National Women & Infants Health Programme

National Clinical Practice Guideline

The Diagnosis and Management of Ectopic Pregnancy

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

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Discussion of risks/benefits of each treatment option with consideration of woman's preference

Expectant

The following criteria are fulfilled

- Haemodynamically stable
- No evidence of rupture
- Pain free
- Woman understands need for follow up and can access medical services
- Serum β-hCG <1500 U/L and falling
- Mass < 3cm

Caution:

When follow-up is uncertain

Management:

Repeat serum β-hCG weekly

Complete follow up when β-hCG levels have resolved

Medical

The following criteria are fulfilled

- Haemodynamically stable
- No evidence of rupture
- Normal FBC/LFT/UE
- Serum β-hCG< 3000 U/L
- Consider if serum β-hCG 3000-5000 U/L
- Mass < 3cm
- No fetal heart pulsations detected on ultrasound
- No contraindications to methotrexate (MTX)
- Available for follow up and can access medical services

Repeat β-hCG on day 4 and day 7

Weekly β-hCG until resolved

Complete follow up when serum β-hCG <levels have resolved

Avoid pregnancy for 3 months following MTX therapy

Surgical

The following criteria are fulfilled

- Haemodynamically unstable

Signs of rupture

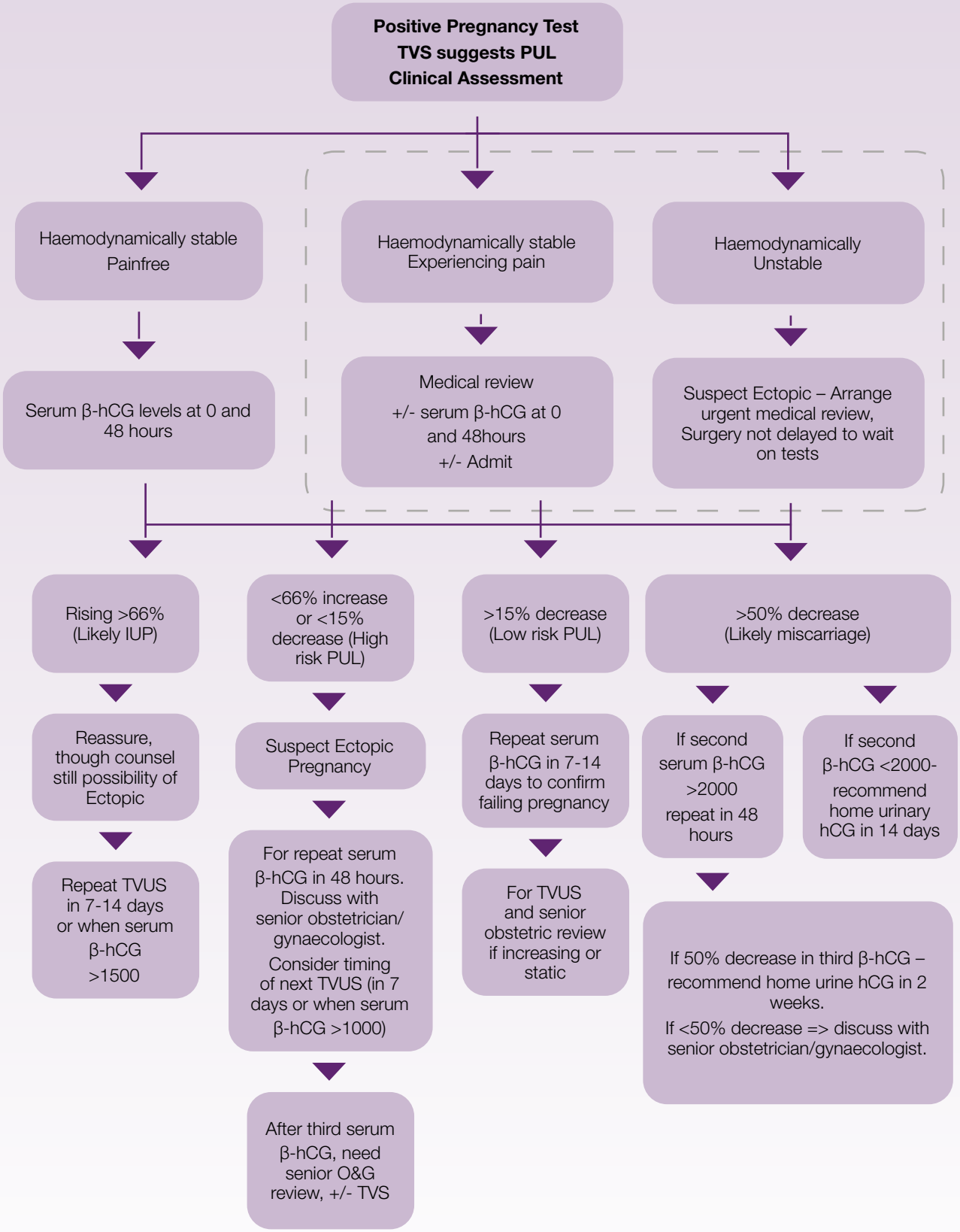
- β-hCG level >5000 U/L or any level with these symptoms
- Contraindications to medical or expectant management
- Fetal heart pulsations present
- Heterotopic pregnancy
- Failed medical or expectant management
- Woman's preference

If salpingostomy :

Repeat serum β-hCG weekly and complete follow up when serum β-hCG <levels have resolved

Adapted from: Queensland Clinical Guideline. Early pregnancy loss. Flowchart: F22.29-3-V6-R27
http://www.health.qld.gov.au/qcg

Management of pregnancy of unknown location



Key Recommendations

Investigation of Ectopic Pregnancy

1. The National Standards for Bereavement Care following pregnancy loss and perinatal death provide a framework for the provision of bereavement care following ectopic pregnancy. *Best Practice*
2. Women should be offered bereavement support at diagnosis and should be offered follow-up bereavement care after ectopic pregnancy. *Best Practice*
3. Women should be given written information at the time of diagnosis of an ectopic pregnancy regarding their diagnosis and management. They should be counselled regarding signs of clinical deterioration when they should present for review and given information about emergency contacts. *Best Practice*
4. A urinary beta-human chorionic gonadotrophin (β-hCG) test should be performed in all women of reproductive age presenting to a maternity or adult general hospital/unit with abdominal pain, vaginal bleeding, gastrointestinal symptoms, dizziness, or collapse. *Grade 1B*
5. A thorough gynaecological, obstetric, medical, and surgical history should be taken to assess for risk factors for ectopic pregnancy in women who present with the above symptoms; however, half of women with an ectopic pregnancy will have no known risk factors. *Best Practice*
6. A physical examination, including measurement of vital signs, should be performed to assess haemodynamic stability in women presenting with the above symptoms. *Best Practice*
7. There should be prompt escalation of care if there are any red flag symptoms on triage assessment or abnormal vital signs in the presence of a positive urinary HCG. This should include referral to an Obstetrics/Gynaecology doctor, IV access and use of an assessment room. *Best Practice*

Diagnosis of Ectopic Pregnancy

8. Transvaginal ultrasound (TVUS) is the first line imaging modality for diagnosing an ectopic pregnancy. *Grade 1B*
9. An ultrasound scan should only be performed by a suitably qualified member of staff. *Best Practice*
10. A TVUS by an experienced sonographer is the gold standard for determining the location of a pregnancy. *Grade 1C*
11. An adnexal mass moving separate to the ovary (and/or with a gestational sac containing a fetal pole or yolk sac) with an empty uterus is highly suggestive of a tubal ectopic pregnancy. *Grade 2A*
12. A serum β-hCG should be performed at diagnosis of a tubal ectopic pregnancy to guide management options. *Grade 1C*
13. If pregnancy location cannot be determined on a TVUS, serial serum β-hCG measurements should be used in conjunction with a woman's history and symptoms to guide management. *Grade 1C*
14. Serum β-hCG cut offs used to guide management decisions can be assay dependent – hospitals/units should discuss this with the relevant laboratory to determine if there is a positive or negative bias in their β-hCG assay. *Best Practice*

Tubal Ectopic Pregnancy Management

15. All hospitals/units should have a local policy on PUL investigation and management, and this should include whether progesterone levels are included in management algorithms. *Best Practice*
16. In PUL management, a senior clinician should be consulted after/at the third serum β-hCG test and should be involved in ongoing decision-making. *Best Practice*
17. Expectant management should be reserved for haemodynamically stable women with β-hCG levels below 1500 U/L which are falling, with no pain, a tubal/adnexal mass <3cm on TVUS and a willingness to complete follow up. *Best Practice*
18. Medical management is appropriate in women with serum β-hCG <5000 U/L, no contraindications to methotrexate, no evidence of fetal cardiac activity and no significant pain or hemoperitoneum. *Grade 1B*
19. Medical management is most successful in women with a serum β-hCG of 3,000 U/L and less. *Grade 1B*
20. All hospitals/units need to have local protocols for assessment, monitoring, and follow-up of women who choose expectant or medical management for ectopic pregnancy. *Best Practice*
21. Surgical management is appropriate when there is evidence of rupture, significant pain, β-hCG levels >5000 U/L, fetal cardiac activity, an adnexal mass >3cm on TVUS, where the ectopic pregnancy is not suitable for medical management or where there has been unsuccessful medical management, and in some scenarios of preference or where the woman is not available for follow up. *Grade 1A*

Interstitial Ectopic Pregnancy

22. TVUS is the first line imaging modality for diagnosing an interstitial ectopic pregnancy. *Grade 1C*
23. A serum β-hCG should be performed at diagnosis of an interstitial ectopic pregnancy to guide management. *Best Practice*
24. The optimal method of treatment for interstitial ectopic pregnancy has not been determined and needs further research. Cases should be managed on an individual patient basis and a Consultant Obstetrician/Gynaecologist should be involved in decision making and management. *Best Practice*
25. Expectant management of interstitial ectopic pregnancy should be used with caution due to the high mortality associated with rupture of an interstitial ectopic pregnancy but can be considered when β-hCG levels are falling and the pregnancy is non-viable. *Grade 1C*
26. Intramuscular or local methotrexate treatment may be considered in asymptomatic women who fit the criteria for medical management, with follow up serum β-hCG levels. *Grade 1C*
27. Surgical management may be considered for interstitial ectopic pregnancy and is required when there is evidence of rupture, with follow up β-hCG levels. *Best Practice*

Cervical Ectopic Pregnancy

28. A cervical ectopic pregnancy is diagnosed using TVUS; the absence of a sliding sign, a gestational sac below the level of the internal os and blood flow on Doppler all raise suspicion for a cervical ectopic pregnancy. (Grade 1B)
29. A cervical ectopic pregnancy can be managed medically with methotrexate, surgically or with uterine artery embolisation; a Consultant Obstetrician/Gynaecologist should be involved in decision making and management. *Grade 1C*

Caesarean Scar Pregnancy

30. High resolution TVUS is the primary imaging modality for diagnosis of a caesarean scar ectopic pregnancy. *Grade 1C*
31. Caesarean scar pregnancy should be discussed within a multidisciplinary team to determine the best management option. Women should be informed of risk: benefits of treatment options to make an informed decision. *Best Practice*
32. A woman who declines treatment for a caesarean scar pregnancy should be counselled regarding associated morbidity and the pregnancy managed as per the 'Diagnosis and Management of Placenta Accreta Spectrum' National Clinical Guideline 2023. *Best Practice*

Ovarian Ectopic Pregnancy

33. An ovarian ectopic pregnancy is diagnosed on TVUS as a mass on the ovary with a negative sliding sign and separate to a corpus luteum. *Grade 1C*
34. Surgical management is the treatment of choice for an ovarian ectopic pregnancy. *Grade 1C*
35. A Consultant Obstetrician/Gynaecologist should be involved in decision making and management of ovarian ectopic pregnancy. *Best Practice*

Rudimentary Horn Ectopic Pregnancy

36. Ultrasound criteria can be used to diagnose a rudimentary horn ectopic pregnancy; visualisation of a single interstitial portion of fallopian tube in the main unicornuate uterine body, gestational sac/products of conception mobile and separate from the unicornuate cavity and completely surrounded by myometrium, and a vascular pedicle adjoining the gestational sac to the unicornuate uterus. *Grade 1C*
37. Treatment for a rudimentary horn ectopic pregnancy is excision of the rudimentary horn via laparoscopy or laparotomy. *Grade 1C*

Follow Up Care

38. All non-sensitised women who are RhD negative should receive Anti-D immunoglobulin if having surgical management for any type of ectopic pregnancy. *Grade 2C*
39. Women should be given a follow up hospital appointment 6-9 weeks following surgical treatment for any ectopic pregnancy and future pregnancy implications discussed. *Best Practice*
40. Routine follow up for all women with ectopic pregnancy should be considered regardless of the mode of treatment, to ensure clinical resolution in expectant/medical management, to facilitate a clinical discussion as well as advise on future pregnancy planning. *Best Practice*

41. General Practitioners should be informed of a woman's treatment for an ectopic pregnancy and of implications for future pregnancy. *Best Practice*
42. An early pregnancy ultrasound scan at 6 weeks' gestation should be performed in any subsequent pregnancy due to the increased risk of ectopic pregnancy recurrence. *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

The purpose of this Guideline was to develop and provide a comprehensive evidence-based guidance for women who have an ectopic pregnancy. The Guideline covers the assessment of a woman presenting with abdominal pain with or without vaginal bleeding and a positive pregnancy test. Content includes the investigation and diagnosis of ectopic pregnancy as well as management options and principles of care.

1.2 Scope

Target Users

The Guideline is a resource for all medical professionals (doctors, midwives, nurses, allied health professions) involved in the care of women who are diagnosed with and treated for ectopic pregnancy.

Target Population

Women who are suspected, diagnosed, and undergo treatment for ectopic pregnancy. The main focus of this Guideline is on tubal ectopic pregnancy.

1.3 Objective

To provide evidence-based recommendations for the care of women with pregnancy of unknown location and ectopic pregnancy as well as promoting a standardised approach to management across all maternity hospitals/units and early pregnancy assessment units in Ireland.

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 the Guideline Programme Process.

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

This Guideline was written by Dr Niamh Fee (Our Lady of Lourdes Hospital), Dr Fionnvola Armstrong (Our Lady of Lourdes Hospital), Dr Sarah Milne (Our Lady of Lourdes Hospital). It was reviewed by Dr Aoife Freyne (Our Lady of Lourdes Hospital) and Briege Begley (Our Lady of Lourdes 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 developers are grateful to Dr Deirdre Hayes Ryan (Consultant Obstetrician/Gynaecologist, Cork University Maternity Hospital), Dr Caroline Joyce (Senior Biochemist, Cork University Hospital), Dr Fergal O'Shaughnessy (Senior Pharmacist, Rotunda hospital) and Professor Keelin O'Donoghue (Consultant Obstetrician/Gynaecologist, Cork University Maternity Hospital) for their review of the draft documents and assistance with guideline development.

Ectopic Pregnancy Ireland reviewed the document and asked women to share their care experience of Ectopic Pregnancy to inform Guideline development. The Guideline incorporates their suggestions and feedback. We are grateful to them for their contribution.

1.6 Disclosure of interests

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

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

It is important that interests are openly declared so they can be appropriately managed. Conflicts of interest can bias recommendations and ultimately be harmful to women and the health system. Disclosures of interests and appropriate management of conflicts of interest, when identified, are therefore essential to producing high-quality, credible health guidelines.[3]

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

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

3 CMAJ 2021 January 11;193:E49-54. doi: 10.1503/cmaj.200651 https://www.cmaj.ca/content/193/2/E49

4 Annals of Internal Medicine, Schünemann HJ, Al-Ansary, LA, Forland F, *et al.* Guidelines International Network: Principles for disclosure of interests and management of conflicts in guidelines, 163(7), 548-53. Copyright © 2015 American College of Physicians. https://www.acpjournals.org/doi/10.7326/m14-1885

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

1.7 Disclaimer

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

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

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

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

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.[5] 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.[6] We also appreciate that there are risks to desexing language when describing female reproduction.[7, 8]

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

6 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/

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

8 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

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.[9] 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.

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

Chapter 2:
Clinical Practice Guideline

Background

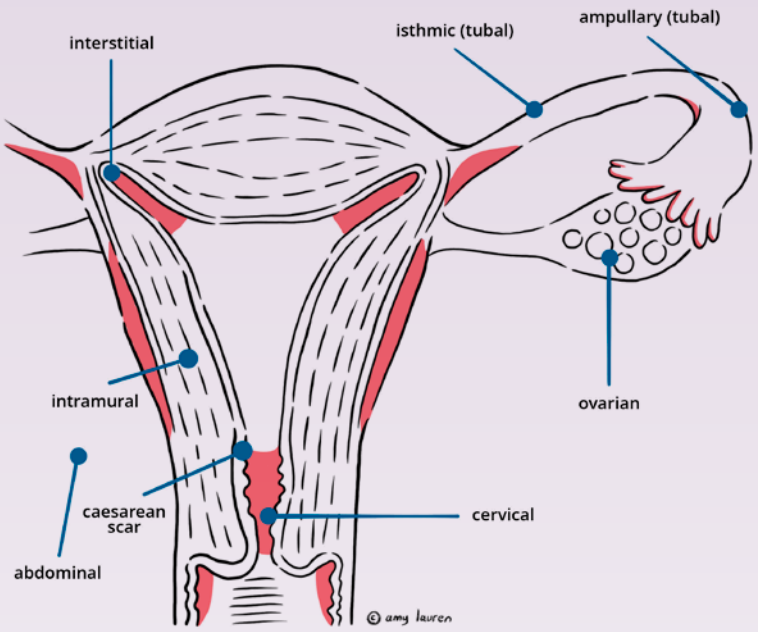
Ectopic pregnancy (EP) occurs when there is implantation and development of a pregnancy in any site other than the endometrial cavity.[1] The ESHRE consensus document on the terminology around early pregnancy states pregnancy can be described either as normally sited, ectopic or of unknown location. Within ectopic pregnancy there are several different types, which are classified based on their location; rudimentary horn, uterine and extra-uterine. Uterine EP includes cervical and caesarean scar. Extrauterine EP includes ovarian, abdominal and tubal which is further subdivided into interstitial, isthmic and ampullary.[2]

The rate of ectopic pregnancy is 11 per 1,000 pregnancies, with a maternal mortality of 0.2 per 1,000 estimated ectopic pregnancies.[1] Ectopic pregnancy ruptures are the leading cause of maternal mortality within the first trimester of pregnancy with a rate of 9%-14% and an incidence of 5%-10% of all pregnancy-related deaths.[3] EP remains a cause of maternal death in pregnancy with those who are vulnerable and young women being disproportionately represented.[4] The fatality rate has decreased over recent years due to earlier diagnosis and treatment.[1]

EP has several risk factors, signs and symptoms, and there are several treatments options which can prevent maternal morbidity and mortality. Early diagnosis of EP is beneficial as it may allow a choice of variety of treatment options depending on clinical status and the woman's preference.[3, 1] Finally, increasing rates of IVF are correlated with rising reports of EPs among those individuals. The EP rate among IVF pregnancies is 2.1%-8.6% after embryo transfer, in comparison to 2% in natural conception.[3]

This Guideline will cover the assessment of a woman presenting with abdominal pain with or without vaginal bleeding and a positive pregnancy test. It will cover the clinical history, examination and investigations required to assess for ectopic pregnancy. It will cover the diagnosis of EP and its treatment, as well as management outlines for different types of uterine and extrauterine EP.

Types of Ectopic Pregnancy



Recommendations relevant to this Guideline can also be found in:

- Unexpected Intraoperative Life Threatening Haemorrhage. NCEC National Clinical Guideline No. 29[10]
- National Clinical Practice Guideline: Prevention and Management of Primary Postpartum Haemorrhage[11]
- National Clinical Practice Guideline: Recurrent Miscarriage[12]
- National Clinical Guideline: First Trimester Miscarriage (due 2024)

10 Department of Health (2022). Unexpected Intraoperative Life Threatening Haemorrhage (NCEC National Clinical Guideline No. 29). Available at: https://www.gov.ie/en/collection/c9fa9a-national-clinical-guidelines

11 Byrne B, Spring A, Barrett N, Power J, McKernan J, Brophy, D, Houston C, Faryal R, McMahon E, Manning C, Murphy P, Ni Ainle F. National Clinical Practice Guideline: Prevention and Management of Primary Postpartum Haemorrhage. National Women and Infants Health Programme and The Institute of Obstetricians and Gynaecologists, December 2022

12 Linehan L, Hennessy M, Khalid A, Whelan J, O'Donoghue K. National Clinical Practice Guideline: Recurrent Miscarriage. National Women and Infants Health Programme and The Institute of Obstetricians and Gynaecologists. January 2023

Section 1: Investigation of Ectopic Pregnancy

Clinical Question 2.1: What are the principles of care in ectopic pregnancy?

Evidence Statement

Caring for a woman diagnosed with an ectopic pregnancy (EP) involves addressing her emotional and psychological needs with sensitivity and compassion. An ectopic pregnancy can be a distressing and emotionally challenging experience, as it involves the loss of a pregnancy and potential medical and/or surgical complications.[5] Healthcare staff should be aware of women's emotional and psychological care needs during diagnosis, treatment and during follow up for an EP. The importance of giving clear information on treatment options and the experience during a diagnostic scan can have an impact upon women's emotional wellbeing.[5, 6]

The National Standards for Bereavement care following pregnancy loss and perinatal death have been published by the HSE and provide the framework for the provision of bereavement care following ectopic pregnancy.[7] The Standards state that women should be offered referral to a specialist midwife in bereavement and loss and be offered support from the hospital/unit's bereavement team at diagnosis and/or afterwards. All staff involved in maternity care should be offered training in the communication of bad news in pregnancy in an open, compassionate and sympathetic manner.[6]

Included in the Bereavement Standards is the provision of suitable rooms within the hospital ultrasound department which can be used to facilitate discussion and support for the woman following bad news.[7] Some women will also have to undergo a number of scans and/or repeat blood tests before a diagnosis of ectopic pregnancy is made. Ideally, a woman who has a complication in early pregnancy should not have to wait with other pregnant women and should be seen in a timely fashion.[7]

The provision of inpatient accommodation on gynaecology wards and giving priority to pregnancy loss surgery at the beginning of a surgical operating list should be facilitated in maternity hospitals/units.[7] Policies should be available on pregnancy tissue sent for histological diagnosis as well as sensitive management of fetal and pregnancy tissue, with women/parents' choices respected.[1, 7]

Counselling and patient education throughout EP intervention has been shown to improve mental health and self-esteem in one randomised controlled clinical trial (RCT). Methods in this trial included education on EP medical intervention, the physical and psychological complications of interventions, and the sadness, self-esteem, and mental health changes that can be seen after an EP.[8] Another RCT which compared basic nursing care with comprehensive nurse care for women undergoing surgical management of an EP found comprehensive care can lower anxiety and depression for these women.[9] Comprehensive nursing care included patient education and psychological care along with the use of heated blankets.

Clinical Practice

Staff should be trained to communicate with women/couples in a sympathetic manner and be able to break bad news following a pregnancy loss diagnosis on ultrasound scan.

Women should be given written information relevant to their diagnosis, management and follow up in suspected or confirmed ectopic pregnancy.

Women may benefit from the availability of a discharge advice document if clinically stable and if allowed to return home from either the emergency department, EPAU (Early Pregnancy Assessment Unit) or maternity hospital/unit. This document should include information about clinical deterioration such as increasing pain, bleeding, fainting or collapse and where to present to if this happens.

Contact details for EPAU, maternity unit and the emergency department should be made available.[10]

Continuity of care is paramount as an inpatient and outpatient and should be prioritised within the context of local resources.

Women should be cared for on a gynaecology ward or non-obstetric ward during admission to hospital for the management of ectopic pregnancy.

Bereavement support and follow-up bereavement care should be offered to all women diagnosed with ectopic pregnancy.

Examples of information resources that should be made available to women include:

- https://www2.hse.ie/conditions/ectopic-pregnancy/
- http://ectopicireland.ie
- http://pregnancyandinfantloss.ie
- https://www.tommys.org/baby-loss-support/ectopic-pregnancy-information-support

Recommendations

1. **The National Standards for Bereavement Care following pregnancy loss and perinatal death provide a framework for the provision of bereavement care following ectopic pregnancy.**
2. **Women should be offered bereavement support at diagnosis and should be offered follow-up bereavement care after ectopic pregnancy.**
3. **Women should be given written information at the time of diagnosis of an ectopic pregnancy regarding their diagnosis, proposed management and plans for follow-up care. They should be counselled regarding signs of clinical deterioration, when they should present for review and given information about emergency contacts.**

Clinical Question 2.2: What are the essential steps when first assessing a woman that presents with pain in early pregnancy?

Evidence Statement

Symptoms of ectopic pregnancy can vary between women. Symptoms of an EP can include pain (unilateral, generalised pelvic or shoulder tip pain), bleeding, gastrointestinal symptoms (diarrhoea and/or vomiting), dizziness/light-headedness or collapse.[11] These symptoms can present clinically similar to appendicitis, urinary caliculi, early pregnancy loss or trauma.[12] The earliest symptom is usually brown discharge, and the intensity of bleeding can vary with some women having heavy blood loss. Pain may be present however may be a later symptom of EP and typically follows tubal miscarriage. Almost 10% of women diagnosed with EP have no abdominal pain.[13] Of those who attend an emergency department with bleeding, pain, or both, in early pregnancy the prevalence of EP is up to 16%.[14] Healthcare professionals should be aware of presenting symptoms, relevant findings on clinical examination and risk factors which will make a woman at higher risk of having an EP.

Women of reproductive age presenting with any symptoms of abdominal pain or vaginal bleeding should have a urinary beta-human chorionic gonadotrophin (β-hCG) performed as an initial investigation.[15] Some women with an EP will present in haemorrhagic shock. Pallor, tachycardia, and hypotension should alert the examiner to major abdominal bleeding, regardless of the intensity of abdominal pain. Relative bradycardia can still be present with significant intraperitoneal bleeding and therefore a high index of concern should remain.[16]

If the woman is haemodynamically stable, a detailed clinical history should be taken paying particular attention to her last menstrual period (LMP) and the potential risk factors for EP. Half of women diagnosed with an EP have no known risk factors.[12] Risk factors include previous ectopic pregnancy, smoking, endometriosis, pelvic inflammatory disease (PID), previous pelvic surgery, invitro fertilisation (IVF), or intrauterine contraceptive device (IUCD) use at conception. Those risk factors which are strongly associated with the occurrence of an ectopic pregnancy include previous ectopic pregnancy, previous tubal surgery and documented tubal pathology for ectopic pregnancy.[17] Endometriosis has been found in a metanalysis to be associated with an odds ratio of 2.16-2.66 however further research is required to further establish this link.[18] The use of assisted reproductive technologies greatly increases the risk of heterotopic pregnancy which is the presence of an intrauterine pregnancy alongside an ectopic to 1:100 from a background risk of 1:30,000[19] and IVF with frozen embryo transfer is associated with an increased odds ratio for ectopic pregnancy of 8.99.[20] When pregnancy occurs with an IUCD in place it is more likely to be an ectopic pregnancy.[20]

Risk factors for tubal ectopic pregnancy

- Smoking
- Pelvic inflammatory disease
- Previous ectopic pregnancy
- Assisted reproduction
- Intrauterine contraceptive device (IUCD)
- Previous tubal surgery or tubal pathology
- Endometriosis

Clinical Practice

- Women presenting to an emergency department or primary care with vaginal bleeding, abdominal pain, gastrointestinal (GI) disturbance, dizziness or collapse should have a urinary hCG performed and a prompt assessment of vital signs.
- Management should not be delayed waiting for urinary or serum β-hCG results in cases of haemodynamic instability.
- There should be prompt escalation of care if there are any red flag symptoms on triage assessment or abnormal vital signs in the presence of a positive urinary HCG. This should include referral to a clinician, IV access and use of an assessment room.
- A clinical history and physical examination should be undertaken to assess for risk factors for EP. An obstetric history should include previous pregnancies and outcomes, date of LMP and if the woman has had an ultrasound in this pregnancy. It is important to know if the woman is currently under the care of an EPAU for either pregnancy of unknown location (PUL) or EP.
- An abdominal, bimanual and speculum examination should be performed. Signs of an EP include abdominal tenderness on palpation, an acute abdomen with signs of peritonism, cervical excitation, rarely an adnexal mass and cardiovascular compromise (tachycardia and hypotension).
- Women can have an ectopic pregnancy and present with only minimal symptoms which will be dependent on the location of the EP. The heaviness of bleeding can vary as can the degree of pain. Pain is more often associated with tubal rupture in EP when pain can be severe and associated with peritonism.
- Clinical concern is important as 1/2 of women will have no risk factors and up to 16% of those attending an emergency department with pain or bleeding in early pregnancy will be subsequently diagnosed with an EP.
- Signs of an EP on physical examination include tenderness on palpation, an acute abdomen, cervical excitation, an adnexal mass and cardiovascular compromise. A normal physical examination does not exclude an ectopic pregnancy.

Recommendations

4. **A urinary beta-human chorionic gonadotrophin (β-hCG) test should be performed in all women of reproductive age presenting to a maternity or adult general hospital/ unit with abdominal pain, vaginal bleeding, gastrointestinal symptoms, dizziness or collapse.**
5. **A thorough gynaecological, obstetric, medical and surgical history should be taken to assess for risk factors for ectopic pregnancy in women who present with the above symptoms; however, half of women with an ectopic pregnancy will have no known risk factors.**
6. **A physical examination, including measurement of vital signs, should be performed to assess haemodynamic stability in women presenting with the above symptoms.**
7. **There should be prompt escalation of care if there are any red flag symptoms on triage assessment or abnormal vital signs in the presence of a positive urinary HCG. This should include referral to an Obstetrics/Gynaecology doctor, IV access and use of an assessment room.**

Section 2: Diagnosis of Ectopic Pregnancy

Clinical Question 2.3: How is a tubal ectopic pregnancy diagnosed?

Evidence Statement

A tubal ectopic is a pregnancy located in the fallopian tube. This type of ectopic pregnancy accounts for more than 95% of all ectopic pregnancies.[11] ESHRE has updated the terminology to be used for ectopic pregnancies and tubal ectopic pregnancy can be further subdivided into ampullary, isthmic and interstitial.[2] In this section we discuss ampullary and isthmic ectopic pregnancies with discussion of interstitial ectopic pregnancy later in the Guideline.

Tubal pregnancies located closer to the uterus have a higher potential to grow larger and to contain a live embryo/fetus which increases the risk of serious complications.[2] The EP can comprise of a solid adnexal mass, gestational sac, a gestational sac with a yolk sac or the presence of a fetal pole with or without a heartbeat.

Transvaginal ultrasound (TVUS) is the gold standard for the diagnosis of tubal EP. TVUS sensitivity and specificity to detect EP are 90.9% and 99.9%, respectively[21] when performed by suitably qualified persons. The British Medical Ultrasound society defines a sonographer as "a healthcare professional who undertakes and reports diagnostic, screening or interventional ultrasound examinations. They will hold qualifications equivalent to a Postgraduate Certificate or Diploma in Medical Ultrasound, BSc (Hons) clinical ultrasound or an honours degree apprenticeship that has been accredited by the Consortium for the Accreditation of Sonographic Education (CASE).[22]" NICE recommends that all ultrasound scans should be performed or directly supervised and reviewed by appropriately qualified healthcare professionals with training in, and experience of, diagnosing ectopic pregnancies.[1]

On ultrasound, the uterus can have a variety of appearances including an empty cavity with a thin endometrium, a thickened endometrium or even fluid filled which is commonly known as a pseudo-sac; there is no uniform appearance to the endometrium in tubal EP.

There are number of signs on ultrasound which can indicate the presence of a tubal EP. When an EP is at a more advanced gestation it can be seen as an adnexal mass with a gestational sac with or without a fetal pole; this occurs in approximately 13% of tubal EP when diagnosed at ultrasound.[23] A tubal EP can also be seen as a mass adjacent to the ovary with a 'bagel sign' or hyperechoic ring and occurs in 20% of cases. Most commonly the ectopic can be seen as an inhomogeneous mass or 'blob sign' adjacent to the ovary which moves separately to it;[15] this occurs in approximately 60% of cases. The diagnosis may not be clear at initial review and may require a repeat ultrasound prior to diagnosis.

Free fluid in the pelvis consistent with hemoperitoneum is suggestive of a ruptured ectopic pregnancy, but it is important to note that a small amount of free fluid in the Pouch of Douglas may also be present in a viable intrauterine pregnancy (IUP).[24] Looking at the echolucency of free fluid on TVUS may help distinguish the presence or blood or blood clots. A haemorrhagic corpus luteal cyst may also present with pain and free fluid; when there is uncertainty in ultrasound findings seeking a second opinion is good practice.

Clinical Practice

- High resolution TVUS is the gold standard for assessment and diagnosis of a suspected ectopic pregnancy. This should be performed by an appropriately trained sonographer.
- Early Pregnancy Units should have access to high resolution TVUS.
- If TVUS is not available immediately and the woman is haemodynamically stable, a referral to an early pregnancy unit is recommended.
- Ultrasound scans should only be performed by a suitably qualified member of staff and the use of informal or 'bedside' ultrasound is discouraged.
- Women should be cared for within an EPAU of a maternity hospital/unit with appropriate governance structures in place.
- Serum β-hCG levels should be performed and will guide management options
- The serum β-hCG cut offs commonly used (Section 3 onwards) to guide management decisions can be laboratory assay dependent – hospitals/units should discuss the performance of the local β-hCG assay with the relevant laboratory.
- Expected turnaround times for laboratory test results should also be available in each maternity hospital/unit.

Recommendations

8. **Transvaginal ultrasound (TVUS) should be the first line imaging modality for diagnosing an ectopic pregnancy.**
9. **An ultrasound scan should only be performed by a suitably qualified member of staff.**
10. **A TVUS by an experienced sonographer is the gold standard for determining the location of a pregnancy.**
11. **An adnexal mass moving separate to the ovary (and/or with a gestational sac containing a fetal pole or yolk sac) with an empty uterus is highly suggestive of an ectopic pregnancy.**
12. **A serum β-hCG should be performed at diagnosis of a tubal ectopic pregnancy to guide management options.**
13. **If pregnancy location cannot be determined on a TVUS, serial serum β-hCG measurements should be used in conjunction with a woman's history and symptoms to guide management.**
14. **Serum β-hCG cut offs used to guide management decisions can be assay dependent – hospitals/units should discuss this with the relevant laboratory to determine if there is a positive or negative bias in their β-hCG assay.**

Section 3: Tubal Ectopic Pregnancy Management

Clinical Question 2.4: How is a pregnancy of unknown location managed?

Evidence Statement

Pregnancy of unknown location is a transient state where a urinary or serum β-hCG is positive but the pregnancy has not yet been identified as an intrauterine or extrauterine pregnancy on ultrasound by a trained sonographer.[25]

A TVUS in the first trimester by an experienced sonographer is the gold standard for locating a pregnancy. When a pregnancy is not identified on a TVUS a serum β-hCG should be performed to guide further management, and both are then interpreted in conjunction with the clinical picture and history. A single serum β-hCG does not differentiate between a viable and non-viable pregnancy.

The ultimate outcome of a pregnancy of unknown location is as follows: intrauterine pregnancy 34-40%, persistent PUL 2%, ectopic pregnancy 8-14% and non-viable resolving PUL 44-69%.[26]

The minimal serum β-hCG rise for an intrauterine pregnancy was first described in 1981 by Kadar *et al.* This study was based on a small sample size of only twenty patients and a 85% confidence interval. It concluded that in an early viable pregnancy 85% will show a serial serum β-hCG rise of at least 66% in 48 hours and 15% will show a rise between 53-66% every 48 hours.[27]

Much larger studies are now published which provide more conservative doubling times. In a larger study of 287 patients who had pain or bleeding and a nondiagnostic ultrasound and were then subsequently diagnosed with an intrauterine pregnancy had their serum β-hCG rise analysed. Within this study the slowest recorded rise for a viable pregnancy was 53% at 48 hours.[28] This study developed serum β-hCG curves which were then applied to a historical cohort of PULs of 1,249 patients. It concluded that a more conservative doubling time of 35% will minimise the potential interruption of a viable pregnancy.[29]

The discriminatory zone is the serum β-hCG level above which a gestational sac should be visible on TVUS if a viable IUP is present.[28] In one study where there was a serum β-hCG level to 2000-3000 IU/L with no IUP and no abnormal TVUS findings there was a 2% chance of a subsequent viable IUP.[30] When the serum β-hCG was greater than 3000 U/L there was a 0.5% chance of a subsequent viable intrauterine pregnancy. Care should be taken when there is no gestational sac visible above the discriminatory zone as reasons for a nonvisible sac include; multiple gestation, fibroids, sonographer experience, obesity, uterine polyps and ultrasound resolution.[31] Follow up for a pregnancy of unknown location will ultimately be determined by serum β-hCG levels, gestation and the woman's symptoms in conjunction with specialist review.

Progesterone has been used in the prediction of PUL outcome. A low serum progesterone level <20nmol/L has a PPV of >95% for a failing PUL. However, low serum progesterone is unable to reliably differentiate between an ectopic pregnancy and a failed PUL.[32] A meta-analysis found that 2.6% of women with an ectopic pregnancy also had a serum progesterone >20nmol/L.[33] This meta-analysis also found that progesterone may be useful in the prediction of pregnancy viability but not its location.

The M4 and M6 prediction models have been developed in order categorise women with a pregnancy of unknown location as either high or low risk for an ectopic pregnancy. The M4 model utilised serum β-hCG level at presentation and the hCG ratio; i.e. serum β-hCG at 48hours/serum β-hCG at 0 hours. [34] The M4 model was found to be the best model for predicting the final outcome in PUL with a sensitivity of 0.82 and specificity of 0.80.[35] Following this the M6 model was developed and includes progesterone, initial serum HCG level and serum β-hCG ratio. This model has been validated in over 3000 women[36] and has been found to be an effective triage tool with <1% misclassified EP and no serious adverse events.

Clinical Practice

- An experienced sonographer performing a TVUS is the gold standard for determining pregnancy location.
- If a pregnancy is not seen on TVUS a serum β-hCG should be taken and a second taken 48 hours later.
- We propose a discriminatory zone of 1500 to 2000 U/L β-hCG in which a trained sonographer should be able to visualise a gestational sac if there is an intrauterine pregnancy.
- An ectopic pregnancy can still present with appropriate doubling of serum β-hCG levels so caution is advised while taking into account the woman's history and symptoms.
- A serum β-hCG result should not be reviewed in isolation. Reviewing the woman's symptoms and history will also guide when to repeat the TVUS and/or serum β-hCG.
- Serum β-hCG testing is not always available outside routine laboratory hours however if the result is required urgently out of hours to aid clinical decision-making a senior clinician should discuss this with the relevant laboratory.
- The β-hCG assay (each test) should be performed on the same analyser throughout management as there can be up to a 30% difference between machines in different laboratories, depending on the assay used.
- Prediction models have been validated for the triaging of women presenting with PUL such as the M4 and M6 model and units/hospitals need to have a policy on whether these are included in their management of PUL.
- Women should be informed of the 8-14% risk of a PUL being an ectopic pregnancy and advised to seek prompt review for worsening or new symptoms (including but are not limited to; worsening pain, GI symptoms, feeling faint and heavy bleeding). They should be given information on emergency contact information.
- Women should be informed of all possible outcomes of a PUL diagnosis; intrauterine pregnancy, failing PUL, ectopic pregnancy and persistent PUL. This means there is a need for close follow up and monitoring while being cognisant of emotional needs of the woman during this time.

Recommendations

15. **All hospitals/units should have a local policy on PUL investigation and management, and this should include whether progesterone levels are included in management algorithms.**
16. **In PUL management, a senior clinician should be consulted after/at the third serum β-hCG test and should be involved in ongoing decision-making.**

Clinical Question 2.5: How is a tubal ectopic pregnancy managed?

Evidence Statement

Once a diagnosis of a tubal ectopic pregnancy has been made on ultrasound, a serum β-hCG should be performed to help guide management. The level of serum β-hCG is a prognostic indicator of success in medical management with methotrexate or expectant management with tubal ectopic pregnancy.[37]

There are three options for treatment of ectopic pregnancy: expectant, medical or surgical. The management should be based on the woman's choice following assessment of her clinical status and serum β-hCG level, with appropriate counselling. Discussion of risk should be undertaken by a clinician with experience of ectopic pregnancy to facilitate informed decision making.

A woman can be helped to make an informed decision by using the 'ask three questions'[38] model:

- What are my options?
- What are the pros and cons of each option?
- How do I get support to make the decision which is right for me?

Expectant Management

Expectant management should be reserved for haemodynamically stable women with β-hCG levels below 1500 U/L which are falling, with no pain, a tubal mass <3cm on TVUS and a willingness to complete follow up.[1] This criterion is similar to the NICE guideline; and is based on the inclusion criteria for the clinical trials[39] comparing expectant management of tubal EP with medical management with methotrexate.

For serum β-hCG levels > 1500 U/L and mass size >3cm there is minimal evidence to make further recommendations. Resolution with expectant management is associated inversely with serum β-hCG levels.[40] Success rates of 80-90% are reported if the serum β-hCG levels are less than 1000 U/L and 60-67% if β-hCG levels are less than 2000 U/L/l.[40] In a RCT comparing expectant management with methotrexate there was found to be no difference in success rate when women were asymptomatic with a serum β-hCG <1500 U/L.[39]

Follow up should be with a serum β-hCG level every 48 hours until the clinician is satisfied that the level is falling over three serum β-hCG results. Monitoring can then be extended to weekly until serum β-hCG is <5 U/L.[41] A retrospective cohort study of successful expectant management of an ectopic pregnancy concluded a median follow up time of 19 days with the longest resolution time 82 days.[42] It should also be noted in that in this study those with plateauing levels of serum β-hCG who remained asymptomatic continued to be managed expectantly however the resolution time is longer compared to those with persistently declining serum β-hCG. A RCT which compared expectant management with methotrexate for EP and PUL with a serum β-hCG <2000 U/L found that expectant management is a safe alternative to methotrexate with 60% of patients having a decline in serum β-hCG with no intervention and no adverse events.[43]

Expectant management should be abandoned if the serum β-hCG levels are not decreasing, a woman develops pain or if there are signs of tubal rupture. There remains a risk of rupture until full resolution and women should be given information on where to present for emergency care if they develop signs or symptoms of rupture. Such signs and symptoms include abdominal or pelvic pain, gastrointestinal symptoms or collapse.

NICE recommends that early pregnancy units will need to ensure that they are able to provide care for women receiving expectant management of a tubal ectopic pregnancy. Local protocols therefore need to be developed for assessment, monitoring, and follow-up of women who choose expectant management.[1]

Medical Management with methotrexate (MTX)

Medical management involves intramuscular (IM) methotrexate as a single dose of 50mg/m^2 calculated from patient body surface area on the day of treatment (Formula provided in Appendix III). The dose of methotrexate should not routinely be capped based on body surface area, but caution is advised with women with a very high BMI, for example where doses of >100mg are being administered [44] due to the potential side effects.

MTX treatment can be offered to women who; are haemodynamically stable with no contraindications to methotrexate, have β-hCG levels of <5000 U/L with an ectopic size of <35mm with no fetal heart activity and are able to return for follow up. There should be no signs of EP rupture and no evidence of an intrauterine pregnancy.

Contraindications to systemic methotrexate therapy include; breastfeeding, sensitivity to methotrexate, immunodeficiency, active pulmonary disease, active peptic ulcer disease, active liver disease, aplastic anaemia or thrombocytopenia.[45] Relative contraindications include renal and liver impairment. Further contraindications to be considered to medical treatment with methotrexate include willingness and ability to return for follow up and the presence of fetal cardiac activity on ultrasound. Women should have a full blood count, urea and electrolytes testing and liver function tests performed prior to administration of methotrexate. Women undergoing treatment with methotrexate should avoid folic acid antagonists which can decrease the effectiveness of methotrexate; causation is also advised in the use of nonsteroidal anti-inflammatory medication.[12] Women should avoid alcohol and vaginal intercourse which could increase the risk of EP rupture.[12]

Predictors of success for methotrexate in resolution of the ectopic pregnancy are based on the initial serum β-hCG level. Success is higher when no gestational sac is visualised and with smaller ectopic pregnancies at earlier gestations with lower β-hCG levels. In a retrospective review to determine the predictors of success for tubal EP managed with methotrexate it was found that a serum β-hCG <1000 U/L was associated with a 92-98% success rate. A serum hCG 10,000 to 14,999 U/L has been associated with a 82% success rate;[46] however this study is over 20 years old and current evidence would not suggest methotrexate is ever used in this β-hCG range. In another study which looked at progressing EP serum β-hCG levels of 1500 U/L to 2000 U/L were 88% successful in resolution which fell to 65% when the level was >4500 U/L.[47] A falling serum β-hCG between day 0-4 predicted success rates of 85% and a fall of >15% between day 4 and 7 has a positive predictive value of 93%.[48]

A systematic review which included 503 women with EP sought to further examine a cut off level for serum β-hCG and success rates with methotrexate treatment. This review found that a statistically significant difference in failure rate is seen with a serum β-hCG level >5000 U/L. A serum β-hCG level <5000 U/L was found to be 96% successful, which fell to 85% between 5,000 U/L to 9,999U/L.[49]

Systemic methotrexate has been shown in RCTs to be equally successful as surgery for ectopic pregnancy in some cases.[50] Serum β-hCG levels should be taken on day 4 and 7 post-IM injection. If there is less than the expected 15% decrease in β-hCG between day 4 and 7, a TVUS can be performed to exclude fetal heart activity and a second dose of methotrexate can be given.[51] Serum β-hCG levels should then be measured at weekly intervals until it is less than 5U/L. Women should be advised to avoid pregnancy for 3 months post-methotrexate use due to its teratogenic effect.

Women should be counselled regarding the need for follow up blood tests, the potential for rupture and the possibility of emergency surgical intervention. Written information should be provided to the woman on the use of methotrexate for ectopic pregnancy, and its implications for future pregnancy timing. When discussing the risk for rupture with a tubal ectopic pregnancy the factors which are most strongly associated with this include; amenorrhea of > 8 weeks (OR 46), amenorrhea of 6-8 weeks (OR 3.6), a serum β-hCG of 1500 to 5000 U/L (OR 4.1) and a serum β-hCG of >5000 U/L (OR 4.4).[52]

Methotrexate is a cytotoxic medication and requires additional consideration for prescribing, transport and administration. See Appendix 3 for prescribing of methotrexate. A local protocol should be in place for the safe prescribing, handling and administration of methotrexate. Methotrexate as folic acid antagonist that inhibits dihydrofolate reductase and results in the inhibition of DNA synthesis.[53] Methotrexate has been shown to be teratogenic or lethal in animal studies and is associated with CNS anomalies, skeletal anomalies and growth restriction in humans.[53] The minimum dose of methotrexate nor the critical period of developmental exposure to methotrexate has not been definitively determined.[54]

There is no robust data on the earliest time to conceive after MTX treatment of ectopic pregnancy. The safe interval from MTX treatment to conception is unclear. Women are advised to delay pregnancy for a minimum of 3 months following methotrexate treatment.[55] In a retrospective review of women who conceived following treatment with methotrexate for an ectopic pregnancy found no difference in pregnancy outcomes including malformations in pregnancies conceived within 6 months.[56] A further study which included 314 women who conceived shortly after methotrexate treatment of an ectopic pregnancy showed no evidence of an increase in fetal malformations or adverse pregnancy outcomes and concluded that conception within the first 6 months after MTX treatment is safe.[57] This study included both single and repeat injection of methotrexate. There is no evidence on the use of high dose folic acid to reduce the risk of malformations.[55]

Surgical Management

Surgical management of tubal ectopic pregnancy should be recommended to all women who are haemodynamically unstable, and where expectant or medical management is not appropriate or has failed. It may also be a woman's preference. Options include salpingectomy or salpingostomy which can be performed laparoscopically or by laparotomy. Laparoscopy is preferable in the haemodynamically stable woman as it associated with decreased hospital stay, less blood loss and fewer analgesic requirements.[58]

The laparoscopy should be performed by a suitably trained operator.[15] Those working in obstetrics and gynaecology should have sufficient exposure to the management and treatment of EP. Training in diagnostic and operative laparoscopy is important and those performing surgical management should be independently competent in the procedure and should have evidence of this in the form of cases performed and workplace-based assessment tools, e.g. OSAT.[59] It is important to ensure that those performing surgical treatment maintain their competency. It is reasonable to perform a laparotomy if based on the availability of resources, including adequately training personnel.

The evidence suggests offering a salpingectomy to women undergoing surgery for an EP unless they have other risk factors for infertility.[60] A systematic review and metanalysis comparing salpingectomy with salpingostomy for tubal ectopic pregnancy found that there was no difference in future intrauterine pregnancy in the RCT between salpingectomy and salpingostomy. However in a subgroup analysis of women with risk factors for tubal disease there was a higher intrauterine pregnancy rate following salpingostomy; this is associated with a higher risk of recurrent ectopic pregnancy (OR 1.9). There is a risk of persistent trophoblastic disease with salpingostomy of between 3 and 11%.[61] For this reason, serum β-hCG levels must be followed weekly until falling and < 5 U/L. The surgical specimen should be sent for histological examination to confirm the diagnosis.

All women with an ectopic pregnancy should be advised that there is a risk of a recurrent EP. In a study examining the fertility outcomes of over 1000 women who were treated for an ectopic pregnancy 10.5% had a recurrent EP.[62] There was an 18.5% recurrence rate after salpingostomy or salpingectomy and 25.5% after medical treatment. Studies examining the recurrence risk for ectopic pregnancy give a recurrence rate from 10-27%.[63] Some risk factors are consistently associated with recurrent EP such as pelvic adhesions and previous pelvic surgery.[64] For this reason, women should be advised to obtain an early TVUS in any subsequent pregnancy at 6 weeks to ensure the pregnancy location is intrauterine.

Clinical Practice

- Women with suspected or diagnosed EP should be cared within an Early Pregnancy Assessment Unit (EPAU) with appropriate governance structures.
- Ultrasound findings, serum β-hCG levels and the woman's symptoms will guide suitable ectopic pregnancy management options.
- Women should be counselled regarding follow up plans for each treatment option, success rate, complications and need for further or repeat treatment.
- The diagnosis and management plan for each case of tubal ectopic pregnancy should be discussed with a Consultant Obstetrician/Gynaecologist.
- After expectant or medical management, serum β-hCG levels need to be followed up until resolution.
- Contraception should be provided for women who have been given methotrexate to treat an ectopic pregnancy as pregnancy should be avoided for 3 months.
- A delay in pregnancy for 3 months following treatment with methotrexate is recommended given the paucity of evidence to delay conception for 6 months which would also delay future pregnancy.
- Salpingostomy can be considered as an alternative to salpingectomy for women with risk factors for infertility such as contralateral tube damage.

The NCEC National Clinical Guideline on Unexpected Intraoperative Life Threatening Haemorrhage applies to patients undergoing interventions and operations where there is a risk that an unexpected intraoperative life threatening haemorrhage can occur. The NCEC guideline covers prevention of intraoperative life threatening haemorrhage, immediate recognition of intraoperative life threatening haemorrhage and timely response and management of intraoperative life threatening haemorrhage and includes recommendations for gynaecology trainees undertaking laparoscopic surgery. This obviously includes surgical management of ectopic pregnancy although the NCEC guideline makes no reference to EP specifically. The NCEC recommendations are relevant for clinical practice in this context for the EP guideline.[13]

13 Department of Health (2022). Unexpected Intraoperative Life Threatening Haemorrhage (NCEC National Clinical Guideline No. 29). Available at: https://www.gov.ie/en/collection/c9fa9a-national-clinical-guidelines

Recommendations

17. Expectant management should be reserved for haemodynamically stable women with β-hCG levels below 1500 U/L which are falling, with no pain, a tubal/adnexal mass <3cm on TVUS and a willingness to complete follow up.
18. Medical management is appropriate in women with serum β-hCG <5000 U/L, no contraindications to methotrexate, no evidence of fetal cardiac activity and no significant pain or hemoperitoneum.
19. Medical management is most successful in women with a serum β-hCG of 3,000 U/L and less.
20. All hospitals/units need to have local protocols for assessment, monitoring, and follow-up of women who choose expectant or medical management for ectopic pregnancy.
21. Surgical management is appropriate when there is evidence of rupture, significant pain, β-hCG levels >5000 U/L, fetal cardiac activity, an adnexal mass >3cm on TVUS, where the ectopic pregnancy is not suitable for medical management or where there has been unsuccessful medical management, and in some scenarios of preference or where the woman is not available for follow up.

Section 4: Interstitial Ectopic Pregnancy

Clinical Question 2.6: How is an interstitial ectopic pregnancy diagnosed?

Evidence Statement

An interstitial pregnancy is one which occurs in the interstitial portion of the fallopian tube i.e. the tubal segment which is within the muscular wall of the uterus.[65] It is the second most common type of ectopic pregnancy after tubal EP, often referred to as a subtype of tubal ectopic pregnancy, with an incidence rate reported between 2%-4%.[66] This portion of the tube contains the anastomosis of the uterine and ovarian arteries and thus on rupture can lead to rapid blood loss. Due to a combination of rich blood supply and difficulty in diagnosis, this diagnosis of this type of EP is often diagnosed late and has a mortality rate of 2.5% which is 7 times greater than EPs in general.[65]

TVUS remains the main method of diagnosis, although MRI may be helpful. The interstitial line sign has a sensitivity of 80% and a specificity of 98%.[67] It refers to an echogenic line that runs from the endometrial cavity to the cornual region, abutting the interstitial mass or gestational sac.[67] Other features on ultrasound include an empty uterine cavity, a chorionic sac separate and at least 1cm from the lateral edge of the uterine cavity, and a thin (<5 mm) myometrial layer surrounding the gestational sac.[68]

Clinical Practice

A TVUS by an experienced sonographer will help diagnose an interstitial pregnancy.

MRI can be helpful if there is uncertainty and if this is available from a Radiologist with experience.

Recommendations

22. **Transvaginal ultrasound is the first line imaging modality for diagnosing an interstitial ectopic pregnancy.**

Clinical Question 2.7: How is an interstitial pregnancy managed?

Evidence Statement

A serum β-hCG test should be carried out at diagnosis of an interstitial ectopic pregnancy. In a large series of 42 women with an interstitial EP examined to determine which factors were could predicted the likelihood of success of conservative management (noting that conservative management in this paper included both expectant and medical treatment with methotrexate), a lower initial serum β-hCG i.e. less than 9,000 U/L was associated with an increase in successful outcome. The initial median serum β-hCG was also significantly lower in women with successful conservative management.[69] Within this case series the highest level of serum β-hCG which was managed expectantly was 11,460 U/L.

Treatment options for interstitial EP include expectant (conservative), medical and surgical management. Expectant management should be used cautiously due to the high rate of mortality in rupture of such pregnancies and may only be considered where the EP is presumed to be failing and β-hCG levels are falling. Likely success of expectant management is related to initial serum β-hCG levels.[69]

Medical management with methotrexate is a reasonable first line treatment in the asymptomatic woman with an unruptured interstitial ectopic pregnancy. In a case series of 11 interstitial EP treated with methotrexate the success rate of methotrexate therapy of an interstitial EP was 91%, including one women with β-hCG levels as high as 106,634 U/L treated, in the presence of fetal cardiac activity.[70] It should be noted that time to resolution was up to 129 days in this case series.

Administration, dosing and monitoring of methotrexate therapy is the same for other types of ectopic pregnancy.[71] There are case reports of successful management of interstitial EP using local injection of methotrexate along with uterine artery embolisation.

Uterine artery embolisation has been described in a number of case reports successfully treating interstitial pregnancy. However currently there is not enough available evidence to determine efficacy. For women planning a future pregnancy embolisation should be cautioned. For women who have had uterine artery embolisation for fibroids (UFE) there have been successful pregnancies reported; however, additional research regarding rates of conception and obstetrical risks of infertility following UFE is necessary.[72]

Surgical management is first line in an interstitial EP where rupture is suspected or following failed methotrexate treatment. There are many surgical techniques described for management of interstitial EP. However, many of these techniques have limited data to recommend one in particular.[73]

Laparoscopic and open approaches have been described in the literature. The laparoscopic approach is preferable if the surgical expertise is available.[73] Surgical options include cornual resection, cornuostomy, or wedge resection. Traditional wedge resection should be preserved for cases of rupture where laparoscopic expertise is not available. Wedge resection is the removal *en bloc* of the involved tissues and surrounding endometrium via an open approach.[74]

Methods to control bleeding include vasopressin injection into the myometrium below the interstitial pregnancy (10iu in 50-100mls 0.9% saline).[65] Another approach is the placement of sutures through the uterus beneath the pregnancy before cornual wedge resection. The ascending branch of the uterine artery can be occluded by electrocoagulation or by suture ligation.[75]

Serial β-hCG levels should be performed post-surgical resection until levels of <5U/L are achieved. If the levels are not falling appropriately, a single dose of methotrexate can be considered.

In terms of future pregnancy risk these should be discussed with the women. There are case reports of uterine rupture in pregnancy following conservative and surgical management.[76] However there are also case reports of uncomplicated pregnancies[77] and successful vaginal deliveries.[78] One case series of 33 women who underwent cornual resection for an interstitial EP were following to determine future pregnancy outcome. There were 26 patients who had undergone a cornual resection and 15 of these went on to have a term pregnancy. Six of these patients had a vaginal delivery and nine a caesarean section.[79] A retrospective cohort study of pregnancies with a history of wedge resection for interstitial EP contained 11 pregnancies carried >20 weeks; 40% had a vaginal delivery and there were no cases of rupture.[80]

However, a retrospective review of cornual wedge resection for an interstitial EP and subsequent pregnancy outcomes found a rupture rate of 30%. Three of the ten patients had a rupture at 13 weeks, 32 weeks and 36 weeks respectively.[81] For those who had a laparoscopic cornuostomy they may be at decreased risk of a rupture, with a case series of six pregnancies; three delivered vaginally and three had a caesarean section with no evidence of dehiscence at the time of C-section.[82] At the time of caesarean, the site of previous wedge resection of cornuostomy should be examined for dehiscence.

Given the effect of surgery on the strength on the myometrium is relatively unknown the mode of delivery in future pregnancy should be discussed with the woman and if a caesarean section is preferred this should be done at term >37 weeks prior to the onset of labour.

Clinical Practice

- A serum β-hCG should be performed at diagnosis of interstitial EP to guide management. Success of expectant or medical management is inversely related to the initial β-hCG level.
- Caution should be used when recommending expectant management for interstitial EP due to the high morbidity associated with rupture.
- Medical treatment can be used in women who are asymptomatic with no sign of rupture; there is no known upper limit of β-hCG to undergo medical treatment with methotrexate in interstitial EP.
- A Consultant Obstetrician/Gynaecologist should be involved in the clinical decision making and clinical review for women with suspected or diagnosed interstitial EP.
- Surgical options include a laparoscopic or open approach with resection of the ectopic pregnancy. This will be determined by surgical expertise.
- Follow up with serial β-hCGs are required following surgical management until levels are <5U/L.
- If a caesarean section is planned for a subsequent pregnancy, it should generally be performed > 37 weeks and prior to the onset of labour.

Recommendations

23. **A serum β-hCG should be performed at diagnosis of an interstitial ectopic pregnancy to guide management.**
24. **The optimal method of treatment for interstitial ectopic pregnancy has not been determined and needs further research. Cases should be managed on an individual patient basis and a Consultant Obstetrician/Gynaecologist should be involved in decision making and management.**
25. **Expectant management of interstitial ectopic pregnancy should be used with caution due to the high mortality associated with rupture of an interstitial ectopic pregnancy but can be considered when β-hCG levels are falling and the pregnancy is non-viable.**
26. **Intramuscular or local methotrexate treatment may be considered in asymptomatic women who fit the criteria for medical management, with follow up serum β-hCG levels.**
27. **Surgical management may be considered for interstitial ectopic pregnancy and is required when there is evidence of rupture, with follow up β-hCG levels.**

Section 5: Cervical Ectopic Pregnancy

Clinical Question 2.8: How is a cervical ectopic pregnancy diagnosed?

Evidence Statement

A cervical ectopic pregnancy is a rare form of EP in which implantation occurs in the endocervical canal. Its incidence is less than 0.1% of ectopic pregnancies.[83]

A cervical EP is diagnosed using TVUS. Care must be taken to avoid mistaking a cervical EP for a miscarriage. On TVUS, the following findings can be used for diagnosis; an empty uterus, a barrel shaped cervix, a gestational sac below the level of the internal os, the absence of the sliding sign and blood flow around the gestational sac using colour doppler.[84]

Clinical Practice

A cervical ectopic pregnancy is diagnosed with TVUS, and care must be taken to avoid mistaking a cervical ectopic pregnancy for a miscarriage.

The absence of the sliding sign, a gestational sac below the level of the internal os and blood flow around the sac on Doppler is suggestive of a cervical EP.

Recommendations

28. **A cervical ectopic pregnancy is diagnosed using TVUS; absence of a sliding sign, a gestational sac below the level of the internal os and blood flow on Doppler all raise suspicion for a cervical ectopic pregnancy.**

Clinical Question 2.9: How is a cervical ectopic pregnancy managed?

Evidence Statement

A cervical ectopic pregnancy is associated with a high level of morbidity due to the propensity for haemorrhage and over 50% of patients will require multiple interventions.[85] This scoping review including 404 cases of cervical EP and there was a hysterectomy rate of 9%. Options for management include methotrexate, dilatation and curettage and uterine artery embolisation. Uterine artery embolisation is associated with higher rates of success compared to the alternative options[85] however future fertility should be considered as previously discussed. Dilatation and curettage alone is associated with an increased risk of blood transfusion.[86]

A serum β-hCG should be carried out at diagnosis. A series of 52 cases of cervical ectopic pregnancy; a β-hCG of > 10,000 U/L, gestational age at > 9 weeks, embryonic cardiac activity, and crown-rump length of >10 mm were factors associated with an lower risk of success medical management with methotrexate.[87]

Systemic methotrexate administration was quoted to be 91% effective in the treatment of cervical EP.[88] This retrospective review examined a total of 62 cases of cervical ectopic pregnancy; a combination of systemic, intra-cervical or intraamniotic methotrexate was used. However, 19 of 62 women required further surgical intervention i.e. dilatation and curettage or embolisation.

Ultrasound-guided intra-amniotic and intrachorionic methotrexate injection (50 mg/m^2) have also been used in conjunction with intracardiac injection of potassium chloride if fetal cardiac activity was seen.[89]

Infiltration of the cervix with a haemostatic vasoconstricting agent, followed by the placement of cervical sutures to temporarily occlude the descending branches of the uterine arteries followed by suction curettage (without dilation) and post-curettage cervical canal balloon tamponade has been shown to be successful in treating first trimester cervical pregnancies.[90] The technique of suction curettage and a balloon tamponade was reported a 13 successfully treated cervical EP with no adverse events.[90]

Clinical Practice

- A cervical EP can be managed medically with methotrexate or by different surgical techniques.
- A Consultant Obstetrician/Gynaecologist should be involved in the clinical decision making and management due to the high level of morbidity associated with cervical EP.
- The use of methotrexate is more effective in cervical EPs less than 9 weeks, in the absence of cardiac activity, a CRL <10mm, and a serum β-hCG < 10,000 U/L.
- The risks of surgical treatment as mentioned above should be discussed with the woman as well as the need for follow up with methotrexate treatment which can vary in length depending on patient response. Medical treatment may require surgical intervention and the woman should be given all information so they can make an informed decision.
- Future fertility implications should be discussed with reference to the treatment options available.

Recommendations

29. **A cervical ectopic pregnancy can be managed medically with methotrexate, surgically or with uterine artery embolisation; a Consultant Obstetrician/Gynaecologist should be involved in decision making and management.**

Section 6: Caesarean Scar Pregnancy

Clinical Question 2.10: How is a caesarean scar pregnancy diagnosed and managed?

Evidence Statement

Caesarean scar pregnancy (CSP) is when a pregnancy implants into a caesarean section scar and can be described as partial or complete. A partial CSP is the most common type where the gestational sac implants anteriorly, at the level of the internal os, invading the myometrium but partially protruding into the uterine cavity. A complete CSP is less common and occurs when the gestational sac is completely implanted into the anterior myometrium close to the internal os without visible communication to the uterine cavity.[2]

The primary modality for diagnosis is TVUS and the initial finding of a low, anteriorly located gestational sac should raise concern for a possible CSP and warrants further investigation.[91]

Caesarean scar pregnancy (CSP) presents a substantial risk for severe maternal morbidity. A systematic review of the outcomes caesarean scan pregnancy according to gestational age concluded that an earlier diagnosis is associated with a significant reduction in maternal complications.[92] A total of 724 case of CSP were included and concluded that a woman who was diagnosed > 9 weeks was associated with a hysterectomy rate of 16.3% whereas if diagnosed under 9 weeks this fell to 3.7%. Massive haemorrhage occurred in 28% of CSP diagnosed >9 weeks and 4.3% diagnosed under 9 weeks. The overall composite adverse outcome rate was 5.9% in those diagnosed <9 weeks and rose to 32.4% diagnosed >9 weeks gestation. CSP and placenta accreta spectrum (PAS) disorder may be part of the same disease spectrum.[93] A caesarean scar pregnancy registry has been developed through Liverpool Women's NHS Foundation Trust and thirty international centres have submitted cases to the registry in order to aid further research into the diagnosis and management of CSP.[94]

Surgical, medical, and expectant management as well as combinations of treatment modalities have all been described in the literature, however the optimum treatment remains unknown. Many factors will need to be considered when discussing treatment options including; patient status, CSP size and location, clinician expertise and local resources. A multidisciplinary approach to management must be considered.

Regarding medical management with methotrexate, a single dose of ultrasound guided local methotrexate[95] has success rates as high as 73.9%, and increases to 88.5% after an additional local or intramuscular methotrexate injection.[96] An RCT comparing local and systemic methotrexate showed similar success rates of 67%-69% with a shorter time to serum β-hCG remission and mass disappearance with systemic methotrexate.[97] An RCT which compared uterine artery embolisation (UAE) with systemic methotrexate prior to dilatation and curettage concluded that UAE appears to be advantageous. The study included seventy-two women with two women in the methotrexate group requiring a hysterectomy due to bleeding.[98] The blood loss with UAE was 36ml +/- 6ml compared with 415ml +/- 68ml in the methotrexate group.

Surgical options for CSP include resection via a transvaginal or laparoscopic approach (where available), or ultrasound-guided vacuum aspiration.[99] A systematic review and metanalysis of treatment options found that dilatation and curettage associated with a success rate of 76%, a risk of haemorrhage of 28%, and a risk of hysterectomy of 3% which was the highest complication rate of all surgical options.[100] A retrospective study of 191 women who underwent ultrasound guided suction curettage with a modified Shirodkar cervical suture in those who required additional haemostatic techniques found a hysterectomy rate of 0.5% with transfusion rate of 4.7%.[101] A case series showed that laparoscopic management to be successful in 97% of cases,[102] with no severe complications reported.

Surgical management at increasing gestational age is associated with increasing complications. A retrospective cohort study examining 62 women with a live CSP who underwent surgical management in the form of transcervical suction curettage with ultrasound.[99] The median blood loss was 100ml however in women >9+0 weeks, 33% required a blood transfusion with no patient under 8 weeks having a blood loss >500ml.

In a systematic review published in 2018 a total of 69 cases of CSP which were managed expectantly, in women who had declined termination of pregnancy, were examined. In those CSP where there was no fetal cardiac activity 69% had an uncomplicated miscarriage with the remainder requiring surgical or medical intervention for heavy bleeding. In those without fetal cardiac activity there was no-one who required a hysterectomy. However, in pregnancies where fetal cardiac activity was present 15% required a hysterectomy in the first or second trimester. Forty women progressed to the third trimester with 74% developing an accreta spectrum disorder. While expectant management may be appropriate for those who have evidence of a failing pregnancy without fetal cardiac activity it is associated with high morbidity if fetal cardiac activity is present.

Within a systematic review published in 2016 expectant management was reviewed in 41 women and associated with a severe complication rate of 53% with resolution in only 41%.[102] There was a hysterectomy rate of 41% within this group. Women who decline treatment of a caesarean scar pregnancy should be counselled regarding the risk for severe morbidity in ongoing pregnancy. [93, 95]

Clinical Practice

- The primary modality for diagnosing a CSP is a TVUS by an experienced sonographer.
- Cases of CSP should be discussed within a Consultant-led multidisciplinary team to decide management.
- Local or systemic methotrexate injection may be considered for CSP.
- US guided vacuum aspiration or laparoscopic resection are the surgical techniques of choice.
- Sharp curettage of CSP should be avoided.
- If a woman declines treatment in early pregnancy, they should be counselled regarding the associated high risk of morbidity in ongoing pregnancy and managed as per the Clinical Practice Guideline: Diagnosis and Management of Placenta Accreta Spectrum.[14]

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14 Bartels H.C, Walsh J.M, Ní Mhuircheartaigh R, Brophy D, Moriarty J, Geoghegan T, O'Leary M, Donnelly J. C, Colleran, G.C, Thompson, C, Cooney, N, Byrne, B, Downey, P, Greene, R, Higgins, S, Brennan, D.J. National Clinical Practice Guideline: Diagnosis and Management of Placenta Accreta Spectrum. National Women and Infants Health Programme and The Institute of Obstetricians and Gynaecologists. December 2022

Recommendations

30. High resolution transvaginal ultrasound is the primary imaging modality for diagnosis of a caesarean scar ectopic pregnancy.
31. Caesarean scar pregnancy should be discussed within a multidisciplinary team to determine the best management option. Women should be informed of the risk: benefits of treatment options to make an informed decision.
32. A woman who declines treatment for a caesarean section scar pregnancy should be counselled regarding associated morbidity and the pregnancy managed as per the Diagnosis and Management of Placenta Accreta Spectrum Guideline (2023).

Section 7: Ovarian Ectopic Pregnancy

Clinical Question 2.11: How is an ovarian ectopic pregnancy diagnosed?

Evidence Statement

An ovarian ectopic pregnancy is where the gestational sac implants within the ovary.[103] The clinical features are like those for tubal EP, and current use of an IUD is more likely in cases of ovarian EP.[103] This type of EP can be particularly difficult to diagnose as it can be difficult to distinguish them from ovarian cysts including the corpus luteum. Findings suggestive of an ovarian EP on TVUS are an empty uterus, and a wide echogenic ring with an internal anechoic area on the ovary, and a negative sliding sign i.e., the mass is not separate from the ovary.[104] It should be visualised separate to the corpus luteum. A yolk sac or embryo is seen less commonly in ovarian EPs.[84] The definitive diagnosis is usually made by histopathology following surgical excision.

Clinical Practice

- An ovarian EP is diagnosed using TVUS; signs suggestive of an ovarian ectopic include a mass which is not separate to the ovary but is separate to the corpus luteum.
- Definite diagnosis is with histopathology following surgical excision.

Recommendations

33. An ovarian ectopic pregnancy is diagnosed using transvaginal ultrasound as a mass on the ovary with a negative sliding sign and separate to a corpus luteum.

Clinical Question 2.12: How is an ovarian ectopic pregnancy managed?

Evidence Statement

The evidence suggests that optimum management of an ovarian ectopic is resection of the ovarian ectopic pregnancy with preservation of healthy ovarian tissue[103] in order to maintain fertility. There is a risk of oophorectomy if there is excessive bleeding which cannot be controlled surgically or if there is other ovarian pathology. For those women who have resection of the ovarian EP with retention of the ovary, they should be followed up with weekly serum β-hCG until < 5 U/L.[103]

Clinical Practice

- Surgical management is recommended for an ovarian EP with excision of the ectopic; oophorectomy may be required in cases of heavy bleeding which cannot be controlled at the time of laparoscopy.
- When surgical risk is deemed to be high, medical management can be used with monitoring of serum β-hCG levels.
- A Consultant Obstetrician/Gynaecologist should be involved in the clinical decision making and clinical review.

Recommendations

34. Surgical management is the treatment of choice for ovarian ectopic pregnancy.
35. A Consultant Obstetrician/Gynaecologist should be involved in decision making and management of ovarian ectopic pregnancy.

Section 8: Rudimentary Horn Ectopic Pregnancy

Clinical Question 2.13: How is a rudimentary horn ectopic pregnancy diagnosed?

Evidence Statement

Previously described as a cornual ectopic pregnancy,[2] a rudimentary horn ectopic is the implantation of a gestational sac within the rudimentary horn of a unicornuate uterus.[105] This is distinct from an interstitial pregnancy where a pregnancy implants within the interstitial portion of the fallopian tube. Rudimentary horn ectopic is rare with a reported incidence of 1:76,000 to 1:150,000.[106]

The following ultrasound criteria can be used to diagnose a rudimentary horn ectopic and to distinguish between either an EP (interstitial or rudimentary horn) or an IUP (laterally sited in a normal uterus or in a uterus didelphys/septate uterus); visualisation of a single interstitial portion of Fallopian tube in the main unicornuate uterine body, gestational sac/products of conception seen mobile and separate from the unicornuate cavity and completely surrounded by myometrium, and a vascular pedicle adjoining the gestational sac to the unicornuate uterus. MRI can also be used as an imaging modality to assist diagnosis.

Clinical Practice

- TVUS is used to diagnose rudimentary horn ectopic pregnancy.
- MRI can also be useful imaging modality to assist in diagnosis of rudimentary horn ectopic pregnancy, if the expertise is available.

Recommendations

36. **Ultrasound criteria can be used to diagnose a rudimentary horn ectopic pregnancy; visualisation of a single interstitial portion of fallopian tube in the main unicornuate uterine body, gestational sac/products of conception seen mobile and separate from the unicornuate cavity and completely surrounded by myometrium, and a vascular pedicle adjoining the gestational sac to the unicornuate uterus.**

Clinical Question 2.14: How is a rudimentary horn ectopic pregnancy managed?

Evidence Statement

To avoid recurrence of a rudimentary horn ectopic pregnancy, the rudimentary horn should be removed. The surgeon should be aware of the possibility of urinary tract abnormalities which are associated with unicornuate uterus.[107] Due to the rarity of these types of ectopic pregnancy and the challenge with diagnosis these pregnancies can present in the second trimester as a rupture and collapse.[108]

A recent publication examined 22 cases of women with a rudimentary horn over a 30-year period; 11 of these women had a rudimentary horn pregnancy and 55% experienced a rupture.[108] There was also a significant risk of massive intra-abdominal haemorrhage with six women going into shock and receiving multiple blood transfusions.

If diagnosed early rudimentary horn ectopic pregnancies can be successfully treated laparoscopically or via laparotomy with a low risk of complications.[105] There are case reports of laparoscopic removal of the rudimentary horn pregnancy into the second trimester and this will depend on the availability of laparoscopic surgical expertise.[109]

Clinical Practice

- Treatment of a rudimentary horn ectopic is via surgical excision of the rudimentary horn with a laparoscopic or open approach.
- Women can present with an acute presentation of a rupture into the second trimester of pregnancy.
- A Consultant Obstetrician/Gynaecologist should be involved in the clinical decision making and review of the woman given the rarity of this form of ectopic pregnancy and the surgery required.

Recommendations

37. **Treatment for a rudimentary horn ectopic pregnancy is excision of the rudimentary horn via laparoscopy or laparotomy.**

Section 9: Follow Up Care

Clinical Question 2.15: Do rhesus D negative women with an ectopic pregnancy require anti-D immunoglobulin?

Evidence Statement

There is evidence that woman who have an ectopic pregnancy are at risk for sensitisation.[110] Fetal red blood cells can be found in up to 24% of women who have a tubal rupture in ectopic pregnancy.[111] As fetal blood cells can be seen in maternal circulation these women are at risk for sensitisation and subsequent haemolytic disease of the fetus and newborn.[110]

NICE recommends non-sensitised women who are RhD negative should receive 1500iu of Anti-D immunoglobulin when undergoing surgical management of an ectopic pregnancy.[15]

In contrast, the British Society for Haematology (BSH) guidelines recommend all non-sensitised women who are treated surgically, medically or expectantly for an ectopic pregnancy should receive Anti D immunoglobulin.[112]

Clinical Practice

- All non-sensitised women who are RhD negative should receive Anti-D immunoglobulin when undergoing surgical management for an ectopic pregnancy.
- Women who are undergoing expectant or medical management for tubal EP should be counselled that there is a lack of consensus in international guidance about the use of Anti-D immunoglobulin in these situations. The option of Anti-D immunoglobulin should be discussed.

Recommendations

38. **All non-sensitised women who are RhD negative should receive Anti-D immunoglobulin if having surgical management for any type of ectopic pregnancy.**

Clinical Question 2.16: What is the appropriate follow up care after ectopic pregnancy?

Evidence Statement

The provision of medical follow up care provides an opportunity to discuss future fertility concerns and assists the woman on making decisions for future pregnancy. A lack of formal follow up care can lead to woman seeking information elsewhere, which may not be specific to their situation.[5] A lack of follow up care after ectopic pregnancy also results in a lack of resolution and prolonged grief [5] The follow up visit should take place in a suitable clinic location (e.g. a gynaecology clinic) which is separate to pregnant women and to infants.[7]

There should be a differentiation between medical follow up care and psychological care following ectopic pregnancy. As previously discussed, medical care should be offered in conjunction with bereavement care services. Women should be offered support in for the form of a bereavement specialist midwife when they are diagnosed with an EP and should be offered bereavement and support services following treatment.[7]

Clinical Practice

- All women who have had surgical management for any type of ectopic pregnancy should have hospital follow up 6-9 weeks following the procedure.
- Routine follow up for all women with ectopic pregnancy should be considered regardless of the mode of treatment, to ensure clinical resolution in expectant/medical management, to facilitate a clinical discussion as well as advise on future pregnancy planning.
- The ectopic pregnancy should be confirmed on histological examination.
- Information on future pregnancy planning should be given to the woman at the time of discussing treatment options and again at a follow up appointment.
- General Practitioners should be informed about the treatment for the ectopic pregnancy and implications for future pregnancies.

Recommendations

39. **Women should be given a follow up hospital appointment 6-9 weeks following surgical treatment for any ectopic pregnancy and future pregnancy implications discussed.**
40. **Routine follow up for all women with ectopic pregnancy should be considered regardless of the mode of treatment, to ensure clinical resolution in expectant/medical management, to facilitate a clinical discussion as well as advise on future pregnancy planning.**
41. **General Practitioners should be informed of a woman's treatment for an ectopic pregnancy and implications for future pregnancy.**

Clinical Question 2.17: What is required when planning for the next pregnancy?

Evidence Statement

The recurrence risk for an ectopic pregnancy is 15%.[62, 113] An early pregnancy scan should be performed at 6 weeks in subsequent pregnancies to ascertain if the pregnancy is intrauterine.[23] Women should be informed that they are at increased risk of an ectopic pregnancy and should be able to self-refer to an early pregnancy unit when they become pregnant again.

Timing and mode of delivery should be discussed with the woman following review of previous surgical notes and obstetric history. As previously discussed, this should be individualised to the woman with evidence limited to case series and retrospective reviews of small numbers.

Clinical Practice

Women treated with methotrexate should be advised to avoid pregnancy for 3 months due to its potential teratogenicity and contraception should be used.

An early ultrasound scan in a future pregnancy at 6 weeks is recommended due to the increased risk of another ectopic pregnancy.

Recommendations

42. **An early pregnancy ultrasound at 6 weeks gestation should be performed in any subsequent pregnancy due to the increased risk of ectopic pregnancy recurrence.**

Chapter 3: Development Of Clinical Practice Guideline

3.1 Literature search strategy

A comprehensive literature review was undertaken which included national and international publications. MEDLINE, EMBASE, PUBMED and Cochrane Library were searched using terms related to ectopic pregnancy including 'ectopic pregnancy', 'pregnancy of unknown location', 'caesarean scar pregnancy' 'interstitial ectopic', 'cornual ectopic', 'ovarian ectopic' 'cervical ectopic', 'methotrexate', 'salpingostomy', 'salpingectomy'. The search took place between September 2022 and May 2023. The search was limited to between the years 1972 and 2023.

International guidelines were reviewed including the National Institute for Health and Care Excellence (NICE) Guideline No: 126[15], Society of Obstetricians and Gynaecologists of Canada (SOGC) Guideline No: 414[25], Royal College of Obstetricians and Gynaecologists Green-top guideline No.21[84] and Queensland Health Australia Early Pregnancy loss guideline[114] were also used to inform this guideline. References included in these guidelines were also reviewed as well as additional references identified through the literature review.

The primary outcome data (cure and improvement) was cross checked against primary trial reports, whereas all other data, including adverse events, were extracted verbatim from the relevant Guideline and Cochrane reviews.

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

Several evidence-based recommendations for management of ectopic pregnancy 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 4) as recommended by the Department of Health in the 'How to Develop a National Clinical Guideline: a manual for guideline developers', 2019.[15]

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.

Two reviewers (NF and FA) carried out the review of relevant literature and selected the literature to be used in the Guideline. High quality systematic reviews and metanalysis were included. Where systematic reviews or RCT were not available retrospective studies, case series and case reports were included.

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.[16]

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.[17] (Appendix 5)

Best practice consensus was reached when a recommendation has been made which has been accepted standard of care.

15 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/

16 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.

17 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/

3.6 Future research

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

The questions of relevance to this Guideline include;

- What (and where) is the optimal management of caesarean scar pregnancy?
- Should a serum b-hCG test be performed on all women of reproductive age attending an emergency department complaining of abdominal pain?
- What is the optimal method and timing of serum b-hCG follow-up after surgical management of an ectopic pregnancy?
- Should women with expectant and medical management of Tubal EP have follow up ultrasound scans to ensure resolution of EP prior to embarking on their next pregnancy?
- Should women who have expectant or medical management of a tubal EP have patency of fallopian tubes assessed prior to next pregnancy?
- Should anti-D be given for this group – and/or does it depend on β-hCG level/size of EP?
- What is the optimal rate of PUL that should be seen in an EPAU?
- What is the ideal proportion of women with PUL having a negative laparoscopy?
- Should women with previous LSCS be routinely scanned in early pregnancy to confirm an intrauterine pregnancy?
- What is the correct/ideal proportion of EP requiring emergency surgery for rupture pre- or post-treatment?
- Are there more effective medical treatment options for EP than methotrexate?

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[18] for developing Policies, Procedures, Protocols and Guidelines (2016) (Appendix 6) 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 7 for list of CAG members.

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

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.[19]

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.

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

Chapter 6: **Implementation**

6.1 Implementation plan

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

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

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.

Collaborative training and support of healthcare professionals in both the primary care, emergency medicine and general surgery is necessary to ensure safe management of women with an acute presentation of ruptured ectopic pregnancy. This can be delivered both nationally by relevant training bodies and at a local hospital level by multidisciplinary simulation training.

6.3 Barriers and facilitators

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

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

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

Potential external barriers include:

- Structural factors (e.g., budget or service redesign)
    - A dedicated EPAU area where women's emotional and psychological needs may be cared for.
- Organisational factors (e.g., lack of facilities or equipment)
    - The provision of a dedicated EPAU service 7 days a week and 24-hour access to serum β-hCG testing.
- Individual factors (e.g., knowledge, skills, training)
    - The availability of sonographers or clinicians trained in early pregnancy ultrasound 7 days a week.
- Bereavement care
    - Provision of a dedicated bereavement specialist midwife to support women.

It is recommended that each local clinical setting to which this Guideline applies should determine what resources are necessary for its implementation. The implementation of the Guideline can be facilitated by ensuring that all clinicians understand and appreciate that the Guideline contributes to the quality and safety of patient care.

6.4 Resources necessary to implement recommendations

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

In the case of this guideline, education surrounding ruptured ectopic pregnancy may be required. Given that some women will present to emergency departments with no on-site or on-call gynaecology support, healthcare workers may not have the same experience to diagnose and surgically manage these women. Therefore, both local and national ongoing collaborative training is required.

Chapter 7: Audit and Evaluation

7.1 Introduction to audit

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

7.2 Auditable standards

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

Each unit should implement a systematic process of gathering information and tracking over time to achieve the objectives and recommendations of this Guideline. Outcomes of audits should be benchmarked against other units, national and international standards for ectopic care.

Auditable standards for this Guideline include:

1. Proportion of women provided with written information and emergency contact information when diagnosed with an ectopic pregnancy.
2. Proportion of women diagnosed with an ectopic pregnancy on the initial ultrasound scan.
3. Proportion of women offered all available management options for ectopic pregnancy.
4. Proportion of PULs subsequently diagnosed as ectopic pregnancies.
5. Proportion of caesarean scar pregnancies who are discussed and managed within a multi-disciplinary team.
6. Success, repeat dosing and complications associated with the use of methotrexate in tubal ectopic pregnancy.
7. Number of women with an ectopic pregnancy who receive an incorrect diagnosis of intrauterine pregnancy or miscarriage.
8. Number of women with ectopic pregnancy undergoing investigation and treatment who subsequently present with a ruptured ectopic pregnancy.
9. Complications of surgery for ectopic pregnancy.

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.[20]

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.

20 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.[21]

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

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

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

8.2 Method for amending the Guideline

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

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

a) 3 years since the Guideline was published

b) 3 years since last review was conducted.

c) Update required as a result of new evidence.

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

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

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Supporting Evidence

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

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

HSE: https://www.hse.ie/eng/about/who/qid/use-of-improvement-methods/nationalframeworkdevelopingpolicies/

Glossary

AGREE Appraisal of Guidelines for Research and Evaluation

ACOG American College of Obstetricians and Gynaecologists

β-hCG Beta-Human Chorionic Gonadotrophin

BSH British Society for Haematology

CAG Clinical Advisory Group

EAG Expert Advisory Group

EP Ectopic Pregnancy

EPAU Early Pregnancy Assessment Unit

ESHRE The European Society of Human Reproduction and Embryology

FIGO International Federation of Gynaecology and Obstetrics

GI Gastrointestinal

GPT Guideline Programme Team

GRADE Grading of Recommendations, Assessments, Developments and Evaluations

HIQA Health Information and Quality Authority

HSE Health Service Executive

IOG Institute of Obstetricians and Gynaecologists

IUCD Intrauterine Contraceptive Device

IUP Intrauterine pregnancy

IVF Invitro fertilisation

LMP Last Menstrual Period

MTX Methotrexate

NICE The National Institute for Health and Care Excellence

NCEC National Clinical Effectiveness Committee

NWIHP National Women and Infants Health Programme

PAS Placenta Accreta Spectrum

PID Pelvic Inflammatory Disease

PPPG Policy, Procedures, Protocols and Guidelines

PUL Pregnancy of Unknown Location

RCOG Royal College of Obstetricians and Gynaecologists

RCPI Royal College of Physicians of Ireland

RCT Randomised Controlled Trial

TA Transabdominal

TV Transvaginal

TVUS Transvaginal Ultrasound

UAE Uterine Artery Embolisation

UFE Uterine Fibroid Embolisation

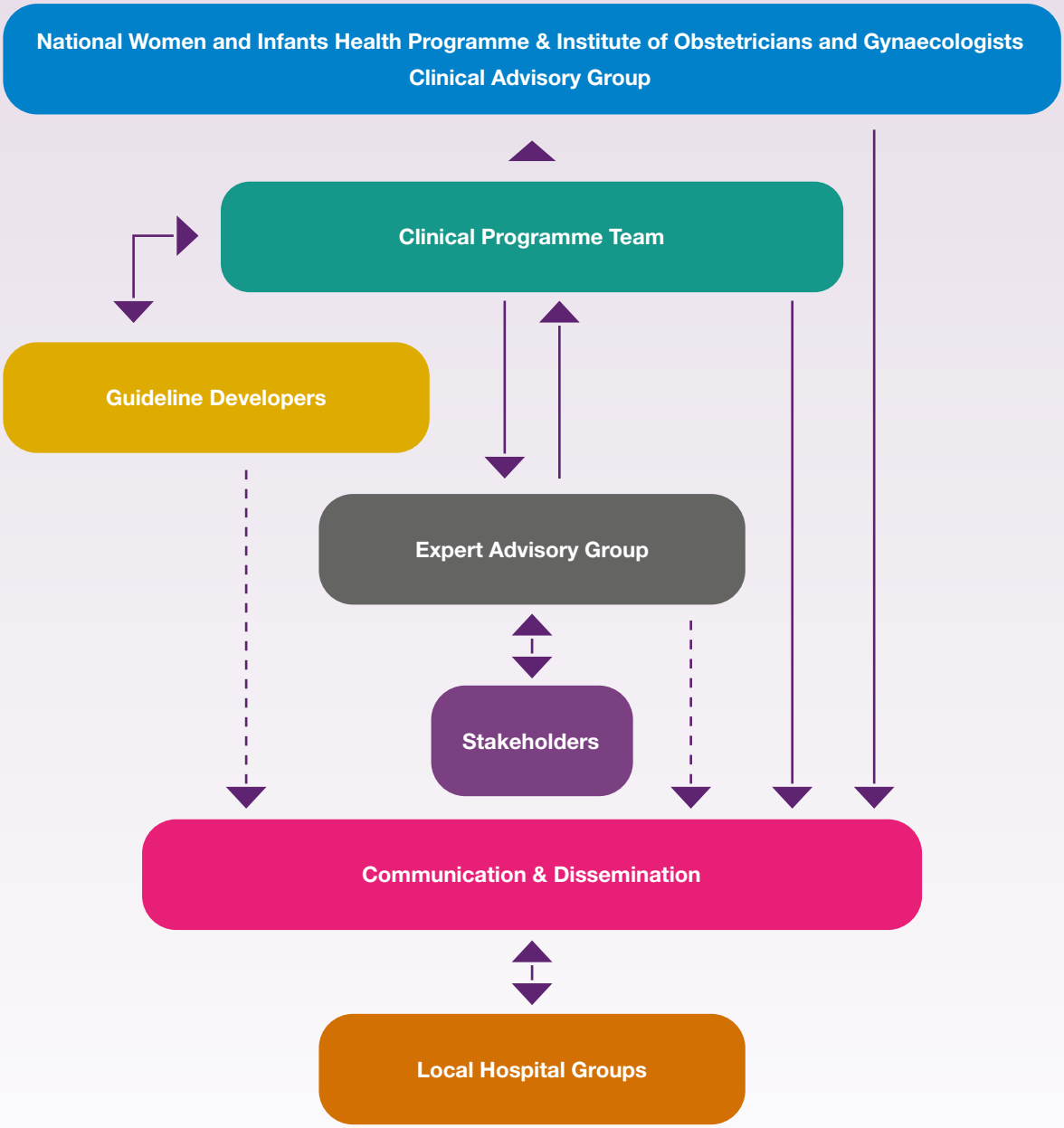
Appendix 1:
Expert Advisory Group Members 2021-

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

Attendee	Profession	Location (2021)
Dr Ciara McCarthy	General Practitioner and ICGP Women's Health Lead	Irish College of General Practitioners
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 & Newborn Clinical Management System	Rotunda Maternity unit Dublin Royal College of Surgeons in Ireland
Ms Marie Finn	Medical Social Work Counsellor	Saolta University Health Care Group
Ms Marie Culliton	Scientific Lead	National Clinical Programme for Pathology
Ms Marita Hennessy	Post-Doctoral Researcher	Pregnancy Loss Research Group, INFANT Centre, University College Cork
Ms Niamh Connolly-Coyne *And* Ms Mandy Daly *(Shared nomination)*	Board of Directors	Irish Neonatal Health Alliance
Ms Caroline Joyce	Principal Clinical Biochemist PhD Candidate	Cork University Maternity unit University College Cork
Dr Richard Duffy	Consultant Perinatal Psychiatrist	Rotunda Maternity unit Dublin
Ms Áine Kelly	Physiotherapy Manager	Coombe Women & Infants University Hospital, Dublin
Ms Sinéad Curran	Dietician Manager	National Maternity Maternity unit
Dr Nicholas Barrett	Lead for Obstetric Anaesthesiology services	Limerick University Maternity unit
Dr Brendan Fitzgerald	Consultant Perinatal Pathologist	Cork University Maternity unit
Dr Niamh Conlon	Consultant Histopathologist	Cork University Maternity unit
Ms Georgina Cruise	National Manager	Patient Advocacy Service

Appendix 2:
Guideline Programme Process

Guideline Programme Process



Appendix 3: **Methotrexate Prescribing**

Contraindications to methotrexate

- Intrauterine pregnancy
- Breastfeeding
- Sensitivity to methotrexate
- Immunodeficiency
- Active pulmonary disease
- Active peptic ulcer disease
- Active liver disease
- Aplastic anaemia
- Thrombocytopenia
- Relative C/I: renal or liver impairment
- Pre-treatment checks:
- Renal and Liver Function tests
- Full blood count
- Height and Weight

Side effects

Common:

- Cramping abdominal pain usually occurs during the first 2 to 3 days of treatment.
- Fatigue
- Vaginal bleeding or spotting
- Nausea, vomiting, and indigestion
- Numbness or pain at the injection site

Less common:

- Skin sensitivity to sunlight, sore mouth and throat, temporary hair loss, bone marrow suppression, pneumonitis

Dosing

Dose of methotrexate = 50mg/m^2

$$\sqrt{\frac{\text{height (cm) x weight (kg}}{3600}}$$

Appendix 4: **AGREE II Checklist**[22]

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	

22 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 & 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 5: **Grades of Recommendation**[23]

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
1 A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from well-performed randomised, 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….
1 B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomised, 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…

23 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

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
1 C. Strong recommendation, low-quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or from randomised, 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 randomised, 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 randomised, 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 randomised, 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 6: **Policies Procedures Protocols and Guidelines Checklist**

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

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

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

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

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

Appendix 7:
NWIHP/IOG CAG membership (2023-)

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.

Dr Peter McKenna (2023-). Clinical Lead, Obstetric Event Support Team, 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.

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

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

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

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

Prof. Mary Wingfield (2024-). Clinical Lead Fertility, National Women and Infants Health Programme.