and 'freeze all' strategy is advised. A frozen embryo transfer can then be planned later. It is important to note that fresh embryo transfer is not recommended without the administration of hCG.

A GnRH antagonist protocol with a GnRH agonist trigger is often used for women undergoing oocyte vitrification or egg freezing as fresh embryo transfer is not the aim in these cycles.

A dual trigger with hCG and a GnRH agonist could be considered in GnRH antagonist cycles where the woman has a predicted or previous low ovarian response as this has been shown to improve oocyte yield and LBR.

Most often, the final oocyte maturation trigger is given when several of the leading follicles have reached a size of 16-22 mm. OCR should be scheduled for 36 hours following the trigger injection and clinics should educate women about the importance of timing of this injection. In practice it is not always achievable for the OCR to occur exactly 36 hours after the trigger is administered but based on recently published evidence clinicians and women can be reassured that an interval of 36-38 hours may lead to improved outcomes.

Recommendations

23. We recommend that an oocyte maturation trigger should be given 36-38 hours prior to egg collection.
24. We recommend that the decision on when to trigger should be individualised, usually when lead follicles have reached 16-22mm size.
25. We recommend that if a fresh embryo transfer is planned, a HCG trigger is given, either alone or combined with a GnRH agonist trigger.
26. We suggest that a dual trigger (hCG and GnRH agonist) may be considered in women who have predicted or previous low ovarian response in a GnRH antagonist cycle.
27. We recommend that in GnRH antagonist cycles, where there is a high risk of OHSS, a GnRH agonist trigger may be given, along with a 'freeze all' approach as this reduces the risk of OHSS.

Clinical Question 2.7: What luteal support should be provided for embryo transfer?

Evidence Statement

In the physiological state, following ovulation, the corpus luteum produces progesterone. Progesterone is essential for early pregnancy, preparing the endometrium to allow implantation and secreting nutrients essential for the early embryo. In an IVF cycle, supplementation with progesterone in the luteal phase improves outcomes. A 2015 Cochrane Review, including a meta-analysis of 5 RCTs and 642 women found a higher LBR/on-going pregnancy rate with luteal phase progesterone support compared with no treatment or placebo (OR 1.77, 95% CI 1.09-2.86) [110].

Route of administration

Progesterone may be administered either orally (PO), vaginally (PV), rectally (PR), subcutaneously (SC) or intramuscularly (IM). Several studies have evaluated the efficacy and safety of the routes of administration. A Cochrane meta-analysis showed oral to be the least effective route of administration but no statistically significant difference was found between IM vs. PV/PR routes (OR 1.37, 95% CI 0.94-1.99) [110]. Another IP meta-analysis comparing SC progesterone versus PV progesterone found no significant difference in on ongoing pregnancy rate (OR = 0.865, 95% CI 0.694 to 1.077; P = n.s.), LBR (OR = 0.889, 95% CI 0.714 to 1.106; P = n.s.) or OHSS risk (OR = 0.995, 95% CI 0.565 to 1.754; P = n.s.) [111]. A recently published retrospective study compared combined IM and PV progesterone vs. PV progesterone only, with similar outcomes in both study arms [112]. The majority of women appear to prefer the PV route of administration, with 87% of women who participated in an RCT (IM vs PV progesterone) reporting the PV method as convenient and painless [113]. The ESHRE guideline on Ovarian Stimulation suggests that any (non-oral) route of progesterone luteal support is acceptable [7].

Dose

There does not appear to be a benefit to higher doses of progesterone. A 2015 Cochrane Review of 5 RCTs mentioned above found no difference in LBR or on-going pregnancy rate (OR 0.97, 95% CI 0.84-1.11, 3720 women) comparing a low dose (≤ 100 mg) with a high dose (≥ 100 mg) of progesterone. The ESHRE guideline recommends the following empiric dosing for natural progesterone[7]:

- 50 mg once daily for intramuscular progesterone
- 25 mg once daily for subcutaneous progesterone
- 90 mg once daily for vaginal progesterone gel
- 200 mg three times daily for micronised vaginal progesterone in-oil capsules.

Timing and duration

Several studies have investigated the timing of initiation of progesterone therapy. A systematic review and meta-analysis of 5 RCTs (872 women) concluded that there appears to be a window for commencing progesterone between the evening of OCR up to 3 days post-OCR [114]. A meta-analysis of 6 RCTs (1,201 women) compared continuing progesterone therapy until positive pregnancy test to continuing to 6/7 weeks' gestation, found no significant difference in LBR (RR: 0.95, 95% CI: 0.86-1.05), miscarriage rate (RR: 1.01, 95% CI: 0.74-1.38) or ongoing pregnancy rate (RR: 0.97, 95% CI: 0.90-1.05) [115]. The ESHRE guideline suggests that luteal support should be commenced from between the evening of egg collection up to 3 days after egg collection and continued at least until the pregnancy test is performed [7].

Clinical Practice

Progesterone should be prescribed as luteal support following oocyte retrieval in all women where the intention is to proceed with a fresh embryo transfer.

The route of administration may be vaginal, IM, SC or PR and should be decided considering local availability of medications, cost and acceptability.

Progesterone support should begin no more than 3 days following OCR and should continue at least until the pregnancy test is performed and may be continued into the first trimester depending on clinician and women's preference. It is our experience that most women prefer to continue progesterone support until fetal viability is confirmed on an ultrasound scan.

Recommendations

28. **We strongly recommend that progesterone is given for luteal phase support following OCR when a fresh embryo transfer is planned.**
29. **We recommend that progesterone support is initiated after OCR (from that evening up to 3 days post-OCR) and continued until at least the date of pregnancy testing.**
30. **We recommend that all routes of administration appear to be efficacious and the decision on the route of administration should be decided upon based on clinician and the woman's preferences.**

Clinical Question 2.8: How should embryo cryopreservation and frozen embryo transfer cycles be managed?

Evidence Statement

The first successful pregnancy following frozen embryo transfer (FET) was reported in 1983, and since then, FET has become a widely utilised technique in AHR, involving the thawing and transfer of cryopreserved embryos [116]. Suitable surplus embryos may be cryopreserved following a fresh embryo transfer, or in cases of a 'freeze-all' cycle, all suitable embryos are cryopreserved and FET can be planned at a later date. As previously discussed, a 'freeze-all' strategy may be adopted following OCR for a number of reasons including:

- To reduce the risk of OHSS
- To allow for pre-implantation genetic testing (PGT)
- For fertility preservation/'embryo banking'
- Individual/couple preference

Not all embryos are suitable to freeze. It is standard practice to freeze and store good quality embryos at the blastocyst stage of development only. Blastocyst culture enables natural embryo selection and good quality blastocysts are more likely to survive the freeze and thaw process. Survival rates in excess of 95% are reported for blastocyst freezing[117].

Whilst previously there was a concern that outcomes would not be as good following FET cycles than fresh cycles, recently published studies are reassuring in this regard [63, 118-120]. A Cochrane Review and meta-analysis of 15 studies including 4712 women found no difference in the cumulative live birth rate (CBLR) between fresh vs frozen embryo transfers but that the 'freeze all' strategy was associated with a lower risk of OHSS [120]. Another systematic review and meta-analysis of 11 studies compared obstetric and perinatal outcomes in elective FET (eFET) [121] vs fresh embryo transfer [119]. They found no difference in LBR in predicted normal responders, a lower risk of OHSS (RR = 0.42; 95% CI: 0.19-0.96) but a higher risk of pre-eclampsia with eFET (RR = 1.79; 95% CI: 1.03-3.09). No difference was observed for preterm birth, low birth weight or congenital anomalies between the two groups [119].

One crucial aspect of FET is optimal endometrial preparation. As with a fresh cycle, an endometrial thickness of >7mm is desirable prior to embryo transfer. A large Canadian retrospective cohort registry data study involving >96,000 embryo transfers (both fresh and frozen) found that in cycles with a fresh embryo transfer, LBR increased significantly until plateauing at an ET of 10-12 mm, in FET cycles the increase in LBR plateaued at an ET of 7-10 mm. An ET <6mm was associated with significantly lower LBR [122].

There are several protocols for endometrial preparation for a FET cycle, the majority consist of either a natural cycle protocol or a hormone replacement therapy (HRT) protocol, these are described below. It is also possible to perform a FET with FSH stimulation or following down-regulation with a GnRH agonist.

Natural cycle protocol

In women who have a regular cycle, a natural cycle FET may be performed. The embryo is transferred during the woman's luteal phase, when implantation would occur in a spontaneous conception. This involves ultrasound monitoring of ET and the development of a dominant ovarian follicle. A hCG injection may be given to trigger ovulation (modified – natural FET). The embryo transfer is usually scheduled for approximately one week following ovulation. Progesterone luteal support is prescribed, as for a fresh embryo transfer.

Hormone replacement therapy (HRT) protocol

An HRT cycle may be used to control the cycle, particularly in women who don't have a regular menstrual cycle. Oestrogen is administered exogenously (orally or via a transdermal patch) throughout the cycle and progesterone is commenced in the second half of the cycle. Ultrasound monitoring is used to measure the ET and decide when to schedule the FET, once the optimal ET has been achieved.

Both HRT FET and natural FET have been shown to yield comparable success rates, although individual characteristics and preferences should be taken into account. A 2017 Cochrane Review including analysis of 18 RCTs did not find sufficient evidence to support one protocol over the other, though they commented that the evidence was of low quality [123]. A subsequently published secondary analysis of a RCT including 908 FET cycles (683 were natural cycles, 225 HRT cycles) found that the LBR was similar in both groups but that the ET was significantly thicker in the natural FET group and there was a significantly higher rate of caesarean section in the HRT FET group [124]. The authors commented that HRT FET is more flexible and convenient and has a lower chance of cycle cancellation than natural FET [124]. A recently published systematic review and meta-analysis of the maternal and neonatal outcomes following pregnancies in FET cycles found a significantly increased risk of caesarean section (OR 1.5, 95% CI 1.4-1.6), hypertensive disorders of pregnancy (OR 1.9, 95% CI 1.6-2.2), postpartum haemorrhage (OR 2.6, 95% CI 1.9-3.4), and preterm delivery ≤32 weeks (OR 1.5, 95% CI 1.1-2.0) in HRT cycles compared with natural FET cycles [125].The authors argue that the high dose oestrogen and progesterone supplementation lead to altered placental regulation which leads to an increase risk of adverse pregnancy outcomes. In an HRT FET, follicular development is prevented, thus there is no corpus luteum formation. The corpus luteum is an important mediator of early pregnancy vascular adaption[126].

As with all AHR treatment protocols, treatment should be individualised, and a treatment plan made using shared decision making between the clinician and the individual/couple.

Clinical Practice

Each laboratory should have SOPs for embryo cryopreservation and storage. Cryopreserved oocytes, sperm and embryos should be safeguarded by means of an electronic continuous monitoring system which contacts the laboratory team (24/7) should the storage conditions become suboptimal.

Individuals/couples can be reassured that outcomes with FET are similar to fresh ET and that a 'freeze-all' strategy is associated with a lower risk of OHSS in those women at high risk of OHSS.

The decision on the protocol for FET should be individualised and involve joint decision making between the individual/couple and clinical team. HRT FET is recommended for women who do not have a regular cycle. Either natural FET or HRT may be appropriate if a woman has a regular menstrual cycle. In practice, the same woman may have multiple FETs and may trial several different FET protocols. The exact timing and preparation of any drugs used will be individualised and clearly stated on the woman's treatment plan.

An endometrial thickness of >7mm is recommended prior to frozen embryo transfer.

Recommendations

31. We recommend embryo cryopreservation to individuals/couples that have surplus embryos suitable to freeze following a fresh embryo transfer.
32. We suggest that the endometrial thickness should ideally be >7mm prior to a frozen embryo transfer (FET).
33. We recommend that the protocol for endometrial preparation should be individualised, taking into consideration the regularity of the woman's cycle, previous treatment if any and her personal preferences.

Clinical Question 2.9: How can the risks of IVF treatment be minimised?

Evidence statement

Risks of Controlled ovarian hyperstimulation (COH) - ovarian hyperstimulation syndrome (OHSS) prevention and management

OHSS is the most reported complication of assisted reproductive technology (ART) and may occur in up to one in three cycles involving controlled ovarian stimulation with gonadotropins [128, 129]. OHSS is usually a self-limiting condition with a spectrum of clinical sequelae occurring as a result of increased vascular permeability [130]. The syndrome can range in severity from mild abdominal discomfort and bloating to severe ascites, acute respiratory distress syndrome (ARDS) and pulmonary embolism. Severe OHSS is much rarer with a reported incidence ranging between 0.5 and 5% [128]. The European In Vitro Fertilisation (IVF) Monitoring Consortium (EIM) for ESHRE, 2019 (published in 2023) reported an incidence of hospitalisation due to OHSS of 0.16% (reduced from 0.3% in 2010), however the report comments that this complication, like other complications of ART, is likely underreported [131]. There is no Irish data available on the incidence of OHSS.

A 2016 Cochrane review found that the GnRH antagonist protocol is associated with a significantly lower chance of OHSS, compared with the GnRH agonist protocol [90]. The GnRH antagonist protocol should be used for LH suppression in women deemed to be at high risk of OHSS. A 2014 Cochrane Review found that the use of a GnRH agonist (e.g. Buserelin) as the oocyte maturation trigger in GnRH antagonist cycles is associated with a significantly reduced risk of OHSS when compared to hCG [132]. However, this comes at the expense of a lower LBR if a fresh ET is performed and thus the ESHRE guideline suggests a strategy of triggering with a GnRH agonist followed by a 'freeze-all' approach where all suitable embryos are frozen so that the woman can recover and undergo a frozen embryo transfer (FET) at a later date[7].

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor which is expressed in human ovaries and found to be elevated in women with OHSS [133]. The dopamine agonist, cabergoline, inhibits phosphorylation of the VEGF receptor, and has been shown to prevent the increase in vascular permeability associated with OHSS [134]. Several studies have evaluated the safety and efficacy of high dose cabergoline (variable doses from 0.5mg/day to 1mg/day from 5 up to 21 days) for prevention of OHSS in at risk women [135-137]. A 2012 Cochrane Review, which evaluated two randomised control trials (RCTs) including 230 women, concluded that prophylactic cabergoline appears to reduce the risk of OHSS in high risk women [138]. A subsequently published RCT found a 60% reduction in the incidence of OHSS in high risk women undergoing IVF/ICSI when cabergoline 0.5mg/day was administered for 8 days after the human chorionic gonadotropin (hCG) oocyte maturation trigger was given [136].

A Swedish cohort study which included over 900,000 deliveries and over 19,000 IVF pregnancies found that OHSS is associated with an up to 100-fold increase in VTE [139]. VTE may complicate up to 10% of cases of OHSS and so VTE prophylaxis should be considered for women diagnosed with OHSS, particularly those who are admitted to hospital. The ESHRE Capri Workshop Group on VTE suggest that in those women who become pregnant, continuing VTE prophylaxis until at least the end of the first trimester should be considered [140]. Duration of VTE prophylaxis should be decided on an individual basis depending on other risk factors and discussion with haematology may be considered.

Risks of oocyte retrieval (OCR)

OCR involves collection of eggs from ovarian follicles using a needle, usually performed via transvaginal ultrasound guidance, with the woman under sedation. OCR can also be performed laparoscopically or abdominally under ultrasound guidance. Complications of OCR are uncommon and are usually the result of blood vessel injury, bowel perforation, ureteric injury or introduction of infection in to the abdomen/pelvis[141]. A review of 3,656 women who underwent OCR found that 0.4% (n=14) presented with an acute abdomen following the procedure and only 3 women required laparotomy [142]. A 2007 literature review found that bleeding and infections occur in 0.4%-1.3% of all ultrasound guided OCRS [143]. A more recent review of 23,827 OCRs also found the complication rate per OCR to be low at 0.4% [144].

The incidence of pelvic infection is low and thus, the routine administration of antibiotics is debated. Additionally, recent evidence suggests that the microbiome can influence ART outcomes [145]. A 2016 Systematic Review, including 24 articles, suggests more judicious use of antibiotic prophylaxis, advising antibiotics only for women with a history of endometriosis, pelvic inflammatory disease (PID), ruptured appendicitis, or multiple prior pelvic surgeries [146]. The choice of antibiotic will depend on local microbiology guidelines and allergies.

Vaginal haemorrhage is estimated to occur in 8.6% of cases with blood loss >100mls occurring in <1% of cases[141]. Authors of a large review of over 3,500 cycles with a low incidence of haemorrhage, suggest the following measures to reduce the risk of haemorrhage at OCR: limit the number of vaginal punctures to two where possible, use ultrasound to visualise peripheral follicles in a cross section prior to puncture, use colour doppler if available to identify and avoid vessels[147].

Clinical Practice

Efforts should be made to reduce the risk of OHSS in women undergoing COH. The antagonist protocol should be used for COH in women who have risk factors for OHSS. The use of a GnRH agonist trigger (in GnRH antagonist protocol stimulation cycles) with a ‘freeze-all’ approach should be considered in women at high risk of OHSS. All women, particularly those at higher risk, should receive information on OHSS and should be advised to present to their clinic/emergency department if they develop symptoms.

Ovarian hyperstimulation syndrome (OHSS)	
Risk factors	**Signs and symptoms**
Polycystic ovary syndrome (PCOS)	Rapid weight gain – more than 1kg in 24 hours
High AFC (>30)	Severe abdominal pain
High AMH (>30)	Severe, persistent nausea and vomiting
Age <35 years	Symptoms/signs of DVT – leg swelling, calf pain etc
Low BMI	Decreased urine output
Previous episodes of OHSS	Shortness of breath
High or steeply increasing serum estradiol levels prior to trigger	Tight or enlarged abdomen.

Cabergoline 0.5mg/day should be prescribed for 5-7 days to women who are at high risk of OHSS for secondary prevention of severe OHSS.

VTE prophylaxis is indicated in women who develop OHSS and should be prescribed unless there is a significant bleeding risk. The duration of VTE prophylaxis will vary depending on the individual but continuation or prophylaxis into the first trimester should be considered in women who become pregnant. Consult with haematology if needed.

All women undergoing OCR should be informed of the potential risks of the procedure and should give informed consent. OCR should be performed under sedation or anaesthetic. Sedation should be administered by an appropriately trained clinician. As discussed in Clinical Question 2.1, women should have a detailed medical history taken prior to ART. Those with additional medical comorbidities may require optimisation or multidisciplinary team in put prior to undergoing stimulation and OCR. Efforts should be made to reduce the risk of procedural complications and antibiotic prophylaxis should be considered in women at high risk of infection (immunocompromised women, diabetic women, women with severe endometriosis or who have had multiple previous surgeries).

All clinicians who carry out OCR independently should be appropriately trained in transvaginal ultrasound and the OCR procedure and know how to recognise and manage complications which may arise. To minimise bleeding the clinician should aim to:

- limit the number of vaginal punctures to two where possible
- use ultrasound to visualise peripheral follicles in a cross section prior to puncture
- use colour doppler if available to identify and avoid vessels.

Women should be monitored in recovery following OCR for 1-2 hours, their vital signs (blood pressure, heart rate, temperature, respiratory rate and oxygen saturation levels) should be checked, they should be able to pass urine and their pain should be well controlled prior to being discharged. All women should be given written information on post-procedure care and a 24-hour phone number to contact. They should be advised to present to their local emergency department if they are unwell.

If a woman presents unwell following OCR consider in the differential diagnosis the possibility of:

1. Haemorrhage-vaginal or intra-abdominal
2. OHSS
3. Pelvic infection.

Recommendations

34. We recommend that all women should have an assessment of risk factors for OHSS and other complications of IVF.
35. We suggest that cabergoline 0.5mg/day for 5-7 days may be prescribed to women at high risk of OHSS.
36. We strongly recommend that the antagonist protocol should be used in women at high risk of OHSS.
37. We recommend venous thromboembolism prophylaxis for women who develop OHSS.
38. We suggest that antibiotics may be considered at OCR in women who are at increased risk of infection.

Clinical Question 2.10: When should an IVF cycle be cancelled?

Evidence Statement

There is no international consensus on the definition for low or high response to COH. For this guideline, as previously discussed, we have adopted the definitions used in the ESHRE guideline on ovarian stimulation [7].

Low ovarian response defined as < 3 follicles on day of oocyte maturation trigger and/or ≤ 3 oocytes collected and high ovarian response defined as > 18 follicles ≥11 mm in size on day of trigger and/or 18 oocytes collected. As discussed above, OCR is associated with potential procedural risks, and women with a high ovarian response are at increased risk of OHSS.

Low predicted number of oocytes

The chance of pregnancy and live birth are lower with a smaller number of oocytes retrieved. A systematic review of 19 studies with a meta-analysis of six studies (14,338 women) found a predicted pregnancy rate of 14.8% for low responders compared with 34.5% for normal responders [148]. A meta-analysis by the same authors was also carried out on four cohort studies (8,744 women) to calculate the chance of pregnancy per oocyte retrieved, this is presented below[149].

1 oocyte retrieved 0-7%

2 oocytes 4.3-15.2%

3 oocytes 8.7-15.6%

4 oocytes 11.5-18.6%

A more recent large retrospective study including over 250,000 cycles reported a LBR of 17% when the number of oocytes retrieved was five or less [150]. The decision to cancel an IVF cycle based on low predicted numbers of oocytes is difficult and should be addressed on a case-by-case basis, considering the age and ovarian reserve of the woman previous response to stimulation and the wishes of the individual.

High predicted number of oocytes

Women with a high predicted number of oocytes are at increased risk of severe OHSS. A large prospective study including 2362 women who underwent COH with the GnRH agonist protocol advised cycle cancellation if there were >30 follicles <12mm in size on ultrasound[151]. Another large prospective cohort study of over 2500 cycles (1801 women) with the GnRH antagonist protocol found that ≥18 follicles ≥11 mm predicted severe OHSS (sensitivity 83%, specificity 84%) [152].

In addition to methods previously outlined above to reduce the risk of OHSS (agonist trigger for antagonist cycles, a 'freeze all' approach and cabergoline prophylaxis), cycle cancellation may be considered in cases of hyper-response.

Other indications to consider cancelling a treatment cycle

- Concomitant medical or social issues that arise during the cycle that could make proceeding with treatment unsafe or unacceptable to the woman.
- Debilitating side effects of medications.

Clinical Practice

Whilst the chances of pregnancy and live birth with a low oocyte yield may be low, they are not zero. A woman who has a low ovarian response may still wish to proceed to OCR, even if there is a chance that no oocytes will be retrieved. Data from the literature can be helpful for counselling people and helping to manage expectations.

Cycle cancellation may be considered, along with other measures to reduce the risk of OHSS, in the case of hyper-response.

If a cycle is cancelled for any reason, adequate follow up should be arranged and the individual/couple should have the opportunity to discuss the previous cycle and if appropriate plan further treatment cycles with appropriate changes/precautions.

Recommendations

39. **We recommend that the decision to cancel an IVF/ICSI should be addressed on a case-by-case basis, considering the age and ovarian reserve of the woman, previous response to stimulation and the wishes of the individual/couple**
40. **We suggest that cycle cancellation may be considered when the response to COH is less than expected for the woman's age/ovarian reserve.**
41. **We suggest that cycle cancellation may be considered when there is a high risk of OHSS based on a high number of follicles, and the woman's clinical condition.**
42. **We suggest that cycle cancellation should be considered if another medical or social issue arises during stimulation that would make proceeding with treatment unsafe or unacceptable to the woman.**

Clinical Question 2.11: How can the risk of multiple pregnancy be minimized during IVF/ICSI?

Introduction

Multiple pregnancy occurs more frequently with ART than in spontaneous conceptions. Multiple birth is the single biggest risk to the health of the woman and babies undergoing IVF. According to the Central Statistics Office, the number of maternities in 1973 which resulted in multiple live births was 845, consisting of 838 sets of twins and seven sets of triplets. This is equivalent to a "twinning rate" (number of live twins per 1,000 maternities which resulted in live births) of 12.4 [153]. Over the years, the twinning rate has increased from 10.1 in 1981, to an all-time high of 19.0 in 2016. The "twinning rate" in 2020 was 18.2 [154]. The observed increase in the multiple gestation rate in Ireland from 0.8% of all births in 1989 to 1.8% in 2020 has been attributed in part to advances in ART [155].

In the early years of IVF and ICSI, there was a trend towards the transfer of all available embryos into the uterus because of low implantation rates and suboptimal culture and cryopreservation techniques. With the advent of medical and technical improvements in ART, however, the transfer of multiple embryos has resulted in an increase in the rate of higher order multiple pregnancies when compared to spontaneous conception rates.

Evidence Statement

Medical Risks

Maternal morbidity and mortality in multiple pregnancies are significantly increased compared with singleton pregnancies. The increased risks to the mother include pregnancy loss, ectopic pregnancy, pregnancy-induced hypertension, pre-eclampsia, gestational diabetes, antepartum and postpartum haemorrhage, caesarean section, and stillbirth[156]. Maternal mortality is 2.5 times greater in women with a multiple gestation[157]. Multiple pregnancy is known to confer increased perinatal risk including mortality, preterm birth, congenital anomalies, fetal growth restriction and twin-to-twin transfusion syndrome [158]. The Perinatal Mortality National Clinical Audit in Ireland Annual Report 2021 found that the increased risk of perinatal mortality in multiple pregnancy accounts for 13.7% of all perinatal deaths in Ireland [159]. Twins are four times more likely than singletons to develop cerebral palsy [160]. The median age for delivery of twins in Ireland is 37.1 weeks, with 20% of monochorionic twins and 7% of dichorionic twins delivering prior to 32 weeks' gestation thus increasing the risk of neonatal intensive care unit (NICU) admission and neonatal morbidity and mortality [161].

Economic cost of multiple births

Multiple pregnancy is a potential serious consequence of ART. In addition to the higher risks of multiple pregnancy for the mother and babies compared to a singleton pregnancy, there are significant costs to the health service and wider public services associated with multiple births. A report by the National Guideline Alliance about twin pregnancy costing commissioned by the Human Fertilisation and Embryology Authority, the British Fertility Society, the Multiple Births Foundation and Fertility Network UK concluded that multiple pregnancies are, on average, almost three times as expensive as single pregnancies, with the mean cost of a singleton pregnancy in the UK over the period of pregnancy, birth, neonatal care and long term disability estimated to be £4,892 [162]. The mean cost of a twin pregnancy over the same period was £13,959. Much of the difference in cost between singleton and multiple pregnancies result from the need for emergency caesarean, neonatal death, admissions to NICU and a range of other conditions such as cerebral palsy. It is also acknowledged in the report the other "costs" to families of multiples; emotional and psychological, which can have a long-term impact on parents and

the children themselves. They conclude that the aim of all IVF treatment should be the birth of a single healthy child in line with the "One child at a time" report from the Human Fertilisation and Embryology Authority (HFEA) in 2006[163].

Elective single embryo transfer

SET refers to single embryo transfer and DET refers to double embryo transfer. If embryologists can choose from more than one embryo, the transfer is considered elective. Thus, elective single embryo transfer (eSET) is the transfer of one embryo in cases where there are more than one to choose from. Other types of SET include cSET (compulsory single embryo transfer), where there is only one embryo available to transfer and mSET (medical single embryo transfer), where single embryo transfer is performed in cases where a multiple pregnancy poses an unacceptable higher risk to the woman, e.g. in severe systemic disease in the woman, in cases where the woman has a known uterine anomaly and where the woman has a poor obstetric history such as prior preterm delivery <32 weeks' gestation.

Elective single embryo transfer is considered the safest effective way to achieve the healthiest pregnancy outcome for both mother and baby and is recommended by several international organisations [164, 165]. While there is a clear European trend overall in a reduction on the number of embryos transferred and an increase in the number of ART cycles employing elective single embryo transfer policies [166, 167], the rate is still higher than the 10% multiple pregnancy rate set as a target by ESHRE in 2000 [168].

A Cochrane review of 17 RCTs (2505 women) demonstrates a lower chance of live birth in fresh IVF/ICSI cycles after eSET in comparison with double embryo transfer (DET) [169]. However, the cumulative live birth rate after repeated SET may be little or no different from the rate after one cycle of DET. The combination of SET with a good quality freezing programme and subsequent replacement of a single frozen-thawed embryo achieves a live birth rate comparable with DET. SET was associated with reduced multiple pregnancy rate compared to a single DET cycle. This means that for a clinic with a 42% chance of live birth following a single cycle of DET, the chance following repeated SET would be between 34% and 46%[169]. The same study also revealed that in cases with 13% risk of multiple pregnancy following a single cycle of DET, the risk following repeated SET would be between 0% and 3% [169].

The most recent European guidance on the number of embryos to transfer during IVF from ESHRE recommends eSET as the standard procedure whenever more than one embryo is available given there is no evidence showing that cumulative live birth rate in eSET is inferior to that in DET and that it has been clearly demonstrated that the multiple birth rate after DET significantly exceeds that after eSET [8].

Furthermore, ESHRE recommends that the decision to perform DET instead of eSET in both fresh and frozen/thawed embryo transfer cycles should not be based on any of the following criteria – the number of previous unsuccessful ART treatments, the duration of infertility, previous pregnancy or live birth numbers resultant from ART, female age, endometrial characteristics and embryo characteristics (morphology/quality). The authors note that advanced maternal age (AMA) is associated with increased obstetric risks including preterm birth, low birth weight, hypertensive disorders, stillbirth, and caesarean delivery [170-172]. As these risks are further increased in multiple pregnancies, avoidance of multiple pregnancies is even more important in women of AMA.

Clinical Practice

The transfer of more than two embryos is not recommended under any circumstances as it carries an unacceptable increase in the risk of higher order multiple pregnancy and ectopic pregnancies.

The strict use of eSET is warranted in donor oocyte and donor embryo recipients, gestational carriers, women at risk of OHSS where it is planned to have a fresh embryo transfer and in cycles where a fresh blastocyst is to be transferred.

DET may be considered, in selected cases, taking into consideration the increased risk that multiple pregnancy may pose to the individual woman, her family, the children conceived and the increased cost of multiple pregnancy to the health services and society. Each clinic providing IVF/ICSI should have their own SOP on cases where DET is considered.

Recommendations

43. **We do not recommend the transfer of more than 2 embryos under any circumstances.**
44. **We recommend that elective single embryo transfer (eSET) should be the standard procedure whenever more than one good quality embryo is available. Double embryo transfer (DET) may be considered in selected circumstances.**
45. **We recommend that medical risk factors should be considered before a DET due to the higher rates of maternal, fetal, and neonatal complications with multiple pregnancy.**
46. **We recommend that when DET is considered, individuals/couples should be provided with clear information about the risks associated with multiple pregnancy.**

Section 3 – AHR standards of practice

Clinical Question 3.11: What are the minimum standards of practice for centres offering AHR?

Evidence Statement

Regulating AHR Activities

Any individual or site which carries out any prescribed activity is required to be authorised by the HPRA. Regulation 6 [9] of S.I. 158 of 2006 states that "A tissue establishment shall not make any substantial change in the prescribed activities which it undertakes without the prior written approval of the HPRA."[173]

Tissue Establishment (TE) Annual Report

Regulation 10 of Statutory Instrument 158 of 2006 requires that all TEs submit an annual report of their activities to the HPRA. A report form with associated guidance specific to reproductive tissues and cells is available on the HPRA website[173].

Clinical Practice

Reporting of Serious Adverse Reactions and Events (SAR/Es)

In accordance with EU and National legislation relating to Human Tissues and Cells [174], the HPRA has established a reporting system for the notification of suspected Serious Adverse Reactions (SARs) and Serious Adverse Events (SAEs) associated with human tissues and cells.

A **'serious adverse event'** is defined as any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for people or which might result in, or prolong, hospitalisation or morbidity. Examples of SAEs reported in AHR include: salpingitis after intra-uterine insemination; bacterial infection of the recipient due to infected sperm; proven cross contamination of samples with an infectious disease; recognition of sample mix-up following sample release.

A **'serious adverse reaction'** is defined as an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity. Examples of SARs reported in AHR include severe OHSS leading to hospitalisation; bleeding after oocyte retrieval; anaphylaxis requiring ventilation; ovarian torsion following oocyte retrieval.

All TEs are required, through the Responsible Person (or delegate), to notify the HPRA of and provide a report analysing the cause of and outcome of:

- Any SAE and reactions which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells
- Any SAR observed during or after clinical application which may be linked to the quality and safety of tissues and cells.

EU Tissue and cells legislation can be accessed on the EU website:

- Directive 2004/23/EC
- Directive 2006/17/EC
- Directive 2006/86/EC
- Directive (EU) 2012/39
- Directive (EU) 2015/565
- Directive (EU) 2015/566
- S.I. No. 158 of 2006
- S.I. No. 598 of 2007
- S.I. No. 209 of 2014
- S.I. No. 32 of 2019
- S.I. No. 33 of 2019

It is also expected that TEs should observe the Guide to the Quality and Safety of Tissues and Cells for Human Application, EDQM 5th Edition, 2022[175].

Recommendations

47. We recommend that any site in Ireland which carries out AHR procedures must be authorised by the HPRA and practice should follow guidance from the HPRA.

Chapter 3: Development Of Clinical Practice Guideline

3.1 Literature search strategy

A comprehensive literature review was undertaken which included national and international publications. The time frame that the review was undertaken was from October 2023 – March 2024. An updated search was carried out in June 2024.

The literature review consisted of a search of the following websites and databases:

- PubMed
- The Cochrane Library
- The European Society of Human Reproduction and Embryology (ESHRE)
- The National Institute for Health and Care Excellence (NICE)
- American Society for Reproductive Medicine (ASRM)

Randomised control trials, systematic reviews with meta-analysis, large observational studies and international best practice guidelines from the last 10 years (2014-2024) were included and are cited. Opinion pieces and case reports are not included.

International best practice guidelines relating to the components of IVF/ICSI from the United Kingdom, Europe and the United States of America were reviewed. ESHRE provides training and accreditation for reproductive medicine and surgery specialists, clinical embryologist and fertility nurses and midwives practicing in Europe, thus ESHRE guidelines inform much of the practice in fertility clinics in Ireland.

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 IVF 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[18].

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

3.4 Literature review

Details of supportive evidence based literature for this Guideline are reported in Chapter two. Literature searches were carried out with a review of international guidelines in October 2023 and an updated search was performed in March 2024. All authors and stakeholders reviewed the final draft.

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.[19]

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.[20] (Appendix 4)

3.6 Future research

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

Some questions of relevance to this Guideline include:

- What are the success rates following embryo transfer in women who cannot achieve an endometrial thickness of >7mm?
- Should endometrial polyps be removed prior to embryo transfer?
- What is the impact of infertility and its treatment on the woman's mental health during pregnancy and the postpartum period?

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

19 Guyatt, Gordon, *et al.* "GRADE Guidelines: 1. Introduction – GRADE Evidence Profiles and Summary of Findings Tables." *Journal of Clinical Epidemiology*, vol. 64, no. 4, 2011, pp. 383-94, https://doi.org/10.1016/j.jclinepi.2010.04.026.

20 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 (GPT). 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[21] for developing Policies, Procedures, Protocols and Guidelines (2023) and under supervision of the Guideline Programme Team.

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 5 for list of CAG members.

21 Health Service Executive (2023). How to develop HSE National Policies, Procedures, Protocols and Guidelines (PPPGs).

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[22].

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 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 standard 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.

In the case of this guideline, we plan to disseminate this guideline to the six regional fertility hubs (see below) and all private fertility clinics offering IVF/ICSI in Ireland. Plain language summaries of the guideline will be available on the HSE and RCPI websites and will be circulated to the National Infertility Support and Information Group (NISIG).

Regional fertility hubs:
Dublin – National Maternity Hospital, Rotunda Hospital and Coombe Women and Infants University Hospital
Galway University Hospital
Cork University Maternity Hospital
Nenagh General Hospital as part of Limerick University Maternity Hospital

22 Department of Health (2018). NCEC Implementation Guide and Toolkit. Available at: https://www.gov.ie/en/collection/cd41ac-clinical-effectiveness-resources-and-learning/?

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 Guideline 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

Currently publicly funded IVF/ICSI is only available to heterosexual couples who meet strict access criteria (discussed in the introduction). State funded IVF/ICSI is not available to same-sex couples, single people, heterosexual couples with secondary infertility or those who require donor gametes to conceive. Many people who do not meet these criteria will continue to access IVF/ICSI privately in Ireland.

At the time of writing this guideline the Health (Assisted Human Reproduction) Bill passed all stages of Dáil Éireann on 30th May 2024 and the Seanad on 26th June 2024. The Health (Assisted Reproduction) Act 2024 was enacted on 2nd July 2024. Specific areas that are covered by this new legislation include:

- Fertility preservation
- Donor assisted conception
- Surrogacy.

The GDG would like to see publicly funded fertility services expand to include same sex couples, couples with secondary infertility, fertility preservation, donor assisted conception and surrogacy. In the case of this guideline, we hope to be able to update and expand this guideline and follow it with further guidelines to address other areas of AHR.

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.

Knowledge of fertility investigations and management amongst healthcare practitioners (HCPs), has been shown to be poor[176, 177]. A recently published study of knowledge of fertility investigations and management amongst GPs and obstetrics and gynaecology (O&G) trainees found knowledge of fertility to be variable and that the vast majority of trainees called for better training in this area[178]. This Guideline's education plan includes providing educational resources and training in fertility to HCPs including GPs, O&G trainees, nurses, midwives and other HCPs who may come into contact with people with infertility.

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:

- Limited public funding of IVF/ICSI as previously discussed
- Organisational factors with long waiting lists to access treatment.
- People's perceptions – it has been demonstrated that people overestimate their ability to conceive and the success of IVF/ICSI treatment[179]. This may result in people delaying seeking help when struggling to conceive.

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.

Better education of the public regarding infertility and age related fertility decline may encourage people to seek help for infertility. Better education of HCPs is needed to ensure that appropriate investigations are carried out and that individuals/couples are referred for treatment in a timely manner.

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 2021, Ireland was one of only four European countries that did not provide ART funding through their national healthcare system and its services were classified as 'exceptionally poor' by the European Parliamentary Forum for Sexual and Reproductive rights [180]. In September 2023, limited public funding was introduced. Current fertility services in Ireland would still be classified as 'poor' by the European Parliamentary Forum for Sexual and Reproductive rights, as access is limited to selected groups and the funding is poor [180].

The guideline development group would like to see public funding for fertility treatments expand to include all service users in particular same sex couples, those who require donor assisted conception or surrogacy.

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 care of the woman. 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 collection of national data on:

1. Outcomes following IVF/ICSI treatment
    - Clinical pregnancy rates
    - Miscarriage rates
    - Ectopic pregnancy rates
    - Live birth rates
2. Rate of multiple births following IVF/ICSI treatment in Ireland
3. Obstetric outcomes following successful IVF/ICSI treatment in Ireland
4. Incidence of OHSS following COH, including number of hospital admissions

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[23].

Implementation of this Guideline will be audited periodically at national level, with standards for this set by the NWIHP. Evaluation of the auditable standards should also be undertaken locally by senior hospital clinical management to support implementation.

23 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.[24]

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.

Enactment of the Health Human Reproduction Bill 2022 may lead to amendments of this guideline or the development of further guidelines.

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 should be submitted to the National Women and Infants Health. Any such requests should be dealt with in a timely manner.

24 Health Service Executive (2023). How to develop HSE National Policies, Procedures, Protocols and Guidelines (PPPGs).

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3. Schmidt L, Sobotka T, Bentzen JG, Nyboe Andersen A. Demographic and medical consequences of the postponement of parenthood. Hum Reprod Update. 2012;18(1):29-43.

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Supporting Evidence

GRADE: http://www.gradeworkinggroup.org/

AGREE: http://www.agreetrust.org/agree-ii/

https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

Glossary

ACOG American College of Obstetricians and Gynaecologists

AFC Antral Follicle Count

AGREE Appraisal of Guidelines for Research and Evaluation

AHR Assisted Human Reproduction

AMA Advanced Maternal Age

AMH Anti-Müllerian Hormone

ARA Advanced Reproductive Age

ART Assisted Reproductive Technology

ASRM American Society for Reproductive Medicine

BMI Body Mass Index

CAG Clinical Advisory Group

CFRA Children and Family Relationships Act

CLBR Cumulative Live Birth Rate

COCP combined Oral Contraceptive Pill

COH Controlled Ovarian Hyperstimulation

CPR Clinical Pregnancy Rate

EAG Expert Advisory Group

EMT Endometrial Thickness

eSET Elective Single Embryo Transfer

ESHRE European Society of Human Reproduction and Embryology

EU European Union

FET Frozen Embryo Transfer

FIGO International Federation of Gynaecology and Obstetrics

FSH Follicle Stimulating Hormone

GP General Practitioner

GPT Guideline Programme Team

GRADE Grading of Recommendations, Assessments, Developments and Evaluations

hCG Human Chorionic Gonadotropin

HCP Healthcare Practitioners

HFEA Human Fertilisation and Embryology Authority

HIQA Health Information and Quality Authority

HPRA Health Products Regulatory Authority

HRT Hormone Replacement Therapy

HSE Health Service Executive

ICSI Intracytoplasmic Sperm Injection

IOG Institute of Obstetricians and Gynaecologists

IUI Intrauterine Insemination

IVF In Vitro Fertilisation

LBR Live Birth Rate

MBRRACE Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

NCEC National Clinical Effectiveness Committee

NICE The National Institute for Health and Care Excellence

NWIHP National Women and Infants Health Programme

OCR Oocyte Retrieval

OHSS Ovarian Hyperstimulation Syndrome

OI Ovulation Induction

PCOS Polycystic Ovarian Syndrome

PGT Pre-Implantation Genetic Testing

PGT-A Pre-Implantation Genetic Testing For Aneuploidy

PGT-M Pre-Implantation Genetic Testing For Monogenic Disorders

PGT-SR Pre-Implantation Genetic Testing For Structural Rearrangements

POR Poor Ovarian Response

PPPG Policy, Procedures, Protocols and Guidelines

RCOG Royal College of Obstetricians and Gynaecologists

RCPI Royal College of Physicians of Ireland

RCT Randomised Controlled Trial

SAE Serious Adverse Events

SAR Serious Adverse Reactions

SOP Standard Operating Procedure

TE Tissue Establishment

TTC Trying To Conceive

VEGF Vascular Endothelial Growth Factor

VTE Venous Thromboembolism

WHO World Health Organisation

Appendix 1:
Expert Advisory Group Members 2021-

Member	Profession	Location
Dr Mairead Butler	Consultant Obstetrician and Gynaecologist	University Hospital Waterford
Dr Nicholas Barrett	Consultant Anaesthesiologist, Lead for Obstetric Anaesthesiology services	Limerick University Hospital
Dr Venita Broderick	Consultant Obstetrician and Gynaecologist	National Maternity Hospital Dublin
Ms Siobhan Canny	Group Director of Midwifery	Saolta University Health Care Group
Ms Triona Cowman	Director of the Centre for Midwifery Education	Centre for Midwifery Education, Coombe Women and Infants University Hospital
Ms Marie Culliton	Lab Manager/Chief Medical Scientist	National Maternity Hospital Dublin
Ms Niamh Connolly-Coyne *And* Ms Mandy Daly *(Shared nomination)*	Board of Directors Members	Irish Neonatal Health Alliance
Ms Sinéad Curran	Dietician Manager	National Maternity Hospital
Dr Niamh Conlon	Consultant Histopathologist	Cork University Hospital
Ms Georgina Cruise	National Manager	Patient Advocacy Service
Dr Orla Donohoe	Specialist Registrar, Obstetrics and Gynaecology and SWEC Fellow	St George Hospital, Sydney, Australia
Ms Alana Dineen	Senior Clinical Pharmacist	Cork University Maternity Hospital
Prof. Maeve Eogan	Consultant Obstetrician and Gynaecologist National Clinical Lead SATU (HSE)	Rotunda Hospital Dublin
Dr Brendan Fitzgerald	Consultant Perinatal Pathologist	Cork University Hospital

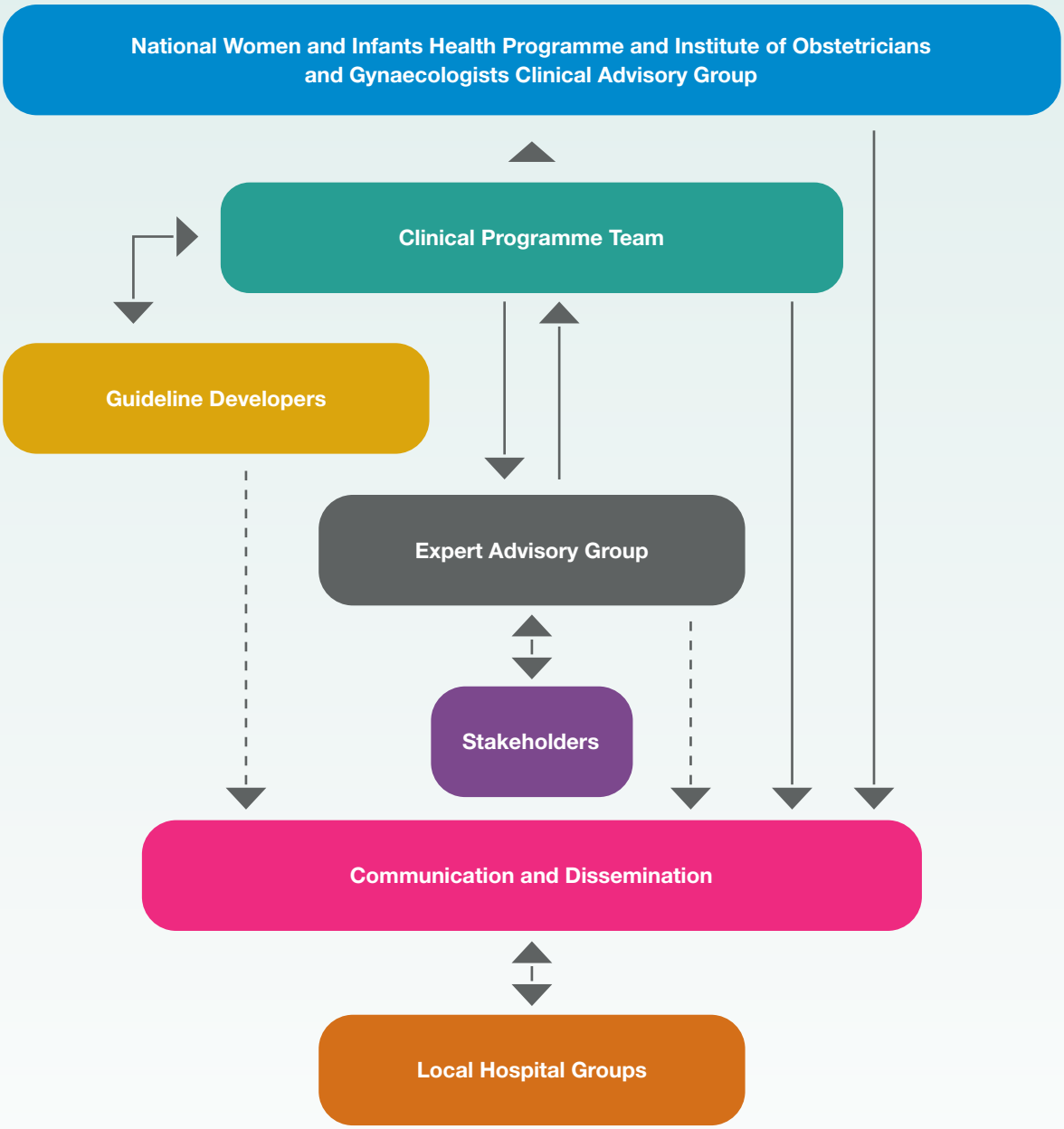
Member	Profession	Location
Dr Daniel Galvin	Specialist Registrar, Obstetrics and Gynaecology	Cork University Maternity Hospital
Ms Stacey Grealis	Patient Research Partner	Independent Living Movement Ireland
Ms Fiona Hanrahan	Director of Midwifery and Nursing	Rotunda Hospital Dublin
Ms Laura Harrington	Principal Medical Social Worker	National Maternity Hospital Dublin
Ms Marita Hennessy	Post-Doctoral Researcher	Pregnancy Loss Research Group, INFANT Centre, University College Cork
Ms Caroline Joyce	Principal Clinical Biochemist PhD Candidate	Cork University Hospital University College Cork
Dr Chaitra Jairaj	Consultant Perinatal Psychiatrist	Coombe Women and Infants University Hospital, Dublin Midland Regional Hospital Portlaoise
Dr Cathy Monteith	Consultant Obstetrician and Gynaecologist	Our Lady of Lourdes Hospital Drogheda
Prof. John Murphy	Consultant Neonatologist Clinical Lead for the National Clinical Programme for Paediatrics and Neonatology	National Women and Infants Health Programme
Ms Janet Murphy	Advanced Midwifery Practitioner	University Hospital Waterford
Dr Jill Mitchell	Specialist Registrar, Obstetrics and Gynaecology	Cork University Maternity Hospital
Dr Aisling McDonnell	Specialist Registrar, Obstetrics and Gynaecology	Mater Misericordiae University Hospital Dublin
Dr Ciara McCarthy	General Practitioner ICGP and NWIHP Women's Health Lead	Irish College of General Practitioners
Ms Orla McCarthy	Clinical Specialist Physiotherapist in Pelvic Health	Cork University Maternity Hospital
Dr Donough J. O'Donovan	Director Neonatal Intensive Care Unit Consultant Neonatologist/Paediatrician	University College Hospital Galway

Member	Profession	Location
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
Dr Gillian Ryan	Consultant Obstetrician and Gynaecologist	University Hospital Galway
Prof. Valerie Smith	Chair of Midwifery	University College Dublin
Ms Nora Vallejo	Advanced Midwife Practitioner	Coombe Women and Infants University Hospital, Dublin

Member 2021-2024	Profession	Location
Dr Katherine Astbury	Consultant Obstetrician and Gynaecologist	University Hospital Galway
Dr Richard Duffy	Consultant Perinatal Psychiatrist	Rotunda Hospital Dublin
Ms Clare Farrell	Physiotherapy Manager	Coombe Women and Infants University Hospital, Dublin
Ms Marie Finn	Medical Social Work Counsellor	Saolta University Health Care Group
Prof. Declan Keane	Consultant Obstetrician, Gynaecologist, Professor of Obstetrics and Gynaecology	National Maternity Hospital Dublin, Royal College of Surgeons in Ireland
Ms Áine Kelly	Physiotherapy Manager	Coombe Women and Infants University Hospital, Dublin
Dr Fergus McCarthy	Consultant Obstetrician, Gynaecologist	Cork University Maternity Hospital, University College Cork
Dr Sarah Petch	Specialist Registrar, Obstetrics and Gynaecology	National Maternity Hospital Dublin
Ms Margaret Quigley	National Lead for Midwifery	Office of Nursing and Midwifery Services Director

Appendix 2:
Guideline Programme Process

Guideline Programme Process



Appendix 3: **AGREE II checklist**[25]

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	

25 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: **Grades of Recommendation**[26]

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…
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…

26 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/

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
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...

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
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: **NWIHP/IOG CAG (2024-)**

Dr Cliona Murphy (Chair, 2023-). Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Director, National Women and Infants Health Programme.

Dr Sam Coulter-Smith (2023-). Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Chair, Institute of Obstetricians and Gynaecologists.

Dr Venita Broderick (2024-). Clinical Lead Gynaecology, National Women and Infants Health Programme.

Dr Brian Cleary (2023-). Chief Pharmacist, Rotunda Hospital. Medications Lead, Maternal and Newborn Clinical Management System Project.

Angela Dunne (2023-). Director of Midwifery, National Women and Infants Health Programme.

Prof. Seán Daly (2023-). Master, Consultant Obstetrician and Gynaecologist, Rotunda Hospital.

Prof. Maeve Eogan (2023-). Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Clinical Lead, Sexual Assault Treatment Units, National Women and Infants Health Programme.

Prof. Richard Greene (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, National Perinatal Epidemiology Centre, University College Cork.

Prof. John Higgins (2023-). Cork University Maternity Hospital, Consultant Obstetrician and Gynaecologist, Clinical Director, Ireland South Women and Infants Directorate.

Prof. Shane Higgins (2023-). Master, Consultant Obstetrician and Gynaecologist, National Maternity Hospital.

Dr Mendinaro Imcha (2023-). Clinical Director, Consultant Obstetrician and Gynaecologist, University Maternity Hospital Limerick.

Prof. John Murphy (2023-). Clinical Lead Neonatology, National Women and Infants Health Programme.

Dr Aoife Mullaly (2023-). Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Lead, Termination of Pregnancy Services, National Women and Infants Health Programme.

Prof. John Morrison (2023-). Consultant Obstetrician and Gynaecologist, University Hospital Galway. Clinical Director, Saolta Maternity Directorate.

Kilian McGrane (2023-). Director, National Women and Infants Health Programme.

Prof. Keelin O'Donoghue (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Lead, National Guidelines, National Women and Infants Health Programme.

Dr Suzanne O'Sullivan (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Director of Education and Training, Obstetrics and Gynaecology, Institute of Obstetricians and Gynaecologists.

Prof. Mike O'Connell (2023-). Master, Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital.

Ms Davinia O'Donnell (2024-). General Manager | National Women and Infants Health Programme

Office of the Chief Clinical Officer, Health Service Executive

Dr Vicky O'Dwyer (2023-). Consultant Obstetrician and Director of Gynaecology, Rotunda Hospital.

Dr Mairead O'Riordan (2024-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital.

Danielle Prenderville (2024-). Senior Executive Assistant – Master's Office.

Prof. Nóirín Russell (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, Cervical Check.

Dr Carmen Regan (April 2024). Clinical Lead Obstetrics, National Women and Infants Health Programme.

Dr Orla Shiel (2024-). Consultant Obstetrician and Gynaecologist, National Maternity Hospital.

Ms Clare Thompson (2023-). Consultant Gynaecological Oncologist, The Mater, Dublin.