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Miscarriage, Recurrent Miscarriage and Ectopic Pregnancy (C-Gyn 38)

Clinical Guideline

Version 1 • March 2025

This guideline has been developed by the Miscarriage, Recurrent Miscarriage and Ectopic Pregnancy Guideline Development Group (GDG) and approved by the Women's Health Committee and Council in March 2025.

A list of the Guideline Development Group members can be found in Appendix A: Guideline Development Group membership. A list of the Women's Health Committee, who provide oversight and approval of this document, can be found in Appendix B: Women's Health Committee Membership.

Conflict of Interest disclosures have been received from all members of this Guideline Development Group (Appendix C).

Disclaimer: this information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the circumstances of each case and the needs of any woman. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances (Appendix D)

Objectives:	To provide clinical guidance and advice to registered health professionals providing care to women with suspected or confirmed early pregnancy loss, including miscarriage, recurrent miscarriage and tubal or non-tubal ectopic pregnancy.
Target audience:	This guideline was developed primarily for use by RANZCOG members. Other registered health professionals providing maternity care are acknowledged as additional audiences. [i]See: RANZCOG's Interim statement on gendered language (below).
Background:	This is the first RANZCOG Guideline on miscarriage, recurrent miscarriage and ectopic pregnancy.
Patient information:	RANZCOG patient resources *Asherman Syndrome*, *Ectopic Pregnancy*, and *Miscarriage* have been updated in line with C-Gyn 38.
Funding:	The development and review of this guideline was funded by RANZCOG.

[i]*RANZCOG currently uses the term 'woman' in its documents to include all individuals needing obstetric and gynaecological healthcare, regardless of their gender identity. The College is firmly committed to inclusion of all individuals needing O&G care, as well as all its members providing care, regardless of their gender identity.*

Contents

1 Purpose and Scope

In 2024, under the auspices of the RANZCOG Women's Health Committee, a Guideline Development Group (GDG) was formed to develop a new RANZCOG Clinical Guideline on early pregnancy loss. The GDG, consisting of members in both Australia and Aotearoa New Zealand, determined the scope of the guideline would be as follows:

The purpose of this guideline is to provide clinical guidance and advice to registered health professionals providing care to women with suspected or confirmed early pregnancy loss, including miscarriage, recurrent miscarriage and tubal or non-tubal ectopic pregnancy.

Information relevant to and written for a consumer/community member audience is not covered in this guideline. A patient information resource will be developed as part of broader implementation of this guideline.

This guideline does not provide any specific early pregnancy loss advice for transgender and gender diverse people. Further resources are available at WPATH Standards of Care for the Health of Transgender and Gender Diverse People, Version 8.

Scope: Early pregnancy losses including miscarriage (and threatened miscarriage[ii]), recurrent miscarriage and all ectopic pregnancies both tubal and non-tubal. The gestational age limit for this guideline is up to 14 weeks, except for investigation of recurrent miscarriage where the gestational age limit is up to 20 weeks.

Out of scope: Abdominal pregnancies, molar pregnancies, detailed medication protocols for methotrexate, detailed guidance about radiological and surgical management of non-tubal ectopic pregnancies, such as caesarean scar ectopic pregnancies and heterotopic pregnancies, and comprehensive mental health management (acute and long term).

2 List of Recommendations and Good Practice Statements

Part 1: Miscarriage (up to 14 weeks)

Management of incomplete miscarriage and missed miscarriage

Recommendation 1	Evidence-based recommendation
Strong: Women with an incomplete miscarriage, who are clinically stable and with no complications, should be offered a choice of medical or surgical or expectant management, after a discussion of benefits and harms. Patient preferences and availability of relevant options should be considered. **GRADE of evidence:** Moderate.	

Recommendation 2	Evidence-based recommendation
Strong: Women with a missed miscarriage, who are clinically stable and with no complications, should be offered a choice of medical or surgical or expectant management, after a discussion of benefits and harms. Patient preferences and availability of relevant options should be considered. **GRADE of evidence:** Moderate.	

[ii] Threatened miscarriage is included in this guideline although, strictly speaking, it is not an early pregnancy loss.

Recommendation 3	Evidence-based recommendation

Conditional: For women choosing a surgical option, it is suggested that suction aspiration (including manual aspiration) is the preferred procedure, and dilatation and sharp curettage is avoided as it is associated with an increased risk of intrauterine adhesions. This risk is further increased for any subsequent miscarriage or uterine evacuation procedure.

GRADE of evidence: Low

Recommendation 4	Evidence-based recommendation

Strong: Antibiotic prophylaxis at the time of surgical management of a miscarriage is recommended.

GRADE of evidence: Moderate.

Good Practice Statement 1

The GDG recognises that there is no clear evidence for a specific antibiotic, although most trials used single dose of doxycycline with or without metronidazole. Ideally, antibiotics should be given two hours pre-procedure. Refer to local protocols (including resistance patterns).

Recommendation 5	Evidence-based recommendation

Conditional: For those women choosing medical management of a missed miscarriage, the recommended regimen is:

- Mifepristone 200 mg oral[iii]
- followed by misoprostol 600 mcg (sublingual or buccal) or 800 mcg (vaginal, buccal or sublingual) 24 to 48 hours later
- If bleeding has not commenced 24 – 48 hours after first dose of misoprostol, then repeat doses of misoprostol 400 mcg may be administered

GRADE of evidence: Low

Recommendation 6	Evidence-based recommendation

Conditional: For those women choosing medical management of an incomplete miscarriage, the recommended regimen is:

- Misoprostol 600 mcg (sublingual or buccal) or 800 mcg (vaginal, buccal or sublingual)
- If bleeding has not commenced 24 – 48 hours after first dose of misoprostol, then repeat doses of misoprostol 400 mcg may be administered

GRADE of evidence: Low

[iii] The use of mifepristone and misoprostol for the treatment of missed miscarriage is subject to regulation by the Australian Register of Therapeutic Goods, and its use for this specific indication may require off-label prescription.

Progesterone treatment for threatened miscarriage

Recommendation 7	Evidence-based recommendation

Strong: For women with threatened miscarriage (having had no more than one miscarriage), progesterone supplementation is not recommended, as there is little to no difference in the rates of live birth, stillbirth or preterm birth.

GRADE of evidence: Moderate.

Part 2 – Recurrent miscarriage

Screening tests

Recommendation 8	Evidence-based recommendation

Strong: Screening tests for recurrent miscarriage as listed in Table 1: Screening Tests, including an explanation of their limitations, should be recommended where supported by the evidence.

GRADE of evidence: Moderate (for tests recommended)

Good Practice Statement 2

The GDG suggests that when discussing whether or not to pursue investigations for recurrent miscarriage, practitioners counsel patients about the benefits and harms of knowing the outcome of testing.

Cytogenetic analysis of pregnancy tissue

Recommendation 9	Evidence-based recommendation

Conditional: Cytogenetic analysis of pregnancy tissue following miscarriage is not routinely recommended as there is no increase in genetic abnormalities in those with recurrent miscarriage. Genetic abnormalities may occur relatively more often in sporadic miscarriage but are unlikely to change clinical management in subsequent pregnancies.

GRADE of evidence: Low.

Good Practice Statement 3

The GDG suggests that when discussing whether or not to pursue cytogenetic analysis of pregnancy tissue, practitioners counsel patients about the benefits and harms of knowing the outcome of testing.

Antiphospholipid syndrome

Recommendation 10	Evidence-based recommendation

Strong: After a discussion of the associated improvement in live birth rate (and possible harms), women with antiphospholipid syndrome and a history of recurrent miscarriage should be offered:

- low-dose aspirin, 75 to 150 mg per day, either starting prior to pregnancy or starting from a positive pregnancy test, in combination with
- low-molecular weight heparin (dose as per local protocols), starting from a positive pregnancy test until at least 34 weeks

Treatment should be stopped before birth.

GRADE of evidence: Moderate.

Genetic/chromosome factors

Recommendation 11	Evidence-based recommendation

Conditional: For people with recurrent miscarriage with balanced translocations, options include natural conception or undertaking IVF with preimplantation genetic testing for structural rearrangements (PGT-SR), taking into consideration the specific translocation and its potential significance.

GRADE of evidence: Very Low.

Recommendation 12	Evidence-based recommendation

Conditional: For people with recurrent miscarriage with no known genetic conditions, evidence suggests there is no improvement with IVF. However, if IVF is being considered for other factors, then preimplantation genetic testing for aneuploidy (PGT-A) is an option after consideration of the risks and benefits of IVF and embryo testing, the conflicting evidence for PGT-A on the outcome of live birth, and the personal preference of the woman/couple.

GRADE of evidence: Very Low.

Good Practice Statement 4

The GDG suggests that people who have an abnormal parental karyotype should be offered genetic counselling. Consider offering genetic counselling to people who have a fetal or pregnancy tissue chromosome anomaly.

Uterine anatomical factors

Recommendation 13	Evidence-based recommendation

Conditional: Septum resection is not recommended in women with or without a history of recurrent pregnancy loss who have a uterine septum.

GRADE of evidence: Very Low

Good Practice Statement 5
The GDG suggests that if septum resection is being considered then it should be on a case-by-case basis taking into account the benefits and harms of the procedure.

Good Practice Statement 6
The GDG suggests that if surgical management of other congenital uterine malformations (arcuate, unicornuate, bicornuate and didelphys uterus) is being considered then it should be on a case-by-case basis, taking into account the benefits and harms of surgery, as there is no evidence to recommend surgical management over expectant management.

Good Practice Statement 7
The GDG suggests that resection of caesarean section niche in women with or without recurrent miscarriage is not offered due to a lack of evidence in this population for improving live birth rates. If being considered then it should be on a case-by-case basis taking into account symptoms, patient preferences, and benefits and harms of the procedure.

Good Practice Statement 8
The GDG suggests that hysteroscopic adhesiolysis in women with or without recurrent miscarriage is considered on a case-by-case basis taking into account symptoms, patient preferences, and the benefits and harms of the procedure, including discussion about recurrence rates.

Good Practice Statement 9
The GDG suggests that polypectomy and/or myomectomy/resection of submucosal fibroids in women with or without recurrent miscarriage is not recommended due to a lack of evidence in this population for improving birth rates. If being considered then it should be on a case-by-case basis taking into account symptoms, patient preferences, and benefits and harms of the procedure.

Hypothyroidism

Recommendation 14	Evidence-based recommendation
Strong: For women with recurrent miscarriage, levothyroxine should be offered to women with overt hypothyroidism. **GRADE of evidence:** Moderate	

Recommendation 15	Evidence-based recommendation
Conditional: For women with recurrent miscarriage and subclinical hypothyroidism, including mild subclinical hypothyroidism (TSH > 2.5 mIU/L), there is insufficient evidence to support offering levothyroxine. **GRADE of evidence:** Very Low	

Recommendation 16	Evidence-based recommendation

Strong: Women with recurrent miscarriage who have a TSH ≤ 2.5 mIU/L and who test positive for thyroid auto-antibodies (TPOAb+) should not be offered levothyroxine.

GRADE of evidence: Moderate

Good Practice Statement 10

The GDG suggests for women with recurrent miscarriage planning a pregnancy and taking levothyroxine, a reasonable target should be based on local pregnancy specific reference intervals.[iv]

Good Practice Statement 11

The GDG suggests that for women with subclinical hypothyroidism and/or thyroid autoantibodies not treated with levothyroxine, TSH be checked in early pregnancy (7-9 weeks) with further monitoring as indicated based on individual circumstances.

Progesterone treatment for recurrent miscarriage

Recommendation 17	Evidence-based recommendation

Strong: First trimester progestogens should not be recommended for pregnant women with two or more previous miscarriages without early pregnancy bleeding as there is no evidence it increases live birth rates.

GRADE of evidence: Moderate

Recommendation 18	Evidence-based recommendation

Strong: Progesterone should be recommended for pregnant women with two or more previous miscarriages and with early pregnancy bleeding as it probably increases the live birth rate and has little to no association with congenital abnormalities or severe adverse events. The duration of treatment should be to 16 weeks' gestation at a dose of 400 mg twice daily of micronised progesterone vaginally.

GRADE of evidence: Moderate

Part 3 – Tubal ectopic pregnancy

Ultrasound features of tubal ectopic pregnancy

Recommendation 19	Evidence-based recommendation

Conditional: In women with the signs and symptoms of ectopic pregnancy, an ectopic pregnancy can be reliably diagnosed if the ultrasound demonstrates an adnexal mass that includes a gestational sac (with or without yolk sac, fetal pole, or fetal heart) or an empty gestational sac ('bagel sign'), or an adnexal mass with sliding sign with an inhomogeneous mass ('blob sign').

GRADE of evidence: Low

[iv] See the RANZCOG Subclinical hypothyroidism and hypothyroidism in pregnancy Statement (C-Obs 46) for further information on pregnancy specific ranges for thyroid function.

Good Practice Statement 12
An empty uterus or fluid in the uterine cavity could indicate an ectopic pregnancy or a persistent pregnancy of unknown location. Consider other ultrasound features, signs and symptoms as well as hCG levels to reach a diagnosis. In situations where the ultrasound features are not diagnostic, consider repeat ultrasound, if the woman is stable. The timing of the repeat ultrasound will depend on the symptoms, hCG level, and availability of local resources.

Management of tubal ectopic pregnancy

Good Practice Statement 13
Women with ectopic pregnancy who are haemodynamically unstable, or with signs of rupture, or a hCG level > 5000 IU/L, or an adnexal mass > 35 mm, or have contraindications to medical or expectant management, should be managed surgically.

Recommendation 20	Evidence-based recommendation

Conditional: Women with an ectopic pregnancy with an adnexal mass of < 35 mm (no fetal heart activity), who are clinically stable, are willing and able to return for follow up and who have:

- hCG < 1500 IU/L, may be offered a choice of expectant management OR medical management with methotrexate OR surgical management
- hCG level of ≥ 1,500 IU/L and < 5,000 IU/L, and have no significant pain or signs of rupture, may be offered a choice of medical management with methotrexate OR surgical management

GRADE of evidence: Low

Good Practice Statement 14
The GDG suggests that treatment options for ectopic pregnancy, including associated benefits and risks, are discussed to reach an informed decision.

Good Practice Statement 15
Women should be informed that emergency treatment for ectopic pregnancy may be required if expectant or medical management is unsuccessful.

Recommendation 21	Evidence-based recommendation

Strong: Women who choose to have medical management of an ectopic pregnancy and have a hCG < 3000 IU/L or adnexal mass < 20 mm should be offered one dose of systemic methotrexate. For women who choose to have medical management of an ectopic pregnancy and have a hCG 3000 to 5000 IU/L or adnexal mass 20 to 35 mm two doses of systemic methotrexate, given 4-7 days apart, should be offered.

GRADE of evidence: Moderate

Good Practice Statement 16
If choosing medical management of an ectopic pregnancy, follow up of levels of hCG is required and further doses of MTX may be necessary.

Recommendation 22	Evidence-based recommendation
Strong: Women should be advised of the increased risk of transient side effects (e.g., nausea, diarrhoea, mucositis, abdominal pain, mildly abnormal laboratory results) associated with two doses of methotrexate. **GRADE of evidence:** Moderate	

Good Practice Statement 17
Women who receive methotrexate treatment should be advised to wait three months before conceiving again and contraception should be discussed.

Recommendation 23	Evidence-based recommendation
Conditional: For women with tubal ectopic pregnancy, medical management may favour subsequent intrauterine pregnancy. However women should be advised that salpingectomy is associated with higher likelihood of resolution of the ectopic pregnancy compared to medical management. **GRADE of evidence:** Low.	

Salpingectomy vs. salpingostomy/salpingotomy in stable ectopic pregnancy

Recommendation 24	Evidence-based recommendation
Strong: For women with tubal ectopic pregnancy salpingectomy should be recommended instead of salpingotomy, as there is a higher likelihood of resolution of tubal ectopic pregnancy, and with a single procedure. **GRADE of evidence:** Moderate	

Good Practice Statement 18
Salpingotomy may be considered depending on the woman's preferences, desire to avoid or lack of access to IVF, and medical history. Women should be advised of the higher risk of treatment failure and need for further treatment, including with methotrexate or salpingectomy.

Part 4 – Non-tubal ectopic pregnancy

Management of interstitial ectopic pregnancy

Recommendation 25	Evidence-based recommendation

Conditional: For interstitial ectopic pregnancy:

Medical management: For women who are clinically stable, medical management with systemic, as outlined in Recommendation 21, or intra-sac methotrexate (under ultrasound guidance) could be offered.

Surgical management: If a woman is at high risk of haemorrhage, does not wish to take methotrexate, or there has been a failure of medical or expectant management, then surgical treatment should be offered as follows:

1. Laparoscopic cornuostomy
2. Laparoscopic wedge/cornual resection with ipsilateral salpingectomy

GRADE of evidence: Low

Good Practice Statement 19

Expectant management for interstitial ectopic pregnancy should only be offered to women who are clinically stable with low initial hCG (< 1500 IU/L) and who agree to be monitored until the hCG is < 20 IU/L.

Good Practice Statement 20

Cornuostomy may be preferable to cornual resection as it may be less likely to damage the uterus and fallopian tube and may be more likely to preserve fertility.

Management of cervical ectopic pregnancy

Recommendation 26	Evidence-based recommendation

Conditional: For cervical ectopic pregnancy:

Women who are clinically stable should be offered medical management with methotrexate either systemically, as outlined in Recommendation 21, or via ultrasound-guided intra-sac injection (depending on local availability).

GRADE of evidence: Low

Good Practice Statement 21

Expectant management of cervical ectopic pregnancy should be avoided due to the risk of severe haemorrhage.

Recommendation 27	Evidence-based recommendation

Conditional: If a woman with cervical ectopic pregnancy is clinically unstable, does not wish to take methotrexate, or there has been a failure of methotrexate treatment, then a dilatation and curettage (D&C) may be recommended.

GRADE of evidence: Low

Good Practice Statement 22

The GDG suggests ultrasound guidance if doing a dilatation and curettage (D&C) for a cervical ectopic pregnancy.

Good Practice Statement 23

The GDG suggests for women with cervical ectopic pregnancy, operative hysteroscopy be considered instead of dilatation and curettage (D&C) where facilities and circumstances permit.

Good Practice Statement 24

The GDG suggests to control bleeding in cervical ectopic pregnancy, the following additional procedures to dilatation and curettage (D&C) or operative hysteroscopy may be offered, where facilities and circumstances permit:

1. tamponade with Foley catheter
2. uterine artery embolisation
3. uterine artery ligation

Management of caesarean scar pregnancy

Recommendation 28	Evidence-based recommendation

Conditional: Women presenting with caesarean scar pregnancies (CSP) are recommended to have counselling that these pregnancies are high risk, associated with a high likelihood of miscarriage, placenta accreta spectrum, preterm birth, haemorrhage, uterine rupture, hysterectomy, perinatal death and maternal death. There may be differences in pregnancy outcomes with Type I and Type II caesarean scar pregnancies, which need to be discussed.

GRADE of evidence: Low

Good Practice Statement 25

The GDG suggests that women with Type I caesarean scar pregnancy who choose to continue the pregnancy should be advised that they will require multidisciplinary care with access to a tertiary hospital. [v]

[v] See Good Practice Point (GPP) 2 in the RANZCOG Placenta Accreta Spectrum (PAS) Clinical Guideline (C-Obs 20) for multidisciplinary team (MDT) details.

Recommendation 29	Evidence-based recommendation

Conditional: In the absence of embryonic activity and if the woman meets the criteria for expectant management of caesarean scar pregnancy (see Recommendation 20), expectant management may be an option, provided the woman is aware of the associated risks.

GRADE of evidence: Low

Recommendation 30	Evidence-based recommendation

Conditional: Women who are clinically stable may be offered medical management of caesarean scar pregnancy with methotrexate, either systemically (intramuscular injection) or via intra-sac injection (with or without potassium). If choosing systemic methotrexate, two doses (4 to 7 days apart) should be given. Decisions about further doses should be made in line with local protocols or as clinically indicated.

GRADE of evidence: Low

Recommendation 31	Evidence-based recommendation

Conditional: When surgical management is required (see Good Practice Statement 13), treatment options should be guided by the type of caesarean scar pregnancy (CSP).

- Type I CSP surgical options include dilatation and curettage (D&C) (with or without balloon tamponade) and uterine artery embolisation
- Type II CSP may be better treated via hysteroscopic and laparoscopic resection, or methotrexate followed by hysteroscopic resection

GRADE of evidence: Low

Part 5 – Rh D immunoglobulin (anti-D)

Good Practice Statement 26

For non-sensitised women with Rh D negative blood group who have experienced threatened miscarriage or miscarriage before 10 weeks' gestation, there is insufficient evidence to determine if routine Rh D testing followed by anti-D immunoglobulin (if indicated) reduces the risk of sensitisation and is no longer recommended.

Good Practice Statement 27

For ectopic pregnancy that is surgically managed the GDG recommends anti-D immunoglobulin be offered to women with Rh D negative blood group.

Good Practice Statement 28

For ectopic pregnancy that is medically or expectantly managed, there is insufficient evidence to determine if anti-D immunoglobulin reduces the risk of sensitisation, therefore anti-D could be considered after informed discussion with women with Rh D negative blood group.

Good Practice Statement 29

A dose of 250 IU of anti-D immunoglobulin is sufficient for a singleton pregnancy up to 12 weeks, beyond 12 weeks' gestation 625 IU should be used.

Pregnancy tissue management

Good Practice Statement 30

The GDG suggests that women with early pregnancy loss are provided with information on the options for pregnancy tissue management, acknowledging the significance of this for many people/groups, including the option to return the pregnancy tissue to the woman and her family.

3 Introduction

Rationale

Early pregnancy loss is an umbrella term and includes losses from miscarriage and from extra-uterine pregnancies such as tubal pregnancies, and non-tubal pregnancies such as interstitial pregnancies. Women with early pregnancy loss need holistic care, of which evidence-based advice and counselling care are an important part. This guideline aims to provide recommendations for early pregnancy losses including miscarriage, recurrent miscarriage and all ectopic pregnancies both tubal and non-tubal, and includes guidance for expectant, medical and surgical management before 14 weeks. The term 'recurrent pregnancy loss' is used to describe two or more pregnancy losses. Threatened miscarriage is included in this guideline although, strictly speaking, it is not an early pregnancy loss.

Epidemiology

Miscarriage is common. Early miscarriage (< 14 weeks of pregnancy) affects between 10 and 25% of known pregnancies depending on the gestation. From a population-based register, nearly 14% of pregnancies that were intended to be carried to term ended with fetal loss.[1] Most miscarriages happen in the first 14 weeks of pregnancy. Miscarriage after 14 weeks occurs in 1-2% of pregnancies. The lifetime risk of a miscarriage is nearly 25%.[2] The risk of miscarriage increases with maternal age. By 40 years of age, 50% of pregnancies may end in a miscarriage.[3] Ectopic pregnancies occur in 1 in 80 (1.25% of pregnancies).
There is no specific data about miscarriages for Australia or Aotearoa New Zealand, as no national register currently exists in either country.

Equity

There were no data identified specific to First Nations Australians or Māori populations. There were limited data identified for rural and remote populations.

As the causes of miscarriage for an individual are usually unknown (especially in first miscarriages), no associations have been made regarding the social determinants of health, with the possible exception of increased body mass index (BMI). (See RANZCOG's Pre-pregnancy counselling (C-Obs 3a) Clinical Guideline for recommendations on pre-pregnancy counselling, including BMI).

Psychological wellbeing following early pregnancy loss

Early pregnancy loss may be a difficult time for a woman and her partner/family. RANZCOG acknowledges the significant impact that appropriate support, or lack thereof, can have on a woman and her partner or social/support network following miscarriage or ectopic pregnancy.[4] While this guideline provides some reference to psychological wellbeing following early pregnancy loss, consideration of this topic in any depth was out of scope.

While some women may have access to a dedicated early pregnancy assessment service, others are likely to receive initial care and information in an emergency department, primary care, or community setting. Regardless of location, it is important that acknowledgement of grief and distress, as well as the offer of counselling, is a routine part of care. While all health professionals have training in recognition and immediate management of mental health issues, it is important to recognise that comprehensive management of psychological wellbeing, including mental illness, is outside the scope of generalist obstetric and gynaecology practice. As such, appropriate referral may be most beneficial for women following early pregnancy loss who need additional review and care.

Communication and terminology

Communication should be clear, empathetic and respectful, using language preferred by the patient and their family. Care should be taken with the terminology and use of certain phrases when discussing pregnancy loss with patients and their support people (e.g., the term spontaneous abortion should not be used). Information provided should include what to expect, helpful contacts (i.e., support services), follow up care and referral to bereavement counselling or mental health support as required.[4, 5] Information may also include the options for pregnancy tissue management, acknowledging the significance of this for many people/groups, including the option to return the pregnancy tissue to the woman and her family. Discussion about available treatment options, including explanation of benefits and harms, should consider a woman's relevant history, including previous early pregnancy losses and treatment experiences. Not everyone will experience grief in the same way so communication should also be sensitive and responsive to individual needs and circumstances.

Miscarriage Australia's tailored resources for healthcare providers available here: For Healthcare Providers - Miscarriage Australia. Resources and useful links for women and families in Australia and Aotearoa New Zealand are available in Links to relevant resources.

4 Methods

The guideline was developed according to approved RANZCOG processes, as set out in the Handbook for the development of evidence-based guidelines and statements. Following these processes, including the development of clinical questions, the Research and Policy Team identified several local and international guidelines published within the past five years. These included: National Institute for Health and Care Excellence (NICE) Ectopic pregnancy and miscarriage: diagnosis and initial management Guideline; Royal College of Obstetricians and Gynaecologists (RCOG) Recurrent Miscarriage (Green-top Guideline No. 17); European Society of Human Reproduction and Embryology (ESHRE) Recurrent Pregnancy Loss Guideline

For each clinical question, literature searches were performed to identify additional peer-reviewed studies where relevant and in accordance with RANZCOG evidence processes. For the complete search strategies and results, see search strategies.

The rigour and certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. For each clinical question 3-5 critical outcomes were agreed by

the GDG and the certainty of the evidence for these outcomes are used to grade the recommendation. These critical outcomes are identified in this guideline in **BOLD**.

The terms and phrases used in recommendations depend on the strength and certainty of the body of evidence - further explanation of recommendation types and classifications can be found in the Handbook. Good practice statements are used if there is insufficient evidence for a recommendation but are agreed by the GDG based on their experience and expertise. Good practice statements are not graded.

For Clinical Question 4 on which investigation should be used for couples with recurrent miscarriage, the RANZCOG Research and Policy Team (RAPT) used evidence from the ESHRE RPL Guideline and the RCOG Green Top Guideline for 18 tests. There was discordance between ESHRE and RCOG Guidelines in 4 of the tests and RANZCOG RAPT decided to do new searches for these four tests only (from the date of the searches in ESHRE and RCOG only).

5 Clinical Questions, Evidence Summaries and Recommendations

This section, presented in five parts, outlines the available evidence for each clinical question including the certainty assessment, which underpins recommendations and good practice statements. See Appendix G for detailed reports of the evidence summary tables and the evidence to decision summaries (based on GRADE methodology).

Part 1: Miscarriage (up to 14 weeks)

Introduction

Miscarriage is the involuntary, spontaneous loss of a pregnancy before 20-24 completed weeks' gestation.[6] The gestational threshold for the definition varies between countries. Australia and New Zealand use 20 weeks, and after this the loss is classified as a stillbirth. Miscarriage may be associated with unprovoked vaginal bleeding, with or without pain.

Most miscarriages (approximately 80% of all cases of pregnancy loss) happen in the first 14 weeks and are known as early miscarriages.[7, 8] Part 1 of this guideline examines evidence related to management options for confirmed incomplete, missed or threatened early miscarriage (< 14 weeks' gestation). The recommendations are intended to guide clinicians in providing information and care to this cohort of women.

Terminology for this chapter

Incomplete miscarriage: the partial loss of pregnancy tissue within the first 20 weeks' gestation. Incomplete miscarriage presents with moderate to severe vaginal bleeding, sometimes with the noticeable passage of tissue, that is typically associated with lower abdominal and pelvic pain.[9]

Complete miscarriage: refers to a miscarriage in which all the pregnancy tissue is expelled from the uterus. A complete miscarriage is characterized by vaginal bleeding, pelvic pain, and passage of pregnancy tissue. With a complete miscarriage, the bleeding and pain should subside quickly.

Missed miscarriage: the embryo or fetus has died, but the pregnancy tissue has not passed and is still in the uterus. Women who have a missed miscarriage may be asymptomatic or have small amounts of vaginal bleeding or pain. Diagnosis may be made during a routine antenatal visit.[10]

Threatened miscarriage: typically refers to vaginal bleeding and uterine cramping in an otherwise viable pregnancy before 20 weeks' gestation, though more commonly occurring in the first trimester.[11]

Recurrent miscarriage: two or more miscarriages in pregnancies up to 20 weeks' gestation (whether or not a gestational sac is present and whether or not the miscarriages are consecutive). Recurrent miscarriage is discussed in Part 2 – Recurrent miscarriage.

The following terms are ambiguous and should be avoided: spontaneous abortion, biochemical pregnancy and blighted ovum.

Equity considerations for this chapter

Depending on the type of miscarriage, and the preferences of the woman, management may be expectant, medical or surgical. Medical management may be provided in person, or by telemedicine. However, surgical management requires access to appropriate surgical facilities and appropriately skilled practitioners. Inequitable access to such facilities and practitioners, and thus inequitable access to choice of treatment, may be experienced by those living in rural or remote locations.

Clinical Question 1 - Incomplete miscarriage

What are the benefits and harms of different treatment options (surgical/medical/expectant management) for incomplete miscarriage?

P: Pregnant women up to 14 weeks with an incomplete miscarriage

I: Expectant management, active management (surgical evacuation of the uterus, medical management with misoprostol [± mifepristone])

C: Any of the above listed interventions

O: **Complete miscarriage**, **need for repeated or alternative management**, time to resolve miscarriage, intrauterine adhesions (future fertility impact), **adverse events (including side effects)**, acceptability, satisfaction.

Clinical Question 2 – Missed miscarriage

What are the benefits and harms of different treatment options (surgical/medical/expectant management) for missed miscarriage?

P: Pregnant women up to 14 weeks with a missed miscarriage

I: Expectant management, active management (surgical evacuation of the uterus, medical management with misoprostol [± mifepristone])

C: Any of the above listed interventions

O: **Complete miscarriage**, **need for repeated or alternative management**, time to resolve miscarriage, intrauterine adhesions (future fertility impact), **adverse events (including side effects)**, acceptability, satisfaction.

Source of evidence

A Cochrane Review was the primary source of evidence for both clinical questions 1 and 2; the 2021 network meta-analysis was identified reporting the effectiveness or safety of methods for (early) miscarriage management, and included 78 randomised trials involving 17,795 women.[7] This was supported by a systematic review about intrauterine adhesions, and a systematic review about antibiotics for incomplete miscarriage.[12,13]

Certainty of evidence

Ranged from moderate GRADE for network meta-analysis, low GRADE for intrauterine adhesions to moderate GRADE for antibiotics.

Summary of evidence

Evidence for clinical questions 1 and 2 was obtained from a Cochrane network meta-analysis.[7] A network meta-analysis can assess multiple treatments at the same time and enable comparisons between treatments that have not been compared head-to-head. A network meta-analysis generates estimates of the relative effects between any pair of interventions in the network, as well as allowing for estimation of the ranking and hierarchy of interventions. The treatment hierarchy framework used for the evidence considered in clinical questions 1 and 2 was surface under the cumulative ranking curve (SUCRA).

SUCRA: *A numeric presentation of overall ranking of treatment options, represented by a single number associated with each treatment. SUCRA values range from 0 to 100%. The higher the SUCRA value, the greater likelihood that a treatment is in the top rank or one of the top ranks; the closer to 0 the SUCRA value, the greater likelihood that a treatment is in the bottom rank, or one of the bottom ranks. SUCRA should be considered alongside the structure*

of the network (for example, a treatment may have a high SUCRA, however fewer trials in the network may support this result).[14, 15]

Incomplete miscarriage

Treatment options for incomplete miscarriage:

- Management with either surgery or medical treatment using misoprostol is associated with an increase in the rate of achieving a complete miscarriage, compared to expectant management. Surgical approaches are probably better than medical and expectant management; suction aspiration (SUCRA 83.6%), dilatation and curettage (D&C) (SUCRA 79.4%), misoprostol (SUCRA 44%) and expectant management (SUCRA 6.7%). Certainty of evidence: Low to Moderate.
- It is uncertain whether active management with surgical or medical treatments increases or decreases days of bleeding in incomplete miscarriage, due to very low certainty evidence.

Missed miscarriage

Treatment options for missed miscarriage:

- Management with either surgical or medical treatment with misoprostol, with or without mifepristone, increases the rate of achieving complete miscarriage in missed miscarriage, compared to expectant management. Surgical approaches are more likely to be the best options for this outcome; suction aspiration (SUCRA 92.7%), D&C (SUCRA 70.8%), mifepristone + misoprostol (SUCRA 53%), misoprostol (SUCRA 33%) and expectant management (SUCRA 0.2%). Certainty of evidence: Moderate.
- It is unclear whether either surgical or medical treatment increases or decreases the days of bleeding in missed miscarriage, due to very low certainty evidence.

Incomplete or missed miscarriage

Management with surgical or medical treatment for incomplete or missed miscarriage, compared to expectant management:

- may decrease the rate of serious complications (including blood transfusion, uterine perforation, need for further life-saving procedures such as hysterectomy) and ICU admission; D&C (SUCRA 84%), misoprostol (SUCRA 70%), suction aspiration (SUCRA 52%), mifepristone + misoprostol (SUCRA 31%), and expectant management (SUCRA 10.9%).
- may have little or no difference on readmission to hospital.
- presents no clear difference in side effects such as nausea, vomiting and pyrexia; however, diarrhoea may be more common in the group using misoprostol (RR 1.61, 95% CI 1.11 to 2.32). Certainty evidence: Low.

Surgical management probably reduces the need for an unplanned, emergency surgical procedure. Medical management using misoprostol, with or without mifepristone, may have little to no difference on the need for an unplanned, emergency surgical procedure, compared to expectant management.

Medical management using misoprostol with or without mifepristone, may have little or no difference on pain scores compared to expectant management.

Other considerations

Psychological considerations

Overall, the Cochrane review reported that all methods of managing a miscarriage were acceptable to women, and trials comparing surgical, medical and expectant management that assessed the psychological impact

(anxiety, depression and fatigue) did not find clear evidence of difference between the groups.[7,16, 17] Women who experience an early miscarriage emphasise the importance of being offered different options for miscarriage management. Other considerations were the likelihood of pain, time to return to normal activities, number of days of bleeding after treatment, chance of complications requiring more time or readmission, and time spent at the hospital receiving treatment.[18]

Intrauterine adhesions (IUAs)

Intrauterine adhesions (IUAs) are a possible complication following miscarriage, intrauterine surgery or infection. IUAs may also be an indication of Asherman syndrome.

A systematic review and meta-analysis of IUAs after miscarriage reported that women who have:

- more than one miscarriage may be more likely to have IUAs.[12]
- more than one D&C may be more likely to have IUAs.[12]

The study reported no difference between incomplete and missed miscarriage in terms of developing IUAs.[12] Certainty of evidence: Low.

The prevalence of IUAs is difficult to assess, and the clinical relevance of this prevalence is uncertain; the focus therefore should be on symptoms and outcomes.

Treatment of IUAs is covered in Clinical Question 8 – Anatomical factors.

Antibiotic prophylaxis

A further question was added about the use of antibiotics at the time of surgical procedures for incomplete or missed miscarriage. A systematic review of 24 trials reported that for the subgroup of women having an incomplete miscarriage, antibiotic prophylaxis is beneficial in reducing post-procedure genital tract infection among women undergoing surgical procedures.[13] Most studies described antibiotic administration up to, or at 2 hours prior to surgery. Doxycycline, with or without metronidazole was the most common treatment.

Limitations in the evidence

The evidence for management of miscarriage may be limited due to a variety of dosages for misoprostol (200 to 800 mcg) and mifepristone (200 to 600 mg), and routes of administration for misoprostol.

Recommendations

Recommendation 1	Evidence-based recommendation
Strong: Women with an incomplete miscarriage, who are clinically stable and with no complications, should be offered a choice of medical or surgical or expectant management, after a discussion of benefits and harms. Patient preferences and availability of relevant options should be considered. **GRADE of evidence:** Moderate.	

Recommendation 2	Evidence-based recommendation
Strong: Women with a missed miscarriage, who are clinically stable and with no complications, should be offered a choice of medical or surgical or expectant management, after a discussion of benefits and harms. Patient preferences and proximity of relevant options should be considered. **GRADE of evidence:** Moderate.	

Recommendation 3	Evidence-based recommendation

Conditional: For women choosing a surgical option, it is suggested that suction aspiration (including manual aspiration) is the preferred procedure, and dilatation and sharp curettage is avoided as it is associated with an increased risk of intrauterine adhesions. This risk is further increased for any subsequent miscarriage or uterine evacuation procedure.

GRADE of evidence: Low

Recommendation 4	Evidence-based recommendation

Strong: Antibiotic prophylaxis at the time of surgical management of a miscarriage is recommended.

GRADE of evidence: Moderate.

Good Practice Statement 1

The GDG recognises that there is no clear evidence for a specific antibiotic, although most trials used a single dose of doxycycline with or without metronidazole. Ideally, antibiotics should be given two hours pre-procedure. Refer to local protocols (including resistance patterns).

Recommendation 5	Evidence-based recommendation

Conditional: For those women choosing medical management of a missed miscarriage, the recommended regimen is:

- Mifepristone 200 mg oral[vi]
- followed by misoprostol 600 mcg (sublingual or buccal) or 800 mcg (vaginal, buccal or sublingual) 24 to 48 hours later
- If bleeding has not commenced 24 – 48 hours after first dose of misoprostol, then repeat doses of misoprostol 400mcg may be administered

GRADE of evidence: Low

Recommendation 6	Evidence-based recommendation

Conditional: For those women choosing medical management of an incomplete miscarriage, the recommended regimen is:

- Misoprostol 600 mcg (sublingual or buccal) or 800 mcg (vaginal, buccal or sublingual)
- If bleeding has not commenced 24 – 48 hours after first dose of misoprostol, then repeat doses of misoprostol 400mcg may be administered

GRADE of evidence: Low

[vi] The use of Mifepristone and Misoprostol for the treatment of missed miscarriage is subject to regulation by the Australian Register of Therapeutic Goods, and it's use for this specific indication may require off-label prescription.

Clinical Question 3 – Progesterone treatment for bleeding in early pregnancy

What are the harms and benefits of treatment with progesterone in pregnant women with bleeding and no history of recurrent miscarriage?

P: Pregnant women up to 14 weeks with bleeding and no history of recurrent miscarriage

I: Progesterone (any route)

C: Placebo, no treatment

O: **Live birth rate**, pregnancy loss, ongoing pregnancy at 12 weeks' gestation (in the absence of live birth data), perinatal mortality, **fetal anomaly** or side effects, birth weight, **birth before 37 weeks**, NICU admission, acceptability, satisfaction

Source of evidence

Three systematic reviews provided most of the evidence for this clinical question, supported by three recently published randomised controlled trials (RCTs).[19-21]

Certainty of evidence

GRADE varied from Low to Moderate certainty.

Summary of evidence

Threatened miscarriage (bleeding) and no previous miscarriage

For women with threatened miscarriage (intrauterine pregnancy confirmed by a scan, and vaginal bleeding) and no previous miscarriage there was little or no difference with progesterone supplementation (regardless of route or progesterone used) compared to placebo in the rates of live birth, stillbirth and preterm birth, and major congenital anomalies. Certainty of evidence: Moderate. [22]

Threatened miscarriage (bleeding) and history of one previous miscarriage

Progesterone (by any route) may have little to no impact on live birth rates for women with early pregnancy bleeding and a history of one previous miscarriage (RR 1.06 [95% CI: 0.97–1.16]. Certainty of evidence: Low.[23]

Other considerations

Threatened miscarriage presents a unique set of challenges, as expecting parent(s) experience worry about the uncertain fate of the pregnancy while it continues. Two studies reported women with threatened miscarriage experience considerable psychological burden including worry, sadness, an inability to look forward, and self-blame.[24, 25] While it is important to avoid offering treatments without clear evidence of benefit, clinicians should acknowledge and empathise with the uncertainty and psychological burden experienced by women with threatened miscarriage.

Limitations in the evidence

For threatened miscarriage and progesterone, the evidence was limited due to the difference in the type, dosage, route of administration and treatment duration in the different studies.

Recommendations

Recommendation 7	Evidence-based recommendation
Strong: For women with threatened miscarriage (having had no more than one miscarriage), progesterone supplementation is not recommended, as there is little to no difference in the rates of live birth, stillbirth or preterm birth. **GRADE of evidence:** Moderate.	

Part 2 – Recurrent miscarriage

Introduction

It is estimated that between 1% and 4% of couples experience recurrent pregnancy losses.[26, 27] RANZCOG acknowledges the impact of each consecutive miscarriage on women and couples.

The GDG did not review the evidence for dedicated recurrent miscarriage clinics however agreed that, where practical and feasible, for women with unexplained recurrent miscarriage ideal care, including regular scans, may be offered in the setting of a dedicated recurrent miscarriage clinic. It is acknowledged that this may not be possible in all sites and settings, particularly for women in rural and remote areas.

Terminology for this chapter

For the purpose of this guideline, RANZCOG defines recurrent miscarriage as the loss of two or more intrauterine pregnancies of up to 20 weeks' gestation (whether or not a gestational sac is present and whether or not the miscarriages are consecutive). The term 'Recurrent miscarriage' should be limited to cases where all pregnancy losses have been confirmed as intrauterine miscarriages.

The variation in the definition of recurrent miscarriage between countries has been considered, including:

- European Society of Human Reproduction and Embryology (ESHRE), who define recurrent miscarriage as the loss of two or more pregnancies, and
- Royal College of Obstetricians and Gynaecologists (RCOG), who use the definition of three or more first trimester miscarriages in the Green-top Guideline No.17 Recurrent Miscarriage.[22, 23]

There is limited evidence that there is any difference in pregnancy outcomes for women who have two miscarriages versus three, with respect to:

- risk factors for pregnancy loss, including antiphospholipid syndrome (APS) and carrier status causing a structural chromosomal anomaly[26, 28]
- whether the losses were consecutive.[26, 29, 30]

Epidemiology

In a longitudinal study in the Danish population, the lifetime risk of specific numbers of losses were: 0: 76.9%, 1: 17.9%, 2: 3.9%, 3: 0.87%, and 4+: 0.35%.[2]

There is a range of modifiable and non-modifiable risk factors that may be associated with risk of recurrent miscarriage, which include maternal and paternal age, lifestyle factors such as excessive alcohol consumption and smoking, obstetric history and maternal medical conditions, such as thrombophilia, diabetes and hypothyroidism (particularly if either are uncontrolled) and uterine structural anomalies. The pre-conception period is the ideal opportunity to discuss potential risk factors that may be associated with recurrent miscarriage; clinicians should refer to RANZCOG's Pre-pregnancy counselling (C-Obs 3a) Clinical Guideline for further recommendations on pre-pregnancy counselling. However, it is important to recognise that for most recurrent miscarriages, no causative factor can be identified.[31]

No data were identified reporting the prevalence of recurrent miscarriage in First Nations women.

Equity considerations for this chapter

Screening tests

Some investigations for recurrent miscarriage, such as sperm DNA fragmentation, may not be publicly funded. Conversations regarding which tests to undertake should consider the associated costs and likelihood of improved outcomes for the couple.

Cytogenetic analysis of pregnancy tissue

Geographical distance may make cytogenetic evaluation by techniques that require tissue culture more challenging. Long transfer times to a laboratory may result in a higher chance of test failure for women in rural and remote areas. New testing techniques using chromosome microarray (CMA) may help to mitigate this as cells do not need to be cultured.

Antiphospholipid syndrome

Unfractionated heparin (UFH) will usually need to be administered in a hospital setting, meaning that women receiving this treatment may need to travel to access it, involving additional costs.

Genetic/chromosome factors

Cost of treatment may create inequity of access to pre-implantation genetic testing (PGT) and may be cost-prohibitive, particularly for pre-implantation genetic testing for aneuploidy (PGT-A) which is not publicly funded in either Australia or Aotearoa New Zealand. Access to public funding for the IVF cycle may remove some of the cost burden but genetic testing of embryos is required to be paid for privately which is a significant barrier for many. Access to public funding in Aotearoa New Zealand, for couples with no identified genetic issue, is dependent on having been trying for a baby for 5 years, and waitlists are often more than 12 months once a patient is accepted for public funding.

The geographic distribution of fertility clinics offering IVF services also presents an access barrier. Clinics are generally located in major cities, which adds further logistical and financial barriers for those who live in rural and remote locations.

Workforce and training implications also need to be considered. The implementation of PGT techniques for women and couples with recurrent miscarriage would require sufficient training of embryologists to undertake biopsy of embryos and ongoing quality auditing. Additionally, access to public funding for pre-implantation genetic testing for monogenic conditions (PGT-M)/pre-implantation genetic testing for structural rearrangements (PGT-SR) in Australia and Aotearoa New Zealand often requires genetic counselling. The feasibility of implementing a recommendation for PGT-M/PGT-SR would be dependent on a sufficient genetic counsellor workforce, which is currently under pressure.

Anatomical factors

Inequity may exist between remote and non-remote areas in accessing expert counselling and surgery. Septum or niche resection and treatment of uterine adhesions may not be available in smaller, remote locations or outside of specialised clinics, necessitating travel for some women.

First Nations women in Australia have a higher rate of caesarean section than non-Indigenous women.[32] This may put First Nations women at an increased risk of developing a caesarean section niche (also known as caesarean scar defect or isthmocele). Conversely, in Aotearoa New Zealand, Māori women have a lower rate of caesarean section compared to women from European/other ethnic backgrounds. This may be associated with a decreased risk of developing a caesarean section niche. However, actual rates of caesarean section niche in these groups have not been reported.

Hypothyroidism

No equity issues have been identified in addition to those common across all healthcare sectors. Levothyroxine is subsidised in Aotearoa New Zealand and Australia and is widely available. There is a lack of evidence and no practical treatment alternative to levothyroxine for hypothyroidism. Prescription of levothyroxine is outside the scope of practice of midwives and requires prescription and monitoring by a woman's general practitioner, obstetrician, endocrinologist or another suitably qualified healthcare professional.

Intravenous Immunoglobulin (IVIg)

Given it is subject to global shortages, the use of IVIg for recurrent miscarriage, where efficacy is yet to be established, may result in IVIg not being available for a condition where there is an established therapeutic role such as immune thrombocytopenia, Kawasaki disease, Guillain-Barré syndrome, lupus or to prevent infection in people who have received a bone marrow transplant.[33]

Clinical Question 4 – Screening tests

What tests should be offered to investigate recurrent miscarriage?

P: People with recurrent miscarriage
I: Test to establish underlying causes and risks (selected tests considered where RCOG and ESHRE guidelines did not agree)
C: No test
O: Live birth or diagnosis of conditions associated with recurrent miscarriage

Source of evidence

Consensual recommendations from RCOG and ESHRE, where both guidelines were in agreement, were considered to be sufficient for recommendation by RANZCOG in this guideline.[26, 34]
The evidence for this clinical question was restricted to the interventions (tests) with disagreement between the two guidelines. See methods. Evidence was reviewed for the following tests:

- Anti-beta-2-glycoprotein-I antibodies (Anti-B2GPI)[35-37]
- Inherited thrombophilia[38, 39]
- Sperm DNA fragmentation[40, 41]
- Antinuclear antibodies (ANA)[42, 43]

Certainty of evidence

Across tests considered, GRADE varied from Moderate to Very Low certainty.

Summary of evidence

Anti-beta-2-glycoprotein I antibodies (anti-B2GPI)

RCOG and ESHRE considered the same systematic review in their recommendations. The systematic review defined recurrent miscarriage as two or more miscarriages; it included five articles published between 1975 and 2003 which compare recurrent miscarriage rates between those with anti-B2GPI and those without.

No significant difference in recurrent miscarriage was found between assay methods (OR 2.12; 95% CI 0.69-6.53; 5 studies; n=1788). The systematic review concluded that the place of testing for anti-B2GPI antibodies remains to be determined.[35] Three further publications since this systematic review were also reviewed.[44-46] Only one article found a significant association between the test and recurrent miscarriage.[45]

The GDG determined that while anti-B2GPI levels may not differentiate between pregnant women with recurrent miscarriage compared to those with no history of recurrent miscarriage, testing for anti-B2GPI could be useful for some women with recurrent miscarriage when considered alongside other antiphospholipid antibody levels. Therefore, the GDG recommends this test could be considered on a case-by-case basis as part of routine testing for recurrent miscarriage.

Inherited thrombophilia

Since the RCOG and ESHRE guidelines were published there has been one new systematic review of 89 studies (30,254 participants), which reported that women with recurrent miscarriage may be more likely to have a mutation of the factor V Leiden gene, and are probably more likely to have a prothrombin gene mutation and Protein S deficiency.[38, 39] However, a multicentre randomised controlled trial (ALIFE2) comparing surveillance and low molecular weight heparin (LMWH) among women with inherited thrombophilia and recurrent miscarriage found LMWH did not result in higher live birth rates.[39] LMWH was also found to be associated with increased adverse effects such as easy bruising.

The GDG recommended that in the absence of an effective treatment for inherited thrombophilia in women with recurrent miscarriage, screening for these conditions should not form part of a routine testing.

Sperm DNA fragmentation

In a recent systematic review of studies where unexplained recurrent miscarriage occurred in a population of couples who naturally conceived, with female partners under 40 with a history of recurrent miscarriage, the male partner was more likely to have sperm DNA fragmentation (irrespective of the definition of recurrent miscarriage). However, the quality of evidence was low/very low due to high heterogeneity between studies.[40] Subgroup analysis from another systematic review indicated differences in association according to the type of test used.[41]

RCOG notes that there are few studies evaluating interventions that may affect sperm DNA fragmentation, which may include but is not limited to lifestyle modification (smoking cessation, weight management including with exercise, reduction in pollutant exposure), treatment of infections, control of diabetes, treatment of varicocele, antioxidant therapy, sperm selection.[34]

The GDG determined that although screening for sperm DNA fragmentation may be included in routine testing for diagnostic purposes, it must be acknowledged that there is limited evidence to demonstrate treatment benefits for recurrent miscarriage. Addressing modifiable lifestyle factors that may improve sperm DNA fragmentation such as smoking, obesity and optimisation of diabetes management will nonetheless have health benefits.[26]

Antinuclear antibodies (ANA)

A systematic review including 22 studies compared the presence of antinuclear antibodies (ANA) in women with and without recurrent miscarriage, and reported that couples with recurrent miscarriage were more likely to be ANA positive irrespective of the definition of recurrent miscarriage used.[43]

These data led the GDG to determine that antinuclear antibodies (ANA) are probably increased in women with recurrent miscarriage and therefore should form part of a routine battery of tests to investigate causes for recurrent miscarriage for diagnostic purposes only.

Other considerations

Recurrent miscarriage is a distressing experience for many. Qualitative evidence indicates that good clinical care for people trying to conceive includes: empathy for both partners regarding pressure to conceive; the provision of clear information including statistics, support with decision making for testing and treatment; and emotional support and coping strategies.[47]

Evidence indicates that individuals experiencing recurrent miscarriage appreciate being offered investigations by their healthcare provider. When individuals or couples have to request these investigations themselves, it may lead to a less satisfactory care experience and delays in care.[48] Additionally, people experiencing recurrent miscarriage may be more likely to give a good care experience rating if their healthcare professional discusses their worries or fears around recurrent miscarriage investigations.[48]

Male factors and recurrent miscarriage

It is important to consider that both female and male factors may contribute to recurrent miscarriage. This should include investigations and treatment where appropriate, for example treatment of varicocele, as well as recommendations about lifestyle modifications (even in the absence of evidence). A flexible approach to assessing male factors in recurrent miscarriage may be useful in addressing barriers attributed to cultural or geographical factors. In instances where a male partner does not attend an appointment for investigations, follow up of potential male factors with a familiar and culturally appropriate primary healthcare practitioner may be preferred.

Recommendations

Recommendation 8	Evidence-based recommendation
Strong: Screening tests for recurrent miscarriage as listed in Table 1: Screening Tests, including an explanation of their limitations, should be recommended where supported by the evidence. **GRADE of evidence:** Moderate (for tests recommended)	
Good Practice Statement 2	
The GDG suggests that when discussing whether or not to pursue investigations for recurrent miscarriage, practitioners counsel patients about the benefits and harms of knowing the outcome of testing.	

Table 1, Clinical Question 4: Screening tests

Investigations	Recommendation	Test	Evidence
Acquired thrombophilia: antiphospholipid Ab	Routinely recommended	Lupus anticoagulant (LA)	Strong
	Routinely recommended	Anti-cardiolipin antibodies (aCL) (IgG and IgM)	Strong
	Consider case-by-case	Anti-B2GPI	Very Low [a]
Imaging	Routinely recommended	3D ultrasound	Conditional
Thyroid screening	Routinely recommended	TSH, TPO antibodies, and thyroid function	Strong
Genetic factor	Consider case-by-case	Parental peripheral blood karyotyping [b]	Conditional
Male factor	Consider case-by-case	Sperm DNA fragmentation [c]	Low
Immunological	Consider case-by-case	ANA antibodies [d]	Low
	NOT routinely recommended	HLA, cytokine and NK cell	Strong
Inherited thrombophilia	NOT routinely recommended	Factor V Leiden, prothrombin gene mutation, protein S deficiency [e]	Moderate
	NOT routinely recommended	Protein C, antithrombin deficiency and methylenetetrahydrofolate reductase deficiency	Strong
Others	NOT routinely recommended	PCOs, fasting insulin and fasting glucose	Strong
	NOT routinely recommended	Prolactin testing	Conditional
	NOT routinely recommended	Ovarian reserve testing	Strong
	NOT routinely recommended	Androgen testing	Strong
	NOT routinely recommended	Vitamin D	Strong
	NOT routinely recommended	Luteinising hormone	Strong
	NOT routinely recommended	Homocysteine plasma levels	Strong

Recommendation:

Routinely recommended: Should be recommended as part of routine testing for recurrent miscarriage.

Consider case-by-case: Could be considered as part of testing for recurrent miscarriage, as appropriate.

NOT routinely recommended: Should not be **routinely** recommended as part of testing for recurrent miscarriage.

[a] ESHRE GPP: could be considered; RCOG: can be used, within the appropriate audit or research context

[b] Could be done if access to pregnancy tissue analysis not available

[c] Could be considered for diagnostic purposes, limited evidence recommending lifestyle changes

[d] Diagnostic purposes only

[e] Should be only used in women with additional risk factors for thrombophilia or in the context of research

Clinical Question 5 – Cytogenetic analysis of pregnancy tissue

What is the benefit of cytogenetic analysis of pregnancy tissue and when should it be offered?

P: Pregnant women with a history of recurrent miscarriage

I: Cytogenetic testing of pregnancy tissue or products of conception (POC)

C: Not testing

O: Diagnosis of cytogenetic conditions associated with miscarriage, live birth in future pregnancy

Source of evidence

Existing literature searches from RCOG and ESHRE were updated.[26, 34] No direct evidence for this clinical question was identified. However, indirect evidence (rates of aneuploidy diagnosed in a subsequent miscarriage by cytogenetic testing between women with a history of a single miscarriage compared with women with a history of recurrent miscarriage) was identified from two systematic reviews and used to inform this clinical question.[49, 50]

Certainty of evidence

Low GRADE.

Summary of evidence

The prevalence of chromosomal anomalies detected in pregnancy tissue was lower in recurrent miscarriage than in miscarriage occurring for women with no or one previous miscarriage. The prevalence of chromosomal abnormalities detected in pregnancy tissue decreased with an increasing number of miscarriages, suggesting that chromosomal anomalies contribute less to recurrent miscarriage than to non-recurrent miscarriage.[50]

Table 2, Clinical Question 5: Outcomes from Lei et al., 2022[50]

	Proportion of POC tests with chromosomal anomalies from women with a history of recurrent miscarriage	Proportion of POC tests with chromosomal anomalies from women with one/no previous miscarriages	Effect estimate [95% CI]
< 2 vs ≥ 2 previous miscarriages	55%	64%	OR 1.20 [1.01 to 1.44]
2 vs ≥ 3 previous miscarriages	-	-	OR 1.50 [1.17 to 1.92]

Age was identified in a further cohort study to be a statistically significant predictor of the chromosomal anomaly risk, with non-viable autosomal trisomies being more commonly found in pregnancy tissue from older women and unbalanced structural anomalies found in younger women.[51]

Published studies have used a variety of techniques to test pregnancy tissue following a miscarriage. Each has its benefits and limitations. Conventional karyotyping is limited by failure to adequately culture tissue, and contamination of the sample with maternal cells, making it difficult to distinguish between maternal contamination and a normal (euploid) female fetus.[49] Fluorescent in situ hybridisation (FISH) is limited by the probes used to detect chromosomal anomalies.[49] Chromosome microarray analysis (CMA), which can include array-comparative genomic hybridisation (aCGH) or single nucleotide polymorphism (SNP) array techniques, has much lower test failure rates than conventional karyotyping but may identify variants of uncertain significance which can be difficult to interpret clinically.[49]

Other considerations

The clinical benefit of cytogenetic testing of pregnancy tissue is unclear with respect to prevention of further miscarriage. Therefore, if testing of pregnancy tissue is offered, it should be accompanied by careful pre-test counselling, including discussion of any potential clinical or psychological benefits or harms of knowing the outcomes of such testing.

Pregnancy tissue has important meaning for Māori which may mean that cytogenetic testing is not preferred for cultural reasons. It is acknowledged that Māori have diverse values and beliefs; discussion of the option of return of pregnancy tissue after testing, as well as of the limitations of the testing, may help a couple come to a decision regarding testing.

Recommendations

Recommendation 9	Evidence-based recommendation
Conditional: Cytogenetic analysis of pregnancy tissue following miscarriage is not routinely recommended as there is no increase in genetic abnormalities in those with recurrent miscarriage. Genetic abnormalities may occur relatively more often in sporadic miscarriage but are unlikely to change clinical management in subsequent pregnancies. **GRADE of evidence:** Low.	
Good Practice Statement 3	
The GDG suggests that when discussing whether or not to pursue cytogenetic analysis of pregnancy tissue, practitioners counsel patients about the benefits and harms of knowing the outcome of testing.	

Clinical Question 6 – Antiphospholipid syndrome

What are the benefits and harms of treatment for antiphospholipid syndrome?
P: Pregnant women with a history of recurrent miscarriage and antiphospholipid syndrome
I: Anticoagulant therapy (aspirin and/or heparin)
C: Placebo, no treatment, other treatment
O: **Live birth rate**, pregnancy loss, ongoing pregnancy at 12 weeks' gestation (in the absence of live birth data), perinatal mortality, **fetal anomaly** or side effects, birth weight, **birth before 37 weeks**, NICU admission, acceptability, satisfaction

Source of evidence

One Cochrane review and one systematic review and network meta-analysis informed the evidence for this clinical question.[52, 53] An updated search for articles published following the search date of the systematic review (2019) identified no additional studies.

Certainty of evidence

Moderate GRADE.

Summary of evidence

The two systematic reviews that informed the evidence for this clinical question considered the effects of aspirin, heparin (either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH)), or a combination of both, on pregnancy outcomes in women with antiphospholipid syndrome and recurrent miscarriage.

Table 3, Clinical Question 4: Outcomes associated with various anticoagulation therapies for women with antiphospholipid antibodies

Comparison	Hamulyák (2020) Cochrane review	Yang (2021) Systematic review	Plain language interpretation
Outcome: Live birth			
Aspirin vs placebo	RR 0.94 95% CI 0.71 to 1.25	OR 1.42 95% CI 0.77 to 2.63	There may be little or no difference between aspirin and placebo in live birth rate
LMWH vs aspirin	RR 1.20 95% CI 1.00 to 1.43	OR 2.42 95% CI 1.04 to 5.66	LMWH may be associated with higher rates of live birth compared to aspirin alone
LMWH plus aspirin vs aspirin alone	RR 1.20 95% CI 1.04 to 1.38	OR 2.93 95% CI 2.33 to 3.68	LMWH in combination with aspirin may be associated with higher rates of live birth compared to aspirin alone
Unfractionated heparin (UFH) plus aspirin vs aspirin alone	RR 1.74 95% CI 1.28 to 2.35	OR 4.99 95% CI 3.18 to 7.84	UFH in combination with aspirin may be associated with higher rates of live birth compared to aspirin alone
Outcome: Subsequent miscarriage			
LMWH plus aspirin vs aspirin alone	RR 0.55 95% CI 0.26 to 1.16	Not reported	There may be little or no difference between LMWH in combination with aspirin and aspirin alone in miscarriage rate
Unfractionated heparin plus aspirin vs aspirin alone	RR 0.46 95% CI 0.29 to 0.71	Not reported	UFH in combination with aspirin may be associated with lower rates of miscarriage compared to aspirin alone

A subgroup analysis of heparin dose found little to no effect on live birth rates.

Low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH)

Women with recurrent miscarriage may be offered either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), taking into consideration that:

1. UFH may increase the likelihood of live birth more than LMWH[52]
2. UFH is more likely than LMWH to result in heparin-induced thrombocytopenia[52]
3. Both UFH and LMWH appear to be safe for the fetus and do not cross the placenta[52]
4. UFH is less practical to administer than LWMH, requiring continuous IV or injection (usually administered at a hospital) with frequent laboratory monitoring, compared to self-administered injection[52]
5. Long term use of UFH has been reported to be associated with osteoporosis. For LWWH, however, the loss in bone mineral density at the lumbar spine has been shown to be similar to that which occurs normally during pregnancy[54]

Low-dose aspirin is generally considered to be safe during pregnancy and there is no evidence to suggest that low-dose aspirin results in an increased risk of congenital malformations or neonatal bleeding conditions. Low-dose aspirin (≤ 150 mg per day) use during pregnancy has, however, been associated with an increased incidence of postpartum haemorrhage (OR 1.20, 95% CI 1.07 to 1.34).[55]

Other considerations

Qualitative evidence regarding the decision to take LMWH in combination with aspirin or aspirin alone suggests that women with recurrent miscarriage wished to do anything they could to prevent another miscarriage, and so were willing to inject LMWH daily.[56] Any concerns around taking LMWH during pregnancy were focused on the safety of the medication for their unborn child.[56]

Recommendations

Recommendation 10	Evidence-based recommendation

Strong: After a discussion of the associated improvement in live birth rate (and possible harms), women with antiphospholipid syndrome and a history of recurrent miscarriage should be offered:

- low-dose aspirin, 75 to 150 mg per day, either starting prior to pregnancy or starting from a positive pregnancy test, in combination with
- low-molecular weight heparin (dose as per local protocols), starting from a positive pregnancy test until at least 34 weeks

Treatment should be stopped before birth.

GRADE of evidence: Moderate.

Clinical Question 7 – Genetic/chromosome factors

What are the benefits and harms of investigations for genetic/chromosome factors?

P: People with unexplained recurrent miscarriage (PGT-A) and recurrent miscarriage with known genetic abnormalities (PGT-SR)
I: Pre-implantation genetic testing
C: No treatment (expectant management)
O: **Live birth rate**, pregnancy loss, ongoing pregnancy at 12 weeks' gestation (in the absence of live birth data), perinatal mortality, **fetal anomaly** or side effects, birth weight, **birth before 37 weeks**, NICU admission, acceptability, satisfaction, time to live birth

Source of evidence

Two systematic reviews and two cohort studies identified in the literature reviews performed for the Recurrent Miscarriage Green-top Guideline No. 17; and ESHRE Recurrent Pregnancy Loss Guideline formed the basis of the evidence for this clinical question.[26,34] Additional searches for articles published since 2022 identified one systematic review (which includes a cohort study included by ESHRE) and three additional cohort studies.[57,58-60]

Certainty of evidence

Very Low GRADE.

Summary of evidence

Preimplantation genetic testing for aneuploidy (PGT-A) for unexplained recurrent miscarriage

The only systematic review of PGT-A for couples with recurrent miscarriage and no known genetic issue included 11 studies (all using FISH techniques) and found no improvement in live birth with PGT-A.[61]

Cohort studies using newer genetic techniques such as CMA have reported mixed results, with some demonstrating improvements in live birth rate, while others have not.[58, 62, 63] Pregnancy complications were only reported in one of the identified cohort studies with no reported association of PGT-A and IVF with the outcomes including preterm birth, small for gestational age, and congenital anomalies.[59]

Indirect evidence from a Cochrane review of PGT-A in the general IVF population found little to no difference in cumulative live birth (polar body biopsy (OR 1.05, 95% CI 0.66 to 1.66; 1 RCT; low certainty evidence) or in live birth following the first embryo transfer (polar body biopsy (OR 1.10, 95% CI 0.68 to 1.79; 1 RCT; low certainty evidence; or blastocyst stage biopsy (OR 0.93, 95% CI 0.69 to 1.27; 1 RCT; low certainty evidence) between those who had PGT-A with genome wide techniques and those who did not.[64] No neonatal outcomes were reported.

Indirect evidence from a systematic review of pregnancy outcomes of PGT-A in the general IVF population reports that pregnancies using PGT-A may be at an increased risk of low birth weight (RR 3.95, 95% CI 2.32 to 6.72; two studies) and preterm birth (RR 5.76, 95% CI 1.30 to 25.48; one study), when compared with pregnancies that were naturally conceived.[65] No differences in congenital anomalies or NICU admission were found between the groups.[65] When compared with pregnancies from IVF/ICSI without PGT-A, maternal and neonatal outcomes from pregnancies with PGT-A were not significantly different (low birth weight: RR 0.92; 95% CI 0.79 to 1.07; 8 studies; congenital malformations (RR 1.16, 95% CI 0.80 to 1.69; 8 studies; preterm birth (0.96, 95% CI 0.88 to 1.05; 9 studies; NICU admission (RR 0.74, 95% CI 0.52 to 1.05; 6 studies).[65]

Preimplantation testing for monogenic/single gene anomalies (PGT-M) or chromosomal structural rearrangements (PGT-SR) for recurrent miscarriage with a known genetic cause

Two systematic reviews were identified that considered PGT-SR for recurrent miscarriage with a known genetic background. One review concluded there was no difference in live birth rate between PGT-SR and natural conception groups but did not include any comparative studies and used FISH techniques that are now rarely used.[66]

The other review similarly found no difference in live birth rates between PGT-SR and expectant management groups (natural conception (OR 0.55, 95% CI 0.11 to 2.62; two studies; low certainty evidence), although they found that IVF with PGT-SR may improve miscarriage rates (OR 0.15, 95% CI 0.04 to 0.51; 2 studies; low certainty evidence).[57]

Other considerations

PGT-A is accompanied by high embryo drop-out rates which may impact on time to conception or live birth. Embryos may not be suitable for transfer due to non-biopsiable and/or non-freezable blastocyst quality, failure of genetic analysis, the diagnosis of a chromosomal anomaly or having mosaic chromosomal anomalies.
A multicentre study from Europe (The DoLoReS Study) found that due to the above factors, in 50.4% of patients and 57.6% of stimulated cycles, no euploid embryo was available for transfer.[67]

Limitations in the evidence

The ability to draw conclusions from the identified evidence is limited by differences in the techniques used to conduct PGT. PGT performed using FISH looks at a specific chromosome at an early stage of embryo development (day 3) when mosaicism is high. This technique is increasingly replaced by chromosome microarray analysis (CMA) techniques performed on day 5-6 embryos, when mosaicism is less common.

Additionally, studies have differed in their selection of control groups for comparing the effectiveness of PGT. The preferable control group for such studies would be those with recurrent miscarriage having IVF but not PGT, rather than those with recurrent miscarriage having natural conception or those without recurrent miscarriage having IVF, which are the commonly encountered control groups in the evidence.

Recommendations

Recommendation 11	Evidence-based recommendation
Conditional: For people with recurrent miscarriage with balanced translocations, options include natural conception or undertaking IVF with preimplantation genetic testing for structural rearrangements (PGT-SR), taking into consideration the specific translocation and its potential significance. **GRADE of evidence:** Very Low.	

Recommendation 12	Evidence-based recommendation
Conditional: For people with recurrent miscarriage with no known genetic conditions, evidence suggests there is no improvement with IVF. However, if IVF is being considered for other factors, then preimplantation genetic testing for aneuploidy (PGT-A) is an option after consideration of the risks and benefits of IVF and embryo testing, conflicting evidence for PGT-A on the outcome of live birth, and the personal preference of the woman/couple. **GRADE of evidence:** Very Low.	

Good Practice Statement 4
The GDG suggests that people who have an abnormal parental karyotype should be offered genetic counselling. Consider offering genetic counselling to people who have a fetal or pregnancy tissue chromosome anomaly.

Clinical Question 8 – Anatomical factors

What are the benefits and harms of treatment for women who are wanting to become pregnant and who have identified anatomical factors (septum/septa, scars, adhesions, polyps and submucosal fibroids)?

P: Women with identified anatomical factors/uterine structural differences, with or without recurrent miscarriage

I: Surgical management

C: Expectant management

O: **Live birth rate**, pregnancy loss, ongoing pregnancy at 12 weeks' gestation (in the absence of live birth data), perinatal mortality, **fetal anomaly** or side effects, birth weight, **birth before 37 weeks**, NICU admission, acceptability, satisfaction, intrauterine adhesions, placenta related complications (placenta previa, placenta accreta)

Source of evidence

This clinical question considered both congenital (septate uterus and other uterine malformations, including arcuate, unicornuate, bicornuate uterus and uterus didelphys) and acquired anatomical factors (caesarean scar niche, adhesions, polyps and submucosal fibroids).

Two systematic reviews, consisting largely of observational data, were included in the evidence for congenital anatomical factors that focused specifically on septate uterus.[68, 69] An additional systematic review was included that focused on other congenital anomalies.[70]

For acquired anatomical factors, one systematic review and two cohort studies were included in the evidence for caesarean scar niche; one systematic review and one cohort study were included for adhesions; one Cochrane review and one systematic review were included for polyps; and one Cochrane review was included for submucosal fibroids. [71-78,79]

Certainty of evidence

Very Low GRADE to Low GRADE.

Summary of evidence

Congenital uterine anomalies

It is estimated that the prevalence of congenital uterine anomalies in women with recurrent miscarriage ranges from 7% to 28%.[80] Of these, the most common type among congenital uterine anomalies is the septate uterus.[80]

A systematic review from 2022 evaluated the effect of hysteroscopic metroplasty (minimally invasive surgery to remove the uterine septum and unify the uterine cavity) on the reproductive outcomes in women with septate uterus.[68] The review reported that, compared to expectant management, it was uncertain whether hysteroscopic metroplasty (in patients with either incomplete or complete septum) increases or decreases the odds of live birth or preterm birth, as confidence intervals were wide and crossed the line of no effect.[68] The odds of miscarriage were reported to be reduced with hysteroscopic resection OR 0.16 (95% CI 0.0 to-0.78); however, very low certainty evidence means a conclusion of true effect is not possible.[68]

Similar findings were reported by a second systematic review on the topic.[69] The 2023 review, on reproductive outcomes after hysteroscopic septum resection in women with septate uterus and recurrent miscarriage, primary infertility, or secondary infertility, reported it was uncertain whether resection of septate uterus (complete or incomplete) increases or decreases the odds of live birth, preterm birth and miscarriage due to very low certainty of the evidence.[69]

Only one randomised controlled trial was identified on the topic (which was included in the Carrera et al. 2022 systematic review discussed above).[81] The trial, which included 80 women, compared septum resection and expectant management and found no impact on live birth, preterm birth or miscarriage between the two groups.[81] Reporting of adverse events was limited to one uterine perforation in the surgical resection group.[81]

No studies were identified that directly compared surgical management and expectant management of other congenital uterine malformation. Indirect evidence suggested bicornuate and unicornuate uteri may be associated with increased odds of preterm birth, and bicornuate uterus with increased odds of miscarriage.[70] No such associations were found for arcuate uterus or uterus didelphys with these outcomes due to very low certainty evidence.[70]

Acquired uterine malformations

It is estimated that acquired uterine anomalies are associated with 6% to 15% of recurrent miscarriage, including impact from intrauterine adhesions, fibroids, and endometrial polyps.[80]

Caesarean scar niche (also known as isthmocele or caesarean scar defect)

A caesarean scar niche is a pouch-like defect in the anterior uterine wall, connected to the uterine cavity, at the site of a previous caesarean section scar.[82]

The evidence for caesarean scar niche and birth outcomes relies on observational studies. A small cohort study (including 166 women with no history of recurrent miscarriage) found hysteroscopic resection of caesarean scar niche had little or no impact on live birth (RR 1.48, 95% CI 0.80 to 2.75) or preterm birth (RR 1.66, 95% CI 0.26 to 10.50) compared to expectant management. Certainty of evidence: Very Low.[73]

Indirect evidence from a systematic review, focusing on women undergoing IVF, found that the presence of a caesarean scar niche during an IVF cycle may decrease live birth rates (OR 0.62, 95% CI 0.53 to 0.72) and increase miscarriage rates (OR 1.38, 95% CI 1.09 to 1.76) compared to women with previous caesarean birth but no niche.[71] Women undergoing IVF with a caesarean scar niche also had decreased live birth rates (OR 0.55, 95% CI 0.42 to 0.71) when compared to women with previous vaginal birth.[71]

There was no statistical difference in live birth rates after IVF, between women with previous caesarean birth but no caesarean scar niche and women with previous vaginal birth, indicating that it is the presence of a niche, rather than previous caesarean birth, that may affect subsequent live birth rates.[71]

One cohort study was also identified, that compared the size of the caesarean scar niche with live birth outcomes.[74] Generally, a larger caesarean scar niche had a lower chance of live birth subsequent to a fresh embryo transfer than a smaller caesarean scar niche (OR 0.42, 95% CI 0.19-0.90, low certainty evidence).[vii] [74]

Adhesions

Although intrauterine adhesions (IUAs) and Asherman syndrome are often used interchangeably, they are not strictly the same. IUAs may be present without Asherman syndrome. Asherman syndrome, however, may be diagnosed in the presence of IUAs with or without amenorrhea. Other symptoms may include cyclical abdominal pain and difficulty conceiving.[83] IUAs are best detected by hysteroscopy, in the hands of an experienced practitioner. Both IUAs and Asherman syndrome were included in the search undertaken. Evidence for the impact of IUAs and Asherman syndrome on reproductive outcomes is limited by the lack of control groups in published studies.

A 2022 systematic review, on the reproductive outcomes of women with mild IUAs who underwent hysteroscopic adhesiolysis, found little to no difference in miscarriage rates, but lower live birth rates compared to the general population.[75] Due to a lack of control group in the included studies, this systematic review compared outcome rates to that of the general Dutch population.[75] Certainty of evidence: Low.

[vii] Size of caesarean scar niche defined as: small size niche - residual myometrial thickness (RMT) > 6mm; medium size - RMT 3-6 mm; large size - RMT <3 mm.

Table 4, Clinical Question 8: Outcome data as reported in Hooker 2022[75]

	Miscarriage	Term delivery	Live birth
Pooled proportion (95% CI) in women with mild IUAs, identified and treated	10% (2-26)	83% (53-95)	86.6% (71-97)
Proportion in the general Dutch population (CI not provided) after two years	10%	Not provided	99.5%

A 2021 cohort study, including 500 women presenting with Asherman syndrome who underwent hysteroscopic adhesiolysis, found that 67.40% of the participants had a live birth following adhesiolysis.[76] Women with severe Asherman syndrome were reported to have reduced live birth rates compared to women with mild Asherman syndrome (OR 0.31, 95% CI 0.12 to 0.84), Certainty of evidence: Low.[76]

Endometrial polyps

No evidence was identified that directly compared surgical treatment and expectant management of polyps. Indirect evidence from women undergoing fertility treatment reported that polypectomy of endometrial polyps may increase clinical pregnancy rates in women undergoing IUI (OR 4.41, 95% CI 2.45 to 7.96). Certainty of evidence: Low.[77]

However, in an separate study of women undergoing IVF/ICSI, no association was demonstrated between hysteroscopic resection of endometrial polyps and live birth rate (OR 1.37, 95% CI 0.90 to 2.09) or miscarriage rate (OR 0.84, 95% CI 0.40 to 1.75) Certainty of evidence- Very Low.[78]

Submucosal fibroids

No evidence that directly compared surgical treatment and expectant management of submucosal fibroids was identified. Indirect evidence from a Cochrane review did not show any benefit, in clinical pregnancy rate or miscarriage, of myomectomy in women undergoing fertility treatment.[79]

Other considerations

Despite low evidence of effectiveness of surgical management over expectant management, women with an anatomical factor identified as a possible contributor to recurrent miscarriage may wish to discuss options including the possible benefits and harms, especially if they are experiencing other symptoms such as pain, menstrual irregularities or bleeding.

Limitations in the evidence

The evidence identified for this clinical question consists of systematic reviews which included mostly observational studies.

Studies comparing surgical management and expectant management of anatomical factors were largely conducted in the general population, rather than in women with recurrent miscarriage specifically, thereby limiting the generalisability of their outcomes.

Recommendations

Recommendation 13	Evidence-based recommendation

Conditional: Septum resection is not recommended in women with or without a history of recurrent pregnancy loss who have a uterine septum.

GRADE of evidence: Very Low

Good Practice Statement 5

The GDG suggests that if septum resection is being considered then it should be on a case-by-case basis taking into account the benefits and harms of the procedure.

Good Practice Statement 6

The GDG suggests that if surgical management of other congenital uterine malformations (arcuate, unicornuate, bicornuate and didelphys uterus) is being considered then it should be on a case-by-case basis, taking into account the benefits and harms of surgery, as there is no evidence to recommend surgical management over expectant management.

Good Practice Statement 7

The GDG suggests that resection of caesarean section niche in women with or without recurrent miscarriage is not offered due to a lack of evidence in this population for improving live birth rates. If being considered then it should be on a case-by-case basis taking into account symptoms, patient preferences, and the benefits and harms of the procedure.

Good Practice Statement 8

The GDG suggests that hysteroscopic adhesiolysis in women with or without recurrent miscarriage is considered on a case-by-case basis taking into account symptoms, patient preferences, and the benefits and harms of the procedure, including discussion about recurrence rates.

Good Practice Statement 9

The GDG suggests that polypectomy and/or myomectomy/resection of submucosal fibroids in women with or without recurrent miscarriage is not recommended due to a lack of evidence in this population for improving birth rates. If being considered then it should be on a case-by-case basis taking into account symptoms, patient preferences, and the benefits and harms of the procedure.

Clinical Question 9 – Hypothyroidism

What are the benefits and harms of treatment for hypothyroidism in women with recurrent miscarriage?

P: Pregnant women with a history of recurrent miscarriage who have abnormally low thyroid function (including subclinical hypothyroidism and those with TPO antibodies)

I: Levothyroxine

C: Placebo

O: **Live birth rate**, pregnancy loss, ongoing pregnancy at 12 weeks' gestation (in the absence of live birth data), perinatal mortality, **fetal anomaly** or side effects, birth weight, **birth before 37 weeks,** NICU admission, acceptability, satisfaction

Source of evidence

One retrospective cohort study and one prospective cohort study provided the evidence for overt hypothyroidism.[84,85] Evidence for subclinical hypothyroidism and thyroid auto-antibodies came from two systematic reviews.[86, 87]

Certainty of evidence

Low GRADE.

Summary of evidence

Treatment of hypothyroidism (an underactive thyroid) was considered for the subpopulations of overt hypothyroidism, subclinical hypothyroidism (SCH) or the existence of thyroid auto-antibodies (thyroperoxidase antibody positivity; TPOAb+).

RANZCOG recommends the following screening tests for thyroid function in women with recurrent miscarriage.

Where hypothyroidism is not due to iodine deficiency (which is common in Australia and Aotearoa New Zealand), it can be treated with levothyroxine, a synthetic version of thyroxine (T4).

Overt hypothyroidism

Overt hypothyroidism is associated with an increase in adverse pregnancy outcomes (including miscarriage and perinatal mortality) and there is wide consensus that it should be treated. [viii] Two retrospective cohort studies reported increased rates of miscarriage and perinatal death in pregnant women with inadequately treated overt hypothyroidism.[84, 85] Irrespective of pregnancy outcomes and pregnancy history, overt hypothyroidism should be treated preconception in women with recurrent miscarriage.

Subclinical hypothyroidism and thyroid auto-antibodies

Evidence for an association between SCH and miscarriage is mixed, and appropriate cut-off limits for diagnosis are unclear. The prevalence of SCH (TSH > 2.5) is reportedly higher in women experiencing recurrent miscarriage than in the general population.[88] However, the reported prevalence of miscarriage (not recurrent) in women with untreated SCH is similar to the prevalence of miscarriage in euthyroid women.[89]

From a systematic review of observational studies, for women with recurrent miscarriage and SCH, treatment with levothyroxine improved live birth rates (RR 1.20, 95% CI 1.01 to 1.42) and miscarriage rates (RR 0.65, 95% CI 0.44 to 0.97). Certainty of evidence: Very Low.[86] The TSH cut-off for defining SCH in these studies was > 2.5, with

[viii] See RANZCOG statement: Subclinical hypothyroidism and hypothyroidism in pregnancy (ranzcog.edu.au)

variable upper limits of 4-10 between studies. A further systematic review reported no improvement in miscarriage outcomes with pre-conception thyroxine treatment for SCH.[87]

The prevalence of TPOAb+ is around 9% in women with a history of miscarriage or subfertility. However, evidence for an association between the presence of thyroid antibodies and increased risk of recurrent miscarriage is mixed, with studies suggesting an association, the degree of which is uncertain.[90, 91] Women with SCH may also have thyroid antibodies, however the risk of progression from euthyroid thyroid antibody positivity to overt hypothyroidism is low (~4-10%).

Two high-quality RCTs have considered the efficacy of levothyroxine treatment in euthyroid women with recurrent miscarriage. Taken in isolation, neither demonstrates an effect on live birth rate (moderate certainty); Dhillon-Smith 2019: subgroup ≥ 3 miscarriages (RR 1.04, 95% CI 0.72 to 1.51); van Dijk 2022: ≥ 2 miscarriages (RR 1·03, 95% CI 0·77 to 1.38).[92, 93]

Levothyroxine treatment was not associated with any adverse pregnancy outcomes. Serious adverse effects were rare with no difference in serious adverse events between the levothyroxine and placebo groups reported in either RCT. Side effects or adverse effects from levothyroxine treatment (other than those related to overdose (i.e., symptoms consistent with hyperthyroidism, such as fatigue) were reported in approximately 5% of trial participants but were usually mild and may subside with continued use or change in dosage or brand.

Table 5, Clinical Question 9: Summary of thyroid disorder and suggested management in women with recurrent miscarriage

Thyroid disorder	Suggested management
Overt hypothyroidism (raised TSH, low T4)	• Treatment strongly recommended prior to pregnancy • Titrate levothyroxine dose to TSH level • Treatment with levothyroxine improved miscarriage rate
Subclinical hypothyroidism (raised TSH, normal T4)	• Insufficient evidence to recommend treatment with levothyroxine • No evidence of benefit that treatment improves live birth rate (very low certainty) • If not treated, check TSH in early pregnancy (7-9 weeks) and monitor as indicated
Antibody positive euthyroid	• Treatment with levothyroxine is not recommended for women with recurrent miscarriage with TSH ≤ 2.5 mIU/L and who have tested positive for TPOAb+ • If not treated, check TSH in early pregnancy (7-9 weeks) and monitor as indicated

Limitations in the evidence

Due to the wide consensus that overt hypothyroidism is associated with adverse pregnancy and neonatal outcomes, including fetal neurocognitive development, clinical trial evidence is limited as it would be deemed unethical to conduct RCTs of levothyroxine in pregnant women with overt hypothyroidism.

Recommendations

Recommendation 14	Evidence-based recommendation
Strong: For women with recurrent miscarriage, levothyroxine should be offered to women with overt hypothyroidism. **GRADE of evidence:** Moderate	

Recommendation 15	Evidence-based recommendation
Conditional: For women with recurrent miscarriage and subclinical hypothyroidism, including mild subclinical hypothyroidism (TSH > 2.5 mIU/L), there is insufficient evidence to support offering levothyroxine. **GRADE of evidence:** Very Low	

Recommendation 16	Evidence-based recommendation
Strong: Women with recurrent miscarriage who have a TSH ≤ 2.5 mIU/L and who test positive for thyroid auto-antibodies (TPOAb+) should not be offered levothyroxine. **GRADE of evidence:** Moderate	

Good Practice Statement 10
The GDG suggests for women with recurrent miscarriage planning a pregnancy and taking levothyroxine, a reasonable target should be based on local pregnancy-specific reference intervals.[ix]

Good Practice Statement 11
The GDG suggests that for women with subclinical hypothyroidism and/or thyroid autoantibodies not treated with levothyroxine, TSH be checked in early pregnancy (7-9 weeks) with further monitoring as indicated based on individual circumstances.

Clinical Question 10 – Intravenous Immunoglobulin

What are the benefits or harms of intravenous immunoglobulin treatment for recurrent miscarriage?

P: Pregnant women with unexplained recurrent miscarriage

I: Immunotherapy intravenous immunoglobulin (IVIg)

C: Placebo, treatment as usual

O: **Live birth rate**, pregnancy loss, ongoing pregnancy at 12 weeks' gestation (in the absence of live birth data), perinatal mortality, **fetal anomaly** or side effects, birth weight, **birth before 37 weeks,** NICU admission, acceptability, satisfaction

[ix] See the RANZCOG Subclinical hypothyroidism and hypothyroidism in pregnancy Statement (C-Obs 46) for further information on pregnancy specific ranges for thyroid function.

Source of evidence

Evidence for this clinical question came from a Cochrane review, a systematic review, a randomised controlled-trial (RCT) and a retrospective cohort study. [94, 95, 96, 97]

Certainty of evidence

Moderate GRADE.

Summary of evidence

Various immunological biomarkers are more prevalent in women with recurrent miscarriage. However, the pathophysiological mechanisms showing how immunological disturbances may contribute to recurrent miscarriage remain unclear. There are currently no validated biomarkers that can be used to diagnose immune-mediated recurrent miscarriage. The common tests for HLA, cytokine and NK cells are not routinely recommended (see Clinical Question 4 – Screening tests).

Intravenous immunoglobulin (IVIg) is an immune-based therapy that has been suggested for women with unexplained recurrent miscarriage. IVIg formulations are made by extracting the immunoglobulin fractions from plasma from blood donors.

A Cochrane review of immunotherapy for recurrent miscarriage reported that moderate dose IVIg (e.g., 0.4 g per kg body weight over 2-3 week intervals) was not associated with an increase in the live birth rate in women with recurrent miscarriage compared to placebo (OR 0.98, 95% CI 0.61 to 1.58).[94] However, IVIg may have an association with increased live birth rates in specific groups, although this is difficult to determine due to heterogeneity between study treatment protocols.

Overall, research has reported a narrow cohort for which IVIg may be appropriate: IVIg may lead to an increase in live birth rates if offered pre-conception or in early gestation (4-6 weeks), to women with a history of 4 or more miscarriages, if it is suspected (due to the exclusion of other risk factors) that the previous miscarriages were immune-mediated.[95, 97] High dose IVIg (e.g., 0.4 g per kg body weight daily for 5 days) may also lead to an increase in live birth rates.[97]

Table 6, Clinical Question 10: Study protocols and outcome results for Yamada 2022 and Banjar 2023

Study	Previous miscarriage	Dose	Treatment period	Live birth (favours IVIg)
Yamada 2022 (N=99)	≥ 4	0.4 g/kg daily for 5 days (high dose)	4-6 weeks' gestation	OR 2.60 95%CI 1.15 to 5.86
Banjar 2023 (retrospective cohort)	≥ 3 (primary RPL only)	0.6-0.8 g/kg (moderate dose)	Before conception and monthly until 16-20 weeks' gestation	18/28 (64%) vs 36/83 (43%), p=0.08
	≥ 5 (primary RPL only)			10/15 (67%) vs 3/16 (19%)

Adverse reactions have been reported to occur in 5%-15% of infusions and are typically mild, including back or abdominal pain, nausea, breathing difficulties, chills, flushing, rash, anxiety, low-grade fever, arthralgia, myalgias, and headache.[98] More serious adverse events, though uncommon, include cerebral ischemia, strokes; myocardial infarction; deep vein thrombosis; pulmonary emboli; renal toxicity.[98] A rare serious adverse event is anaphylaxis; however, reactions are often unpredictable.

Blood products are strictly regulated in Australia and Aotearoa New Zealand and there is little risk of introducing transmissible infections to people receiving IVIg.

Other considerations

Use of IVIg for the treatment of recurrent miscarriage is not approved in Australia and Aotearoa New Zealand, as authorities who regulate the donation and use of blood and blood products report no clear evidence of benefit for this condition. The cost of purchasing IVIg privately, if it could be obtained, would have an out-of-pocket cost that may be prohibitive for women and/or couples.

Outcome

IVIg is not available for women with recurrent miscarriage in Aotearoa New Zealand or Australia from government blood product suppliers (the National Blood Authority (NBA) in Australia and the New Zealand Blood Service).

There is no evidence that medium dose IVIg in women with unexplained recurrent miscarriage improves live birth rates and limited evidence that high dose IVIg in women with unexplained ≥ 4 miscarriages improves live birth rates.

Following consideration of the above, no recommendation was made.

Clinical Question 11 – Progesterone treatment for recurrent miscarriage

What are the benefits and harms of treatment with progesterone in pregnant women with a history of recurrent miscarriage (with or without bleeding)?

P: Pregnant women up to 14 weeks with or without bleeding and a history of recurrent miscarriage
I: Progesterone (any route)
C: Placebo, no treatment
O: **Live birth rate**, pregnancy loss, ongoing pregnancy at 12 weeks' gestation (in the absence of live birth data), perinatal mortality, **fetal anomaly** or side effects, birth weight, **birth before 37 weeks,** NICU admission, acceptability, satisfaction

Source of evidence

Two systematic reviews. [23, 99]

Certainty of evidence

Moderate GRADE.

Summary of evidence

Asymptomatic (not bleeding) and recurrent miscarriage (≥ 2)

Progestogen treatment may have little to no impact on the live birth rate for women with two or more previous first trimester miscarriages who do not have any bleeding (RR 1.08, 95% CI 0.98 to 1.19). Certainty of evidence: Low. Exclusion of the oldest study, that used IM progesterone administered weekly, did not significantly influence the observed effect.

A Cochrane review reported miscarriage in women with recurrent pregnancy loss.[99] Sensitivity analysis excluding studies with a high risk of bias reported no clear evidence of difference (RR 0.86, 95% CI 0.60 to 1.24).[99]

RANZCOG recalculated the sensitivity analysis by removing an additional study that has been retracted and found similar results (RR 0.98, 95% CI 0.82 to 1.18). This led the GDG to determine that progestogens probably have little to no impact on the rate of miscarriage in asymptomatic women with a history of recurrent pregnancy loss.

Threatened miscarriage (bleeding) and two or more previous miscarriages

RANZCOG used the data from two studies included in the 2024 systematic review limited to those with early pregnancy bleeding and a history of two or more previous miscarriages, as described in the table below:[23]

Studies	Live birth		
	Progesterone	Placebo	RR
McLindon 2023	22/26	27/34	1.07 (0.84-1.35)
Coomarasamy 2019	276/367	252/384	1.15 (1.04-1.26)
Total	298/393	279/418	1.14 (1.04-1.24)

The data suggest that progesterone (by any route) probably improves the live birth rate for women with early pregnancy bleeding and two or more previous miscarriages.[100]

Progesterone use for recurrent miscarriage, with or without threatened miscarriage, probably results in little or no difference in congenital anomaly rates or serious adverse events.[100]

Other considerations

The duration of progesterone treatment varied between studies but appears not to influence the likelihood of live birth. The two most recent studies used treatment for 12 and 16 weeks.[23]

Recommendations

Recommendation 17	Evidence-based recommendation

Strong: First trimester progestogens should not be recommended for pregnant women with two or more previous miscarriages without early pregnancy bleeding as there is no evidence they increase live birth rates.

GRADE of evidence: Moderate

Recommendation 18	Evidence-based recommendation

Strong: Progesterone should be recommended for pregnant women with two or more previous miscarriages and with early pregnancy bleeding as it probably increases the live birth rate and has little to no association with congenital abnormalities or severe adverse events. The duration of treatment should be to 16 weeks' gestation at a dose of 400 mg twice daily of micronised progesterone vaginally.

GRADE of evidence: Moderate

Part 3 – Tubal ectopic pregnancy

Introduction

An ectopic pregnancy occurs when a fertilised egg implants and matures outside the uterus. The majority of ectopic pregnancies (97%) implant in the fallopian tubes.[101] Other non-tubal ectopic pregnancies such as interstitial (sometimes referred to as cornual, though interstitial and cornual pregnancies are not the same), cervical, and caesarean scar pregnancies, are discussed in Part 4 – Non-tubal ectopic pregnancy.

Contraception and investigation of contributing factors to ectopic pregnancy (i.e., STIs, endometriosis) are out of scope of this guideline. Evidence-based recommendations and advice for clinicians related to contraception following pregnancy (including ectopic) can be found in this RANZCOG guideline: C-Gyn 3 Contraception Clinical Guideline.

Terminology for this chapter

Salpingectomy: removal of the fallopian tube

Salpingotomy/salpingostomy: incision in the fallopian tube and removal of the ectopic tubal pregnancy. Salpingotomy aims to preserve the tube.

Equity considerations for this chapter

Ultrasound features diagnostic of a tubal ectopic pregnancy

Women living in rural and remote communities may have limited access to ultrasound services.

Management of tubal ectopic pregnancy

Though specific literature about equity issues around ectopic treatment is scarce, it is recognised that treatment of ectopic pregnancy can be resource-dependent and time-sensitive. As such, for those groups that are known to experience disparities with access to health services, including First Nations women, equity issues are likely to exist. This may impact timely diagnosis and availability of treatment options (with both expectant and medical management requiring frequent monitoring and prompt access to surgical services should treatment fail). Access to surgery may also be reduced.

Clinical Question 12 – Ultrasound features diagnostic of a tubal ectopic pregnancy

What ultrasound features are diagnostic of a tubal ectopic pregnancy?

P: Pregnant women presenting in early pregnancy with pain and/or bleeding or asymptomatic with PUL

I: Index Test: Ultrasonography with any of the following features, singularly or in combination:

Uterus:

- Empty uterus/no evidence of intrauterine pregnancy
- Cystic areas/sacs (including pseudo-gestational sac/decidual cyst, cystic area in uterus, or pseudo sac)
- Fluid inside the uterus
- Heterotopic pregnancy (co-existing intrauterine and ectopic pregnancies)

Tube and ovary:

- Adnexal mass (yolk sac, fetal pole, fetal heartbeat)
- Tubal ring sign (also known as bagel sign, donut sign or blob sign)
- Adnexal cyst (simple)
- Complex extra-adnexal mass

Peritoneal cavity:

- Identification of fluid/blood (including free fluid, haemoperitoneum, or free blood in the pelvis)

T: Target condition: Confirmation of diagnosis of ectopic pregnancy by one or more of the following index tests:

- Surgical/histological confirmation of ectopic pregnancy
- Confirmation of ectopic pregnancy on follow up ultrasound scan
- Rising hCG levels with no chorionic villi within products of conception following evacuation
- Suspected/confirmed ectopic pregnancy that resolved after medical treatment

A: Analysis: Diagnostic test accuracy • Sensitivity • Specificity • Positive likelihood ratio (LR+) • Negative likelihood ratio (LR-) • Positive and negative predictive values

Source of evidence

The evidence review for the NICE guideline subchapter on ectopic pregnancy informed this clinical question.[102] This review included ten studies published up to 2019. No further studies of diagnostic test accuracy of individual ultrasound signs were identified on updated searching to August 2024.

Certainty of evidence

Ranged from high GRADE to very low GRADE depending on feature seen on ultrasound. Overall, evidence was assessed as low GRADE.

Summary of evidence

All studies included features seen using transvaginal ultrasonography (TVUS), and two studies of transabdominal ultrasonography (TAS).

Overall, the presence on an ultrasound scan of an adnexal mass with features of an early pregnancy (a gestational sac containing a yolk sac or a fetal pole with or without a fetal heartbeat), has a very high positive likelihood ratio (LR+ 197.37, 95% CI 27.35 to 1424.15) and specificity (100%).[102]

- The high specificity indicates with certainty that the presence of an adnexal mass is an ectopic pregnancy in symptomatic women
- The positive likelihood ratio indicates how many times more likely an adnexal mass is to be found in a woman with an ectopic pregnancy, compared to a woman without an ectopic pregnancy. As well as signs and symptoms, and hCG tracking, a high positive likelihood ratio allows us to rule on the diagnosis of an ectopic pregnancy if an adnexal mass is present.

The presence on an ultrasound scan of an inhomogeneous mass (''blob sign'') or an adnexal mass with an empty gestational sac (containing no yolk sac, fetal pole or fetal heartbeat or “bagel sign”) has a high positive likelihood ratio (LR+ 18.92, 95% CI 12.89 to 27.8) and specificity (98%) and probably indicates an ectopic pregnancy.[102] These findings must also be interpreted alongside the woman's history, symptoms and hCG levels.

Other features that do not have a high enough LR+ and specificity alone to indicate an ectopic pregnancy, but should be taken into account during the diagnosis include:

- fluid in the uterine cavity (pseudo-sac)
- empty uterus
- free fluid in the peritoneal cavity.

Other considerations

Ultrasound combined with hCG testing remains the best diagnostic tool, however approximately 12% of ectopic pregnancies may still not be identified by this method.[103]

Other diagnostic aids, such as a Bayesian statistical approach, the M4 model, or online probability calculators are available, to use alongside ultrasonography and hCG testing. The M4 and M6 model were validated in an Australian population of 360 women.[104]

It is acknowledged that there may be additional tests, such as serum progesterone, used in combination with hCG testing when investigating pregnancies of unknown location. However, this evidence was not reviewed as part of this clinical question and clinicians should refer to their own health service protocols to confirm the preferred approach. An adapted flowchart to guide assessment of early pregnancy loss, including location and viability, is provided in Appendix F.

Limitations in the evidence

The sensitivity of individual features was not found to be particularly high. However, women with an ectopic pregnancy may have a variety of different features identified on scan, and thus a single feature may not be expected to be present in all women.

Many of the studies were conducted in the 1990s and early 2000s. The technical capabilities of ultrasound machines have improved since then, and the diagnostic accuracy of ectopic pregnancy features in studies from pre-2000 may not reflect current practice.

Recommendations

Recommendation 19	Evidence-based recommendation
Conditional: In women with the signs and symptoms of ectopic pregnancy, an ectopic pregnancy can be reliably diagnosed if the ultrasound demonstrates an adnexal mass that includes a gestational sac (with or without yolk sac, fetal pole, or fetal heart) or an empty gestational sac ('bagel sign'), or an adnexal mass with sliding sign with an inhomogeneous mass ('blob sign'). **GRADE of evidence:** Low	

Good Practice Statement 12
An empty uterus or fluid in the uterine cavity could indicate an ectopic pregnancy or a persistent pregnancy of unknown location. Consider other ultrasound features, signs and symptoms as well as hCG levels to reach a diagnosis. In situations where the ultrasound features are not diagnostic, consider repeat ultrasound, if the woman is stable. The timing of the repeat ultrasound will depend on the symptoms, hCG level, and availability of local resources.

Clinical Question 13 – Management of tubal ectopic pregnancy

What are the benefits and harms of different treatment options (surgical/medical/expectant management) for tubal ectopic pregnancy?

P: Pregnant women with suspected ectopic pregnancy that meet local policy criteria for methotrexate (MTX)

I: Expectant management, surgical management by laparoscopy or open surgery with or without preservation of the fallopian tube, medical management with methotrexate (all dosing regimens)
C: Any of the above listed interventions
O: **Resolution of the ectopic pregnancy, needed further treatment, adverse events** (including abnormal blood tests, hair loss, nausea and vomiting, ruptured ectopic), time to return to normal activities, acceptability, satisfaction, long term outcomes such as fertility – time to next pregnancy (have a standdown period post MTX), recurrence of ectopic in future pregnancy

Source of evidence

Four systematic reviews were included in this clinical question.[105-108] A Cochrane Review informed comparison of surgery versus methotrexate. [109] An updated search, in May 2024, did not identify new studies.

Certainty of evidence

Varied from Low GRADE to Moderate GRADE.

Summary of evidence

The following evidence applies to treatment of stable ectopic pregnancies.

A systematic review with network meta-analysis provided the table below ranking best treatment options for a tubal ectopic pregnancy:[105]

Table 7, Clinical Question 13: Surface under the cumulative ranking curve (SUCRA) table, adapted from Al Wattar et al. 2024

Treatment failure - from least to greatest (n = SUCRA*)	Treatment resolution - from best to worst (n= SUCRA*)
Salpingectomy (0.1)	Salpingotomy + MTX (95.4)
Single dose MTX + Mifepristone (21.1)	Single dose MTX + Mifepristone (80)
Multi dose MTX (30.1)	Salpingectomy (71.5)
Single dose MTX (33.1)	Multi dose MTX (58.3)
Expectant (47.4)	Expectant (56.1)
Salpingotomy (53.1)	Salpingotomy (50.2)
Salpingotomy + MTX (56)	Single dose MTX (40.1)

*Treatment options with a SUCRA value close to 100% have the highest cumulative rank (i.e., highest likelihood) for achieving the primary outcome (complete resolution of the ectopic or treatment failure).

*Does not include glucose intra-sac instillation, MTX intra-sac instillation, prostaglandin intra-sac instillation.

Salpingectomy and multi-dose methotrexate (MTX) both ranked higher than expectant management, with a lower likelihood of failure, and a higher likelihood of resolution of an ectopic pregnancy:[105]

- salpingectomy (SUCRA failure: 0.1 | SUCRA success: 71.5)
- single dose MTX + mifepristone (SUCRA failure: 21.1 | SUCRA success: 80)
- multi-dose MTX (SUCRA failure 30.1 | SUCRA success: 58.3).

Treatment failure was defined in the review as the need for emergency surgery following a primary elective treatment option and/or the need to convert a primary surgical treatment option to salpingectomy (e.g., performing a salpingectomy after a failed salpingotomy).

Resolution of the ectopic pregnancy was confirmed either via adequate decline of blood hCG levels or when no more treatment was needed by the end the follow up period (as defined in each study).

Methotrexate treatment

Methotrexate compared with surgery

Overall, laparoscopic surgery compared with multidose methotrexate had similar outcomes for treatment success, noting that the mean hCG levels in women treated with methotrexate in some included studies were higher than the levels of women treated with surgery, which may have influenced the result.[109]

Methotrexate may increase the likelihood of an intrauterine pregnancy after a tubal ectopic pregnancy compared to surgery (salpingectomy or salpingotomy) (OR 1.52, 95% CI 1.20 to 1.92), low certainty evidence). The number of doses of methotrexate given was not reported.[106]

It is unclear whether methotrexate increases or decreases recurrent ectopic pregnancy compared to surgery (salpingectomy or salpingotomy) (OR 1.12, 95% CI 0.84 to 1.51) due to very low certainty evidence.[106]

Methotrexate: one versus two doses

A systematic review of 4 studies, including 485 participants, reported that treatment success was increased with two doses, especially in women with:

- a high baseline hCG (3,000-5,500 IU/L) (OR 3.23, 95% CI 1.53 to 6.84). Certainty of evidence: Moderate, or
- a large size adnexal mass (20-35 mm) (OR 2.92, 95% CI 1.23 to 6.93). Certainty of evidence: Moderate.[108]

However, the side effects were probably also increased (OR 1.53, 95% CI 1.01 to 2.30). Certainty of evidence: Moderate. Side effects reported were transient and none required hospitalisation or treatment discontinuation.[108]

Methotrexate: one versus multiple doses

Compared to one dose methotrexate, multiple doses may have little to no effect on treatment success, treatment failure, or risk of tubal rupture. Certainty of the evidence: Low.[108] However, it may increase side effects (OR 2.10, 95% CI 1.24 to 3.54).[108]

Only one study reported on the impact of multidose methotrexate compared to single dose for patients with high hCG (defined as > 800 IU/L) or with a large adnexal mass (> 20 mm), and demonstrated that multiple doses of methotrexate made no difference to treatment success.[108]

Alternating doses of leucovorin were used in the above studies of multidose methotrexate, to reduce side effects. It was noted in the review that this could limit efficacy of the treatment and potentially explain the lack of difference in treatment success between multidose vs single dose regimens.[108]

Single-dose methotrexate + mifepristone

While the SUCRA for single dose methotrexate plus mifepristone positioned the treatment as having a low likelihood of treatment failure, and high likelihood of treatment resolution, the SUCRA ranking should be

considered alongside the structure of the network. The evidence for single dose methotrexate plus mifepristone largely came from smaller, older studies. This treatment option was re-evaluated with these evidence considerations in mind, together with the uncommon use of single-dose methotrexate plus mifepristone in Australia and Aotearoa New Zealand for management of tubal ectopic pregnancy, and a recommendation made to reflect this information.

Other considerations

Methotrexate is teratogenic and should only be given if an ectopic pregnancy is confirmed without doubt.[110]

Limitations in the evidence

The cut-off hCG levels in the included studies is higher (up to 20,000 IU/L in some studies) than what is currently accepted for expectant or medical management in clinical practice in Australia and New Zealand. Significant variations in baseline hCG levels between participants may impact the outcomes as women with higher hCG levels may not respond to MTX protocols.

Recommendations

Good Practice Statement 13
Women with ectopic pregnancy who are haemodynamically unstable, or with signs of rupture, or a hCG level > 5000 IU/L, or an adnexal mass > 35 mm, or have contraindications to medical or expectant management, should be managed surgically.

Recommendation 20	Evidence-based recommendation
Conditional: Women with an ectopic pregnancy with an adnexal mass of < 35mm (no fetal heart activity), who are clinically stable, are willing and able to return for follow up and who have: • hCG < 1500 IU/L, may be offered a choice of expectant management OR medical management with methotrexate OR surgical management • hCG level of ≥ 1,500 IU/L and < 5,000 IU/L, and have no significant pain or signs of rupture, may be offered a choice of medical management with methotrexate OR surgical management **GRADE of evidence**: Low	

Good Practice Statement 14
The GDG suggests that treatment options for ectopic pregnancy, including associated benefits and risks, are discussed to reach an informed decision.

Good Practice Statement 15
Women should be informed that emergency treatment for ectopic pregnancy may be required if expectant or medical management is unsuccessful.

Recommendation 21	Evidence-based recommendation
Strong: Women who choose to have medical management of an ectopic pregnancy and have a hCG < 3000 IU/L or adnexal mass <20 mm should be offered one dose of systemic methotrexate. For women who choose to have medical management of an ectopic pregnancy and have a hCG 3000 to 5000 IU/L or adnexal mass 20 to 35 mm, two doses of systemic methotrexate given 4-7 days apart should be offered. **GRADE of evidence:** Moderate	

Good Practice Statement 16
If choosing medical management of an ectopic pregnancy, follow up of levels of hCG is required and further doses of MTX may be necessary.

Recommendation 22	Evidence-based recommendation
Strong: Women should be advised of the increased risk of transient side effects (e.g., nausea, diarrhoea, mucositis, abdominal pain, mildly abnormal laboratory results) associated with two doses of methotrexate. **GRADE of evidence:** Moderate	

Good Practice Statement 17
Women who receive methotrexate treatment should be advised to wait three months before conceiving again and contraception should be discussed.

Recommendation 23	Evidence-based recommendation
Conditional: For women with tubal ectopic pregnancy, medical management may favour subsequent intrauterine pregnancy. However women should be advised that salpingectomy is associated with higher likelihood of resolution of the ectopic pregnancy compared to medical management. **GRADE of evidence:** Low.	

Clinical Question 14 – Salpingectomy vs. salpingostomy/salpingotomy

What are the benefits and harms of salpingectomy compared with salpingostomy/salpingotomy for surgical management of ectopic pregnancy?

P: Pregnant women with suspected ectopic pregnancy who do not meet the criteria for non-surgical management

I: Salpingectomy

C: Salpingostomy/salpingotomy

O: **Resolution of the ectopic pregnancy, needed further treatment,** adverse events, time to return to normal activities, **long term outcomes such as fertility, recurrence of ectopic in future pregnancy (include cornual/interstitial),** satisfaction, acceptability, need for follow up

Source of evidence

Two systematic reviews were included in this clinical question. [105, 111]

Certainty of evidence

Moderate GRADE.

Summary of evidence

The below data applies to treatment of stable ectopic pregnancies.

A systematic review with network meta-analysis provided the table below ranking salpingectomy and salpingotomy (for surgical management of a tubal ectopic), by treatment resolution and treatment failure:[105]

Table 8, Clinical Question 14: Surface under the cumulative ranking curve (SUCRA) table, adapted from Al Wattar et al. 2024

Treatment failure - from least to greatest (n = SUCRA*)	Treatment resolution - from best to worst (n= SUCRA*)
Salpingectomy (0.1)	Salpingectomy (71.5)
Expectant (47.4)	Expectant (56.1)
Salpingotomy (53.1)	Salpingotomy (50.2)

* Treatment options with a SUCRA value close to 100% have the highest cumulative rank (i.e., highest likelihood) for achieving the primary outcome (complete resolution of the ectopic or treatment failure)

In the ranking of treatment, salpingectomy ranks higher than salpingotomy, with a lower likelihood of treatment failure (SUCRA 0.1 versus 53.1) and a higher likelihood of treatment resolution (SUCRA 71.5 versus 50.2).

Treatment failure was defined in the review as the need for emergency surgery following a primary elective treatment option and/or the need to convert a primary surgical treatment option to salpingectomy (e.g., performing a salpingectomy after a failed salpingotomy).

Treatment resolution was confirmed either via adequate decline of blood hCG levels or when no more treatment was needed by the end the follow up period (as defined in each study).

Compared to salpingectomy, salpingotomy probably increases the likelihood of treatment failure (RR 12.46 [95% CI 5.10-30.48])[105], however has little to no difference on the likelihood of:

- resolution of the ectopic pregnancy (RR 0.94, 95% CI 0.84-1.04)[105]
- subsequent intrauterine pregnancy (RR 1.04, 95% CI 0.98-1.21)[105]
- repeat ectopic pregnancy (RR 1.30, 95% CI 0.72-2.38)[111]
  Certainty of evidence for all outcomes: Moderate.

Other considerations

Various considerations may also influence a woman's decision to favour salpingotomy over salpingectomy, such as status/patency of the other fallopian tube, and ability to access and afford assisted reproductive treatment (ART) if needed. ART is funded in New Zealand for women with no fallopian tubes; however, there may be a waitlist to access treatment.

Salpingotomy is less frequently practiced, particularly in recent years. Salpingotomy may not be available to all women, particularly where surgical expertise in this technique is lacking.

Recommendations

Recommendation 24	Evidence-based recommendation

Strong: For women with tubal ectopic pregnancy salpingectomy should be recommended instead of salpingotomy, as there is a higher likelihood of resolution of tubal ectopic pregnancy, and with a single procedure.

GRADE of evidence: Moderate

Good Practice Statement 18

Salpingotomy may be considered depending on the woman's preferences, desire to avoid or lack of access to IVF, and medical history. Women should be advised of the higher risk of treatment failure and need for further treatment, including with methotrexate or salpingectomy.

Part 4 – Non-tubal ectopic pregnancy

Introduction

Non-tubal ectopic pregnancy occurs when an embryo implants outside of the uterine cavity or fallopian tubes.[112] These pregnancies are rare, with estimated incidence ranging between 5% and 8.3% of all ectopic pregnancies although they are becoming more common, especially caesarean scar pregnancy.[112, 113] Early diagnosis and effective treatment are essential to avoid the potentially serious maternal morbidity and mortality consequences of non-tubal ectopic pregnancy.[112]

This section examines evidence related to three clinical questions regarding interstitial pregnancy, cervical pregnancy and caesarean scar pregnancy, and includes treatment options for each to guide clinicians in providing care to women with these rare but clinically important pregnancies.

Terminology for this chapter

Interstitial ectopic pregnancy: occurs when a fertilised ovum implants in the most proximal part of the fallopian tube (called the interstitial section). The interstitial section is about 1–2 cm in length, traversing the muscular myometrium of the uterine wall, opening via the tubal ostium into the uterine cavity.[114, 115]

Cervical ectopic pregnancy: occurs when a fertilised ovum implants in the endocervical canal below the level of the internal os.[116]

Caesarean scar pregnancy (CSP): occurs when a fertilised ovum implants into the myometrial defect occurring at the site of a previous uterine incision.[115] These pregnancies all carry the risk of leading to life-threatening complications, including severe haemorrhage, uterine rupture and development of placenta accreta spectrum (PAS) disorders.[115, 117]

Several classification systems exist for caesarean scar pregnancy; this guideline will use two types (I and II).

- A Type I (or endogenic) CSP implants on the scar and progresses towards the cervico-isthmic space or uterine cavity. This type has the potential to result in a viable pregnancy but is high risk.
- A Type II (or exogenic) CSP implants on the scar and progresses towards the bladder and abdominal cavity. This type is more likely to lead to uterine rupture and haemorrhage.

Equity considerations for this chapter

Cervical ectopic pregnancy

There may be geographical challenges to accessing medical or expectant management for women living in rural and remote regions, as frequent monitoring and blood tests are needed. Geographical isolation may also be an issue if medical or expectant management fails and urgent surgical care is needed, leading to an increased risk of maternal morbidity or mortality for those living in remote or very remote areas. Emerging procedures such as operative hysteroscopy and uterine artery embolisation (UAE) (interventional radiology) may need to be performed by specialist medical staff who may not be easy to access outside large centres.

Equity issues related to access to early pregnancy care for First Nations women may result in a decreased likelihood of an ectopic pregnancy being identified early. This may mean an increased risk of an emergency procedure.

In Aotearoa New Zealand, data on ectopic pregnancy are sparse. However, Māori women are at higher risk of maternal death than non-Māori women.[118]

Caesarean scar pregnancy

First Nations women in Australia have a higher rate of caesarean section than non-Indigenous women. This could increase the risk of caesarean scar pregnancy over time. This inequity may be compounded by issues related to access of care.

In Aotearoa New Zealand, Māori women have a lower rate of caesarean section compared to women from European/other ethnic backgrounds. However, equity issues related to access of care remain.

For women who choose to continue with the pregnancy, frequent monitoring will be necessary, and urgent intervention may be required, which may be a concern for those living in rural and remote locations.

Clinical Question 15 – Management of interstitial ectopic pregnancy

What are the benefits and harms of surgical management compared to medical management for interstitial ectopic pregnancy?

P: Pregnant women with suspected cornual/interstitial ectopic pregnancy
I: Surgical management by laparoscopy or open surgery
C: Medical management with methotrexate or other medications, ultrasound-guided injections
O: **Resolution of the cornual/interstitial ectopic pregnancy, needed further treatment, adverse events** (including abnormal blood tests, hair loss, nausea and vomiting), time to return to normal activities, acceptability, satisfaction, long term outcomes such as fertility – time to next pregnancy (have a standdown period post MTX), recurrence of ectopic in future pregnancy

Source of evidence

Two review articles: one of case series, and one of case series and case reports provided the majority of evidence for this clinical question, with additional evidence obtained from a further six case series. [119,120,121-126]

Certainty of evidence

Low GRADE.

Summary of evidence

Interstitial ectopic pregnancy is not the same as cornual ectopic pregnancy, though the terms are often used interchangeably. Whilst an interstitial ectopic pregnancy occurs when the fertilised egg implants within the proximal intramural portion of the fallopian tube, which is within the myometrium, a cornual ectopic pregnancy refers to a pregnancy in a rudimentary horn or within one horn of a septate or uni- or bicornuate uterus.[127, 128]

The evidence for this clinical question was limited to interstitial pregnancy.

Conservative management (expectant and medical)

A case series of clinically stable women reported interstitial pregnancy resolved for:

- 5 out of 7 women offered expectant management (women who had decreasing or plateauing hCG levels)
- 21 out of 23 women treated with local methotrexate
- 4 out of 5 women treated with systemic methotrexate.[121]

This was supported by another case series that reported interstitial pregnancy resolved for 17 out of 19 clinically stable women offered expectant management (women with decreasing or plateauing hCG levels).[122]

Collated data from 9 case series found interstitial pregnancy resolved for 127 out of 148 women (86%) treated with methotrexate, including:

- Local and systemic methotrexate: 85.81% (95% CI 84.17 to 87.45)
- Systemic methotrexate only: 79.98% (95% CI 72.68 to 87.29%)
- Local methotrexate only: 97.83% (95% CI 93.59 to 100%).[119]

No study reported a significant difference between systemic and local methotrexate.

One study reported that methotrexate administered locally may reduce the incidence of side effects, such as constipation, however this study was not limited to use in interstitial pregnancy.[125]

Surgical management

Surgical management of interstitial pregnancy may involve:

1. Laparoscopic cornuostomy/cornuotomy
2. Laparoscopic wedge/cornual resection with ipsilateral salpingectomy

A systematic review of 354 cases of interstitial pregnancy compared women treated with conservative surgery (including cornuostomy, extended salpingostomy, salpingotomy and/or minicornual excision) (N=156) versus radical surgery (including cornual resection and/or salpingectomy) (N=198).[120] The findings are summarised below:

Outcomes	Conservative surgery group	Radical surgery group
Major complications (%)	0%	0.6%
Overall success rate (%)	86.8%	87%
Operating time (mean)	42 mins	71 mins
Hospital stay (mean)	2.7 days	3.8 days
Live birth rates in subsequent pregnancy (%)	62%	48%

Despite a notable difference in operating time, there was no evidence of a statistical difference between groups in any of the reported outcomes (all $p \geq 0.05$).[120]

Two other studies also reported comparable clinical results between cornuostomy/cornuotomy and cornual resection, with one also showing a reduction in operating time, which may be reduced in laparoscopic cornuotomy. [119, 123]

Other considerations

Monitoring β-hCG levels

There was limited data in the included evidence about the timeframe for decreasing hCG level for expectant management for an interstitial ectopic pregnancy. Women who are having expectant management should be made aware that the decline to hCG < 20 IU/L may take at least 4-6 weeks.

Table 9, Clinical Question 15: Management of interstitial pregnancy – benefits, limitations and harms (Table adapted from Brincat et al., 2019[119])

Legend:	Benefit	Limitation

Factors	Treatment options					
	Expectant management	Systemic methotrexate (MTX)	Local methotrexate (MTX)	Laparoscopic wedge resection	Laparoscopic cornuostomy	Open surgical management
Pretreatment criteria	Need to satisfy strict inclusion criteria, as outlined in Recommendation 20)			Suitable for all cases		
Expertise required	No expertise required	Able to be administered by IV or IM	Requires ultrasound expertise	Requires surgical expertise		
Side-effect profile	No side effects; eliminates surgical risks	Risk of transient side effects from MTX, delay in conceiving		Risk of intra-operative and post-operative complications		
Mitigating risk of rupture	Requires 24-hr access to emergency services and is also dependent on availability of anaesthetists, plus clinicians with adequate experience for transfer. No further than 2 hours to specialist surgical facilities		Local MTX requires specialist surgical facilities	Requires specialist surgical facilities		
Place of care	Outpatient care			Requires hospital admission		
Follow up	Requires close and prolonged follow up			Reduced length of follow up		
Success	Success rates estimated to be between 84% and 87%			Success rates estimated to be between 80% to 90%		
Harms	Non-invasive		Minimally invasive			Invasive
Risk in the current pregnancy	Higher risk of rupture of ectopic pregnancy and associated haemorrhage			Lower risk of rupture, risk of intraoperative haemorrhage		
Risk in future pregnancy	Lower risk of uterine rupture in subsequent pregnancy			Higher risk of uterine rupture in subsequent pregnancy		

Limitations in the evidence

Interstitial pregnancy is rare, and it would be impractical to undertake RCTs to investigate how they should be treated. Evidence as to how they are best treated, therefore, has so far been limited to case reports or case series.

Recommendations

Recommendation 25	Evidence-based recommendation
Conditional: For interstitial ectopic pregnancy: Medical management: For women who are clinically stable, medical management with systemic, as outlined in Recommendation 21, or intra-sac methotrexate (under ultrasound guidance) could be offered. Surgical management: If a woman is at high risk of haemorrhage, does not wish to take methotrexate, or there has been a failure of medical or expectant management, then surgical treatment should be offered as follows: 1. Laparoscopic cornuostomy 2. Laparoscopic wedge/cornual resection with ipsilateral salpingectomy **GRADE of evidence:** Low	
Good Practice Statement 19	
Expectant management for interstitial ectopic pregnancy should only be offered to women who are clinically stable with low initial hCG (< 1500 IU/L) and who agree to be monitored until the hCG is < 20 IU/L.	
Good Practice Statement 20	
Cornuostomy may be preferable to cornual resection as it may be less likely to damage the uterus and fallopian tube and may be more likely to preserve fertility.	

Clinical Question 16 – Management of cervical ectopic pregnancy

What are the benefits and harms of surgical management compared to medical management for cervical ectopic pregnancy?

P: Pregnant women with cervical ectopic pregnancy

I: Surgical management: dilation and curettage, dilation and curettage combined with uterine artery embolisation, uterine artery embolisation, hysterectomy, balloon tamponade, other surgical techniques, ultrasound-guided injections of methotrexate and other medications (e.g., potassium chloride)

C: Medical management with methotrexate

O: **Resolution of the cervical ectopic pregnancy, needed further treatment, adverse events** (including abnormal blood tests, hair loss, nausea and vomiting), time to return to normal activities, acceptability, satisfaction, long term outcomes such as fertility: time to next pregnancy (have a standdown period post MTX), recurrence of ectopic in future pregnancy, complications such as hysterectomy, future pregnancy complications

Source of evidence

Case series and case reports informed this clinical question.[129-131]

Certainty of evidence

Low GRADE.

Summary of evidence

Cervical ectopic pregnancy is rare, and the appropriate therapeutic approach is determined from case reports or case series. There is wide variation in administration of treatments.

Early accurate diagnosis is essential in cervical ectopic pregnancy as it can lead to life threatening haemorrhage (due to implantation near the uterine vessels) and potential hysterectomy.

Conservative management (expectant or medical)

A review of 52 cases (reported in 28 case reports or series) of women with cervical ectopic pregnancy, treated with a range of methotrexate protocols, including both local and systemic methotrexate, reported: [132]

- resolution in 61.5% (32 out of 52 women) of all cases treated with methotrexate
- resolution was more likely if the gestational age of the fetus was less than or equal to nine weeks at the time of treatment (OR 6.44, 95% CI 1.46 to 28.52).

A separate prospective case series reported 38 cases of cervical ectopic pregnancy, with all successfully resolved following treatment with local methotrexate.[133]

It is generally accepted that expectant management of cervical ectopic pregnancy should be avoided due to the risk of severe haemorrhage. It has been suggested, however, that expectant management may be appropriate when hCG levels are < 1000 IU/L with levels continuing to fall on follow up.[134]

Surgical management

Dilatation and curettage (D&C) is associated with a risk of severe bleeding during suction evacuation or sharp curettage, and if an option, medical management should instead be offered.

To control bleeding at the time of D&C, the following additional procedures have been reported in case series:

- tamponade with Foley catheter (most common)[135]
- uterine artery embolisation (UAE)[130]
- uterine artery ligation.

An emerging surgical management option is operative hysteroscopy with or without UAE or uterine artery ligation. One paper reported a case series including 27 women: three women were successfully treated with operative hysteroscopy alone; 7 with operative hysteroscopy performed following failure of methotrexate; and 5 cases with operative hysteroscopy in combination with UAE or uterine artery ligation.[136] Additional case reports described successful treatment of 5 women with cervical ectopic pregnancy with operative hysteroscopy and UAE.[131]

One case report described the successful resolution of a case of cervical pregnancy with UAE and methotrexate. This report also discussed UAE having a lower risk of complications compared to more invasive treatments (such as hysterectomy) but carrying risks of infection, injury to healthy tissue and infertility (though the use of UAE may be chosen to help preserve fertility).[137]

Limitations in the evidence

Cervical pregnancy is rare and carries risk of severe haemorrhage, and it would be impractical and unethical to undertake RCTs to investigate how they should be treated. Evidence as to how these pregnancies are best treated, therefore, has so far been limited to case reports or case series.

Recommendations

Recommendation 26	Evidence-based recommendation

Conditional: For cervical ectopic pregnancy:

Women who are clinically stable should be offered medical management with methotrexate either systemically, as outlined in Recommendation 21, or via ultrasound-guided intra-sac injection (depending on local availability).

GRADE of evidence: Low

Good Practice Statement 21

Expectant management of cervical ectopic pregnancy should be avoided due to the risk of severe haemorrhage.

Recommendation 27	Evidence-based recommendation

Conditional: If a woman with cervical ectopic pregnancy is clinically unstable, does not wish to take methotrexate, or there has been a failure of methotrexate treatment, then dilatation and curettage (D&C) may be recommended.

GRADE of evidence: Low

Good Practice Statement 22

The GDG suggests ultrasound guidance if doing a dilatation and curettage (D&C) for a cervical ectopic pregnancy.

Good Practice Statement 23

The GDG suggests for women with cervical ectopic pregnancy, operative hysteroscopy be considered instead of dilatation and curettage (D&C) where facilities and circumstances permit.

Good Practice Statement 24

The GDG suggests to control bleeding in cervical ectopic pregnancy, the following additional procedures to dilatation and curettage (D&C) or operative hysteroscopy may be offered where facilities and circumstances permit:

1. tamponade with Foley catheter
2. uterine artery embolisation
3. uterine artery ligation

Clinical Question 17 – Management of caesarean scar pregnancy

What are the benefits and harms of different treatment options (surgical/medical management) compared to expectant management for caesarean scar pregnancy?

P: Pregnant women with caesarean scar pregnancy

I: Surgical management, uterine arterial embolisation and/or methotrexate, dilation and suction curettage, medical management with methotrexate, hysterectomy, ultrasound guided injections of methotrexate and other medications (e.g., KCl)

C: Any of the above listed interventions/expectant management

O: **Resolution of the caesarean scar pregnancy, needed further treatment, adverse events** (including abnormal blood tests, hair loss, nausea and vomiting), time to return to normal activities, acceptability, satisfaction, long term outcomes such as fertility – time to next pregnancy (have a standdown period post MTX), recurrence of ectopic in future pregnancy, heavy maternal blood loss, complications such as hysterectomy, future pregnancy complications (such as uterine rupture)

Source of evidence

Four systematic reviews, two randomised controlled trials, and three observational studies were identified. [112, 138-140,141-143]

Certainty of evidence

Low GRADE.

Summary of evidence

The evidence for this clinical question considered two types (I and II) for caesarean scar pregnancy (CSP), as defined below:

- A Type I (or endogenic) CSP implants on the scar and progresses towards the cervico-isthmic space or uterine cavity. This type has the potential to result in a viable pregnancy but is high risk.
- A Type II (or exogenic) CSP implants on the scar and progresses towards the bladder and abdominal cavity. This type is more likely to lead to uterine rupture and haemorrhage.

A comparison of birth outcomes between Type I CSP and Type II CSP, reported in a 2017 retrospective study, found Type I CSP had significantly better outcomes than Type II, demonstrated by the following results:[143]

	Type I CSP (n=6)	Type II CSP (n=11)
Placental disorder	17%	100%
Mean gestational age at delivery	38w (37-39)	34w (20-36)
Live birth	100%	91%
Caesarean hysterectomy	17%	100%
Blood transfusion	0%	55%

Several approaches exist for the management of a non-viable CSP, including surgical, medical and expectant management. Use of a combination of approaches was often described in the evidence.

Success rates and complications of different management options for CSP in the first trimester were assessed in a 2024 comparative study, using data from the international caesarean scar pregnancy registry.[141] The evidence reported:

- Surgical excision had the highest success rate at 91.8% [95% CI 83.8 to 99.9], followed by suction evacuation at 91.5% (95% CI 87.8-95.2)
- Local MTX or potassium chloride injection had a success rate of 74.5% (95% CI 64.1 to 85.1), compared to 59.4% for systemic MTX (95% CI 48.4 to 70.4).

Surgical management

Surgical management approaches reported in the evidence included hysteroscopic, vaginal, laparoscopic, and open resection of CSP, often performed in combination or with adjuvant medical or vascular techniques.

A 2023 systematic review of observational studies reported the following success rates of various surgical interventions (inclusive of studies where surgical intervention was the sole procedure or used in combination with another approach. Certainty of evidence: Low):[140]

	Success rates	Adverse events
Hysteroscopic removal of CSP	62% to 100%	Haemorrhage (10%) Retained trophoblastic tissue (7%) Uterine rupture (2.6%) Hysterectomy (< 1%)
Vaginal removal of CSP	97% to 100%	< 5%
Laparoscopic resection	90% to 100%	Varied One study reports transfusion rate (43%)
Laparotomy and CSP removal	91% to 100%	Haemorrhage (10%) Transfusion (24%) Bladder injury (2%)

Several studies were identified that considered surgical management of CSP in combination with another treatment.

A Cochrane systematic review on suction curettage under hysteroscopy compared with suction curettage under ultrasound guidance after UAE or uterine artery chemoembolisation (UACE), reported little or no difference in:

- treatment success (RR 0.91, 95% CI 0.81 to 1.03) after UAE, RR 1.02, 95% CI 0.96 to 1.09) after UACE. Certainty of evidence: Low
- complications (RR 0.18, 95% CI 0.01-3.72) after UACE, low certainty). Very low certainty after UAE (RR 4.00, 95% CI 0.47-33.9).[112]

A randomised controlled trial compared hysteroscopic resection of CSP with dilatation and evacuation (D&E), in 54 women with CSP of < 9 weeks' gestation, a myometrial layer thickness > 1 mm, and who had received two to three doses of intramuscular MTX (prior to surgery). This study reported that hysteroscopic resection may increase treatment success/resolution rate compared to D&E (RR 1.22, 95% CI 1.01 to 1.48). Certainty of evidence: Low.[144]

A systematic review of 37 non-randomised studies reported a success rate with UAE of 93.4% (95% CI 91.8 to 95.1). Severe complications were reported in 1.3% (95% CI 0.8 to 1.8). Certainty of evidence: Low.[139]

Success of surgical management between Type I and Type II CSP was reported in a retrospective study including 27 women with Type I CSP and 44 women with Type II CSP. Success rate of surgical intervention by type were as follows (Certainty of evidence: Low):[142]

	Type I CSP (n=27)	Type II CSP (n=44)
Uterine curettage (D&C)	95%	27%
UAE with curettage	100%	67%
Hysteroscopy + laparoscopy	100%	95%

Medical management

In a randomised controlled trial, 104 women with CSP were managed with either local or systemic MTX.[145] No difference was found in the success rate, but a shorter time to hCG remission and resolution of the uterine mass was noted in the systemic MTX group. Certainty of evidence: Low.[145] The mean (± standard deviation) pretreatment hCG levels were 35,472±28,263 for local injection and 22,532±19,547 for systematic administration. Success was more likely in both groups in participants with hCG levels < 20,000 IU/L and lesion size < 30 mm.[145] Outcomes from the study are presented below:

	Local MTX	Systemic MTX	P value
Success rate	36.5%	38.5%	
Delayed cure (additional D&C after uterine artery embolisation needed when ultrasound or hCG did not become normal within 60 days)	32.7%	28.8%	
Overall cure rate (complete + delayed)	69.2%	67.3%	0.232
Mean time for hCG remission (days)	56 (24-92)	42 (21-69)	0.029
Mean time for uterine mass disappearance (days)	53 (23-88)	40 (20-67)	0.046

Two studies were identified that compared medical management with surgical intervention.

A 2020 Cochrane review reported that UAE, compared to systemic MTX, may have little or no difference on:

- treatment success (RR 1.00, 95% CI 0.90 to 1.12)
- risk of complications (RR 0.47, 95% CI 0.13 to 1.75)
- risk of adverse events (RR 1.58, 95% CI 0.41 to 6.11)

Certainty of evidence: Low for all outcomes.[112]

However, it was reported that blood loss was lower with UAE compared to systemic MTX (MD -378.70 ml lower [95% CI -401.43 to -355.97). Certainty of evidence: Low.[112]

The Cochrane review also looked at UACE plus MTX compared to systemic MTX; and reported that, compared to systemic MTX, UACE plus MTX may have little or no impact on:

- treatment success (RR 0.87, 95% CI 0.54 to 1.38)
- risk of complications (RR 0.62, 95% CI 0.26 to 1.48)
- risk of adverse events (RR 1.16, 95% CI 0.32 to 4.24).

Certainty of evidence: Low for all outcomes.[112]

However, UACE may decrease blood loss compared to systemic MTX (MD -879 lower, 95% CI -1135.23 to to622.77). Certainty of evidence: Low.[112]

Expectant management

One systematic review was identified on expectant management of CSP, which included 52 women with a CSP with embryonic activity and 17 women with a CSP without embryonic activity. The following outcomes were reported (Certainty of evidence: Low):[138]

	Embryonic activity (n=52)	No embryonic activity (n=17)
Uncomplicated miscarriage	13%	69%
Complicated miscarriage (required surgical or medical treatment)	20%	26%
Hysterectomy	61%	0%
Uterine rupture during third trimester	10%	13%
Third trimester pregnancy	77%	0%
Live birth	100%	
Severe bleeding	39%	
Abnormal implantation of the placenta	75%	
Placenta percreta	70%	

Other considerations

Diagnosis

The diagnosis of a caesarean scar pregnancy relies on ultrasound features. The features suggestive of a caesarean scar pregnancy, as reported in case series, include one or several of the below:

- empty uterine cavity and endocervix
- placenta and/or gestational sac or solid mass of trophoblast located anteriorly at the level of the internal os, embedded at the site of the previous lower uterine segment caesarean section scar
- a triangular (at < 8 weeks' gestation) or rounded or oval (at > 8 weeks' gestation) gestational sac that fills the scar "niche"
- thin or absent layer of myometrium between the gestational sac and the bladder
- evidence of prominent trophoblastic/placental circulation on Doppler examination
- empty endocervical canal.[146]

Limitations in the evidence

Most studies use combination therapy, which makes comparison difficult, as combinations vary widely from one study to another.

Treatment options and risk profile also vary between type I and type II pregnancies.

No studies tested the upper limits for hCG levels for systemic and local administration but the evidence suggested an upper limit <20,000 IU/L.[145]

Table 10, Clinical Question 17: Management of caesarean scar pregnancy – benefits, limitations and harms

Legend:	Benefit	Limitation

<table>
<tr><th rowspan="2">Factors</th><th colspan="8">Treatment options</th></tr>
<tr><td>Expectant Management (exclude ongoing pregnancy)</td><td>Systemic methotrexate (MTX)</td><td>Local methotrexate (MTX)</td><td>D&C</td><td>Suction evacuation</td><td>UAE</td><td colspan="2">Surgical resection/excision</td></tr>
<tr><td>Pre-treatment criteria</td><td colspan="3">Need to satisfy strict inclusion criteria – clinically stable, no fetal heart activity, and with hCG < 20,000 IU/L and mass < 30 mm for MTX management</td><td colspan="3">Suitability may depend on the type of scar</td><td colspan="2">Suitable for all cases</td></tr>
<tr><td>Expertise required</td><td colspan="2">No specific expertise required, but close monitoring is needed</td><td>Requires ultrasound expertise</td><td colspan="5">Requires surgical expertise</td></tr>
<tr><td>Side-effect profile</td><td>No side effects, eliminates surgical risks</td><td colspan="2">Risk of transient side effects from MTX</td><td colspan="5">Risk of intra-operative and post-operative complications</td></tr>
<tr><td>Mitigating risk of rupture</td><td colspan="3">Requires 24-hr availability of anaesthetists, plus clinicians with adequate surgical experience</td><td colspan="5">Requires specialist surgical facilities</td></tr>
<tr><td>Place of care</td><td colspan="3">Outpatient care</td><td colspan="2">May be performed as a day case</td><td colspan="3">Requires hospital admission</td></tr>
<tr><td>Follow up</td><td>Prolonged follow up</td><td>Shorter remission compared to local MTX</td><td>Slower remission compared to systemic MTX</td><td colspan="5">Reduced length of follow up</td></tr>
<tr><td rowspan="2">Success</td><td rowspan="2">69% uncomplicated miscarriage</td><td colspan="2" rowspan="2">Success rate 35-40%</td><td>95% for type I</td><td rowspan="2">91.5%
(no data per type of scar)</td><td>100% for type I</td><td colspan="2">100% for type I</td></tr>
<tr><td>27% for type II</td><td>67% for type II</td><td colspan="2">95% for type II</td></tr>
<tr><td>Harms</td><td>Failure of expectant management: complicated miscarriage, requires surgical or medical intervention

Risk of uterine rupture</td><td colspan="2">Failure of medical management - requires surgery
Risk of haemorrhage, MTX toxicity, sepsis, retained product, gestational trophoblastic neoplasia</td><td>Risk of haemorrhage, Asherman</td><td>Risk of haemorrhage, uterine perforation, Asherman</td><td>Risk of haemorrhage, retained product, thrombosis, sepsis, bladder injury, Asherman</td><td>Risk of haemorrhage, uterine ischemia, hysterectomy</td><td colspan="2">Risk of haemorrhage, sepsis, Asherman, broad ligament haematoma</td></tr>
</table>

Recommendations

Recommendation 28	Evidence-based recommendation

Conditional: Women presenting with caesarean scar pregnancies (CSP) are recommended to have counselling that these pregnancies are high risk, associated with a high likelihood of miscarriage, placenta accreta spectrum, preterm birth, haemorrhage, uterine rupture, hysterectomy, perinatal death and maternal death. There may be differences in pregnancy outcomes with type I and type II caesarean scar pregnancies, which need to be discussed.

GRADE of evidence: Low

Good Practice Statement 25

The GDG suggests that women with type I caesarean scar pregnancy who choose to continue the pregnancy should be advised that they will require multidisciplinary care with access to a tertiary hospital. [x]

Recommendation 29	Evidence-based recommendation

Conditional: In the absence of embryonic activity and if the woman meets the criteria for expectant management of caesarean scar pregnancy (see Recommendation 20), expectant management may be an option, provided the woman is aware of the associated risks.

GRADE of evidence: Low

Recommendation 30	Evidence-based recommendation

Conditional: Women who are clinically stable may be offered medical management of caesarean scar pregnancy with methotrexate, either systemically (intramuscular injection) or via intra-sac injection (with or without potassium). If choosing systemic methotrexate, two doses (4 to 7 days apart) should be given. Decisions about further doses should be made in line with local protocols or as clinically indicated.

GRADE of evidence: Low

Recommendation 31	Evidence-based recommendation

Conditional: When surgical management is required (see Good Practice Statement 13), treatment options should be guided by the type of caesarean scar pregnancy (CSP).

- Type I CSP surgical options include dilatation and curettage (D&C) (with or without balloon tamponade) and uterine artery embolisation
- Type II CSP may be better treated via hysteroscopic and laparoscopic resection, or methotrexate followed by hysteroscopic resection.

GRADE of evidence: Low

[x] See Good Practice Point (GPP) 2 in the RANZCOG Placenta Accreta Spectrum (PAS) Clinical Guideline (C-Obs 20) for multidisciplinary team (MDT) details.

Part 5 – Rh D immunoglobulin (anti-D)

Introduction

Rh D immunoglobulin has been available in Australia since 1967. Prior to this, the incidence of Rh D alloimmunisation in Rh D negative women following two births of Rh D positive, ABO-compatible infants was approximately 16 per cent, and haemolytic disease of the newborn (HDFN) due to anti-D was a significant cause of morbidity and mortality. Following routine postpartum administration of Rh D Ig to all Rh D negative women, the rate of alloimmunisation dropped to approximately 2 per cent. A further reduction in the sensitisation rate to about 0.2 per cent was achieved by introducing routine mid and third trimester antenatal prophylaxis in 2002.

This clinical question considers the evidence for anti-D administration in threatened, medically or surgically managed miscarriage, and ectopic pregnancy.

Equity considerations for this chapter

Anti-D immunoglobulin is widely available across Australia and Aotearoa New Zealand currently and is routinely used later in pregnancy and during the postnatal period. Some evidence from the early 2000s suggests that anti-D is less frequently discussed in ED and GP settings than by health professionals who specialise in providing pregnancy care (midwives, GP obstetricians, O&G clinicians etc.), however, no newer publications on these rates were identified.[147, 148] First Nations women, and Māori women, are more likely to book with a maternity care provider after the first trimester according to national maternity clinical indicator statistics, so may be more likely to receive care for early pregnancy bleeding from ED or a GP.[118, 149] Continued education for healthcare providers regarding when anti-D administration is recommended, and clarity and consistency in guidelines, may help to address any equity issues. Although anti-D requires cold storage in a refrigerator, cold chain mechanisms and protocols to manage safe storage and handling of medications and vaccinations, including those used in antenatal and postpartum care, already exist and are widely implemented in both countries.

Clinical Question 18 – Anti-D rhesus prophylaxis

What are the benefits and harms of anti-D rhesus prophylaxis for women with a positive pregnancy test and vaginal bleeding, miscarriage or ectopic pregnancy up to 12 weeks?

P: Pregnant women up to 12 weeks with a positive pregnancy test and vaginal bleeding, miscarriage and ectopic pregnancy

I: Anti-D rhesus prophylaxis

C: Placebo, no intervention

O: Rhesus sensitisation

Rhesus sensitisation

It has been reported that as little as 0.1 mL of Rh D positive blood is required to cause sensitisation.[150] The total fetoplacental blood volume of a 12-week pregnancy is 3 mL, approximately 1.5 mL of which is fetal red cells.[151] The average volume of fetal red cells (RBCs) in maternal circulation at 8 weeks of pregnancy has been calculated to be 0.33 mL.[152] Studies have shown that fetal RBCs can be detected in the circulation of up to 32% of women after miscarriage; in 26% of these patients, the volume of fetomaternal haemorrhage (FMH) was 0.05 mL or more.[153] However, the overall risk of developing Rh D sensitisation after miscarriage or abortion in the absence of anti-D administration is estimated to be between 3% and 6%.[154, 155] The risk of sensitisation likely increases when there is a greater likelihood of maternal tissues being exposed to fetal blood; surgical intervention in miscarriage or ectopic pregnancy greatly increases the risk of this happening.

Source of evidence

One Cochrane review, one randomised controlled trial, three cohort studies and one case-control study were included as evidence for this clinical question. Additional data from the Serious Hazards of Transfusion (SHOT) database in the UK provided context for the prevalence of Rh D sensitisation.

Certainty of evidence

Very low GRADE.

Summary of evidence

Threatened miscarriage

A single case-control study of women with threatened miscarriage (1995-2001) reports little to no difference in anti-D antibody seroconversion during pregnancy between women with symptoms of a threatened miscarriage compared to those without symptoms (OR 3.7, 95% CI 0.6 to 32.2). Certainty of evidence: Very Low.[156]

Spontaneous, medical or surgical management of miscarriage

Historic evidence from two small RCTs and a cohort study indicate a possible benefit of Rh immunoglobulin in preventing Rh sensitisation, however it is likely they lack the statistical power to detect a difference between treated and untreated groups for this rare outcome.

In the first RCT, Rh D negative women who had a miscarriage between 8-24 weeks' gestation received 1500 IU Anti-D immunoglobulin or 1 mL of a placebo within 72 hours of the miscarriage.[157] No instances of Rh D sensitisation (a positive Kleihauer Betke test) were observed in the study after 2 years of follow up.

The second RCT included women having a range of treatments for miscarriage, including expectant management, D&C, suction curettage, and hysterotomy between 4 and 20 weeks' gestation.[158] One case of ectopic pregnancy was included in the placebo group. No women in the anti-D group and 2 women in the placebo group were sensitized. Both sensitisation events occurred after abortion rather than miscarriage.

The cohort study considered a smaller dose of anti-D (1000 IU) for women who had a miscarriage or therapeutic abortion in the first and second trimester, compared to no treatment (gestational age was not specified).[159] No cases of Rh D sensitisation were identified at 6 months' follow up in the treated group. Five cases of sensitisation were identified in the untreated group, 2 of which were from miscarriages (1 in the first trimester, and 1 in the second trimester).

Ectopic pregnancy

There was insufficient evidence identified to determine the efficacy of anti-D in preventing sensitisation for Rh D negative women with an ectopic pregnancy.

A single small cohort study from South Africa was the only study identified looking at Rh D sensitisation in women with ectopic pregnancy.[160] This study provides only indirect evidence as it did not include anti-D administration, but did report that the volume of fetal cells in the maternal circulation following surgery for ruptured ectopic pregnancy (gestational age between 6 and 10 weeks) is sufficient to cause sensitisation in approximately 25% of women.

In summary, limited evidence exists for the effectiveness of anti-D in preventing Rh D sensitisation in miscarriage, threatened miscarriage, or ectopic pregnancy in the first trimester. Insufficient evidence was identified to

determine the efficacy of anti-D in preventing sensitisation for Rh D negative women with a miscarriage at less than 10 weeks, or an unruptured ectopic pregnancy.

Other considerations

Side effects and adverse reactions

Anti-D is a blood product that contains small amounts of globulins, including IgA, which may cause hypersensitivity reactions. Adverse reactions associated with administration of Rh D immunoglobulin are rare, however anti-D should be administered in a clinical setting capable of treating such reactions if they arise.

Product shortages

The availability of anti-D is dependent on supply from plasma donors, and this is not always guaranteed. Efforts to ensure continuity of sufficient supply should be undertaken by responsible government bodies in both countries. If shortages occur, potential disruptions to supply should be clearly communicated to clinicians and health services in a timely manner. RANZCOG continues to work with government and regulatory stakeholders to reduce the impact of potential shortages of critical medicines and products used in obstetrics and gynaecology, including Rh D immunoglobulin.[161]

Dosage of anti-D immunoglobulin required in the first trimester

No evidence was identified, on which to base a recommendation for anti-D dosage. An RCT comparing two doses of anti-D after first trimester abortion (300 µg (1500 IU) vs 50 µg (250 IU)) was conducted by Keith & Bozorgi (1977), however, no cases of Rh D sensitisation were reported in either group, limiting the conclusions able to be drawn from this study.[162]

In early pregnancy, the amount of fetomaternal haemorrhage is likely to be low; therefore, a dose of 250 IU before 12 weeks and 625 IU after 12 weeks is generally recommended by most national guidelines. Testing to determine the size of fetomaternal haemorrhage is not thought to be required, may cause delays in anti-D administration and may increase the risk of sensitisation whilst awaiting results.

National surveillance data

In a comparison of Rh alloimmunisation rates in Canada and the Netherlands, which have different policies regarding anti-D administration for miscarriage and abortion, the authors concluded that clinically significant perinatal antibodies do not occur at a rate that is significantly higher in the Netherlands than in Canada, despite a higher rate of Rh negativity in the Netherlands (14.5% compared to 13.0%) and far less frequent anti-D immunoglobulin administration.[163]

The UK Serious Hazards of Transfusion (SHOT) database has monitored and reported on Rh D sensitisation events since 2013. Based on an estimated 100,000 miscarriages among Rh D negative women since the SHOT database began (approximately 600,000 births per year in UK, estimated 10% prevalence of Rh D negative blood types, and 20% miscarriage rate) we estimate that 0.024% of pregnancies may have been sensitised due a first trimester miscarriage. This equates to approximately one in 4,167 women. This may reflect the policy of anti-D administration being effective in preventing sensitisation, however only in one of the 24 cases where a miscarriage may have been the sensitising event was anti-D given (although a large proportion lack information on whether or not anti-D was given).

Table 11, Clinical Question 18: Serious Hazards of Transfusion (SHOT) database - annual reports on Rh D sensitisation and cumulative tally since 2013

	New in 2022	New in 2023	Cumulative since 2013
New sensitisations	36	35	393
Sensitisation found in 1st trimester	13	16	159
Potentially sensitizing event in preceding pregnancy related to first trimester miscarriage or ectopic pregnancy	5 miscarriages ((1 at 6 weeks, 3 unknown, 1 surgical management at 9 weeks)	1 miscarriage (at 6 weeks without anti-D given)	24 miscarriages (7 at 8 weeks or less, 7 between 8-12 weeks)

The Serious Transfusion Incident Reporting system (STIR) in Victoria, Australia, reported one case of Rh D sensitisation in its 2021/22 annual report (the first year this data was reported) - this was a case of a woman with a molar pregnancy who did not receive any anti-D.

No national surveillance programme for anti-D sensitisation events exists in Aotearoa New Zealand (only anti-D administration error reporting is collected).

Limitations in the evidence

In theory, the documented quantity of fetomaternal haemorrhage in first trimester miscarriage and ectopic pregnancy meets the minimum amount required to cause sensitisation, however, no study has been undertaken that is able to clinically demonstrate this relationship. Additionally, no studies report the incidence of haemolytic disease in the newborn, the consequence of Rh D sensitisation, as an outcome.

Recommendations

Good Practice Statement 26

For non-sensitised women with Rh D negative blood group who have experienced threatened miscarriage or miscarriage before 10 weeks' gestation, there is insufficient evidence to determine if routine Rh D testing followed by anti-D immunoglobulin (if indicated) reduces the risk of sensitisation and is no longer recommended.

Good Practice Statement 27

For ectopic pregnancy that is surgically managed the GDG recommends anti-D immunoglobulin be offered to women with Rh D negative blood group.

Good Practice Statement 28

For ectopic pregnancy that is medically or expectantly managed, there is insufficient evidence to determine if anti-D immunoglobulin reduces the risk of sensitisation, therefore anti-D could be considered after informed discussion with women with Rh D negative blood group.

Good Practice Statement 29

A dose of 250 IU of anti-D immunoglobulin is sufficient for a singleton pregnancy up to 12 weeks; beyond 12 weeks' gestation 625 IU should be used.

6 Legal and ethical implications

As of 2021, compassionate and bereavement leave for employees who have a miscarriage, or for their spouse or de facto partner, is a legally protected entitlement under national law in both Australia (Fair Work Act 2009) and Aotearoa New Zealand (Bereavement Leave for Miscarriage) Amendment Act 2021).

This guideline provides evidence-based recommendations and advice to guide best practice, however we acknowledge that a person's ability to access timely care and a full range of management and treatment options following a miscarriage or ectopic pregnancy may be affected by factors such as socioeconomic status, cultural and linguistic factors, and geographical location.

Informed consent should be used according to established practice by the Australian Medical Council and the New Zealand Medical Council.

7 Recommendations for future research

- Where care is provided and by who (e.g., early pregnancy assessment service)
- Women's experiences using ED services rather than maternity services for acute early pregnancy complications
- Medical management of miscarriage: preparation for, best analgesia to treat pain, women's experiences
- Early pregnancy outcomes (included miscarriage and ectopic pregnancy) associated with women who have endometriosis
- Intrauterine adhesions (IUAs): incidence following uterine instrumentation, impact and treatment options
- Late miscarriage (pregnancy loss between 13 and 20 weeks) studies to test the effectiveness, safety, and acceptability of medical and surgical management, and options for pain management
- The role of screening for ANA, sperm DNA fragmentation and B2GP1 antibodies in women with recurrent miscarriage
- Evaluating the best thresholds for diagnosing subclinical hypothyroidism.

8 Implementation

A series of flowcharts that offer simplified visual aids for the management of miscarriage and ectopic pregnancy may be useful in clinical practice and are provided in Appendix F. RANZCOG thanks Clinical Excellence Queensland for permission to adapt these resources for the purposes of this clinical guideline.

Information relevant to and written for a consumer/community member audience is not covered in this guideline. RANZCOG patient resources *Asherman Syndrome*, *Ectopic Pregnancy*, and *Miscarriage* have been updated in line with the (C-Gyn 38) guideline.

9 Links to relevant resources

Links provided in the body of the guideline are collated here. Where guidance from individual hospitals has been cited, this has been done as it was the best available evidence provided to the Guideline Development Group and has been reviewed by the entire group. This list should not be implied as RANZCOG endorsement of the material.

Source	Name of resource and hyperlink
Bears of Hope	Bears of Hope
Miscarriage Australia	Miscarriage Australia - Navigating miscarriage together
National Blood Authority Australia	Guideline for the prophylactic use of Rh D immunoglobulin in pregnancy care
New Zealand Blood Service	Use of Rh D Immunoglobulin (Anti-D Immunoglobulin) During Pregnancy and the Post Partum Period (111G130)
Pink Elephants Support Network	The Pink Elephants Support Network - Home
Red Nose Foundation	Home | Red Nose Australia
Sands New Zealand	Sands New Zealand - Pregnancy, Baby and Infant Loss Support, New Zealand
Tommy's National Centre for Maternity Improvement UK	Tommy's Miscarriage Support Tool
Whetūrangitia – online service supporting bereaved parents and whānau in Aotearoa New Zealand	Information for bereaved family and whānau experiencing the death of a baby or child | Whetūrangitia

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11 Appendices

Appendix A: Guideline Development Group membership

Name	Position on GDG
Dr Kasia Siwicki	Chair
Dr Ashleigh Smith	Member
Prof Thierry Vancaillie	Member
Dr Lisa Bedson	Member
Dr Nicole Liesis	Member, Diplomat (DRANZCOG)
Dr Letitia McGinness	Member
Dr Julia Coffey	Member
Dr Sam Holford	Member
Dr Shelley Reilly	Member
Dr Joanne Ludlow	Member
Ms Nicole Freeman	Member, Midwifery Representative, Australia
Ms Alison Weatherstone	Member, Midwifery Representative, Australia
Ms Tessa Kowaliw	Member, Consumer Representative
Research & Policy Team	
Professor Cindy Farquhar, University of Auckland	Dean of Research and Policy, RANZCOG
Ms Katie Coulthard, RANZCOG	Research and Policy Lead
Dr Jasmine Schipp, RANZCOG	Research and Policy Senior Coordinator
Ms Angela Hunter, RANZCOG	Research and Policy Senior Coordinator
Research Evidence Team (University of Auckland)	
Professor Cindy Farquhar, University of Auckland	Dean of Research and Policy, RANZCOG and University of Auckland
Dr Karyn Anderson	Research Fellow
Dr Magdalena Bofill	Research Fellow
Dr Angela Beros	Research Fellow
Ms Solène Bertrand	Research Assistant

Appendix B: Women's Health Committee membership

Name	Position
Associate Professor Scott White	Chair
Dr Anna Clare	Deputy Chair (Gynaecology) and Councillor
Professor Amanda Henry	Deputy Chair (Obstetrics) and Councillor
Dr Samantha Scherman	Member and Councillor
Dr Marilla Druitt	Member and Councillor
Dr Kasia Siwicki	Member and Councillor
Associate Professor Jared Watts	Member and Councillor
Dr Victoria Carson	FRANZCOG/DDU representative
Dr Nisha Khot	Vice President, Specialist International Medical Graduate (SIMG) Representative
Dr Marilyn Clarke	First Nations Women's Health Committee Representative
Dr Angela Beard	He Hono Wāhine Representative
Dr Martina Mende	DRANZCOG Representative
Dr Pallavi Desai	SIMG Representative
Professor Kirsten Black	Sexual and Reproductive Health Committee Representative
Dr Frank Clark	State Representative- TAS
Dr Elizabeth Gallagher	Territory Representative- ACT
Dr James Brown	State Representative- NSW
Dr Kathy Saba	State Representative- QLD
Dr Divya Viswanathan	Trainee Representative
Ms Adrienne Priday	Midwifery Representative, Aotearoa New Zealand
Dr Angela Brown	Midwifery Representative, Australia
Ms Leigh Toomey	Community Representative
Ms Emma Preece-Boyd	Community Representative
Dr Steve Resnick	Co-opted member (Neonatologist)

Appendix C: Overview of the development and review process for this guideline

i. Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of RANZCOG Women's Health Committee or working groups.

A declaration of interest form specific to guidelines and statements was approved by the RANZCOG Board in September 2012. All members of the Guideline Development Group and Women's Health Committee were required to declare their relevant interests in writing on this form prior to participating in the review of this guideline.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this guideline. The following interests were disclosed. Members provided consent for any relevant information to be published, in the interests of integrity and transparency.

Name	Disclosure
Dr Kasia Siwicki	Previous guideline development- NT Health/Alice Springs Hospital Early Pregnancy Bleeding Referral and Management Guideline
Dr Lisa Bedson	Employment - Repromed. Ownership- shares in Monash IVF. Previous guideline development - International Guidelines for assessment and management of PCOS 2023 and the Australian Adaptation of ESHRE guidelines for Unexplained Infertility
Dr Sam Holford	Previous guideline development - Middlemore Hospital local guidelines for Early Pregnancy Assessment Clinic; Methotrexate for management of ectopic pregnancy; and Mid-trimester termination of pregnancy.
Dr Ashleigh Smith	Other - Host of 'The Glimmer Project' podcast.
Ms Nicole Freeman	Previous guideline development - EPAS services at KEMH WNHS, Perth WA Other - Recipient of Future Health Research and Innovation Fund (FHRI) Curtin University Clinician Researcher Training (CRT) Scholarship (PhD student). Additional research involvement in early pregnancy care research related to role and scope of midwives in Australia.
Ms Tessa Kowaliw	Consultancy - Provision of consulting services as consumer advisor.

ii. Steps in developing and updating this guideline.

This guideline was developed between February and November 2024 by the Miscarriage, Recurrent Miscarriage and Ectopic Pregnancy Guideline Development Group, a working group established by the Women's Health Committee. It was most recently reviewed by the Women's Health Committee in February 2025. The Women's Health Committee carried out the following steps in reviewing this guideline:

- Structured clinical questions were developed and agreed upon.

- An updated literature search to answer the clinical questions was undertaken by the research team at the University of Auckland.
- Evidence was presented to guideline development group members, quality appraisal using the GRADE methodology conducted and recommendations developed (as set out in the Methodology section).
- The Research and Policy Team and Guideline Development Group developed a draft guideline, for review by the Women's Health Committee.
- The draft guideline underwent targeted stakeholder consultation.
- The final guideline published by RANZCOG was approved by the Women's Health Committee and Council respectively.

iii. Developing recommendations using GRADE methodology

The relevant GRADE assessments for each recommendation are presented within the online platform used to structure the clinical guideline (MAGICapp; https://magicevidence.org/magicapp/).

Appendix D: Full disclaimer

10.1 Purpose

This guideline has been developed to provide general advice to practitioners about women's health issues concerning Miscarriage, Recurrent Miscarriage and Ectopic Pregnancy and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any person. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual person and the particular circumstances of each case.

10.2 Quality of information

The information available in this guideline is intended as a guide and provided for information purposes only. The information is based on the Australian/New Zealand context using the best available evidence and information at the time of preparation. While the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) has endeavoured to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available. The use of this information is entirely at your own risk and responsibility.

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10.3 Third-party sites

Any information linked in this guideline is provided for the user's convenience and does not constitute an endorsement or a recommendation or indicate a commitment to a particular course of action of this information, material, or content unless specifically stated otherwise.

RANZCOG disclaims, to the maximum extent permitted by law any responsibility and all liability (including without limitation, liability in negligence) to you or any third party for inaccurate, out of context, incomplete or unavailable information contained on the third-party website, or for whether the information contained on those websites is suitable for your needs or the needs of any third party for all expenses, losses, damages and costs incurred.

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The College disclaims, to the maximum extent permitted by law, all responsibility and all liability (including without limitation, liability in negligence) to you or any third party for any loss or damage which may result from your or any third party's use of or reliance of this statement, including the materials within or referred to throughout this document being in any way inaccurate, out of context, incomplete or unavailable for all expenses, losses, damages, and costs incurred.

10.5 Exclusion of warranties

To the maximum extent permitted by law, RANZCOG makes no representation, endorsement or warranty of any kind, expressed or implied in relation to the materials within or referred to throughout this statement being in any way inaccurate, out of context, incomplete or unavailable for all expenses, losses, damages and costs incurred.

These terms and conditions will be constructed according to and are governed by the laws of Victoria, Australia.

Appendix E: Definitions

Term	Interpretation/Definition
Antibiotic prophylaxis	The administration of antibiotics before infection has occurred
Anti-D (Rh D immunoglobulin)	A medication to prevent Rh D sensitisation in women who are Rh D negative
Buccal (medication administration route)	Medication is placed between the gum and the inner cheek. This allows the medication to enter the blood stream from the mucous membrane in the mouth
Dilatation and curettage (D&C)	Dilatation of the cervix using surgical dilators and removal of pregnancy tissue using a surgical curette. D&C is usually used before 14 weeks
GDG	Guideline Development Group
hCG	Human chorionic gonadotropin
HDFN	Haemolytic disease of the fetus and newborn
IgG	Immunoglobulin G
IgM	Immunoglobulin M
Informed consent	A person's decision, given voluntarily, to agree to a healthcare treatment, procedure or other intervention that is made, following the provision of accurate and relevant information about the healthcare intervention, the risks involved, and alternative treatments available
NICE	The National Institute for Health and Care Excellence (United Kingdom)
Pregnancy tissue	Tissue produced by the union of an egg and a sperm (may also be referred to as products of conception, POC)

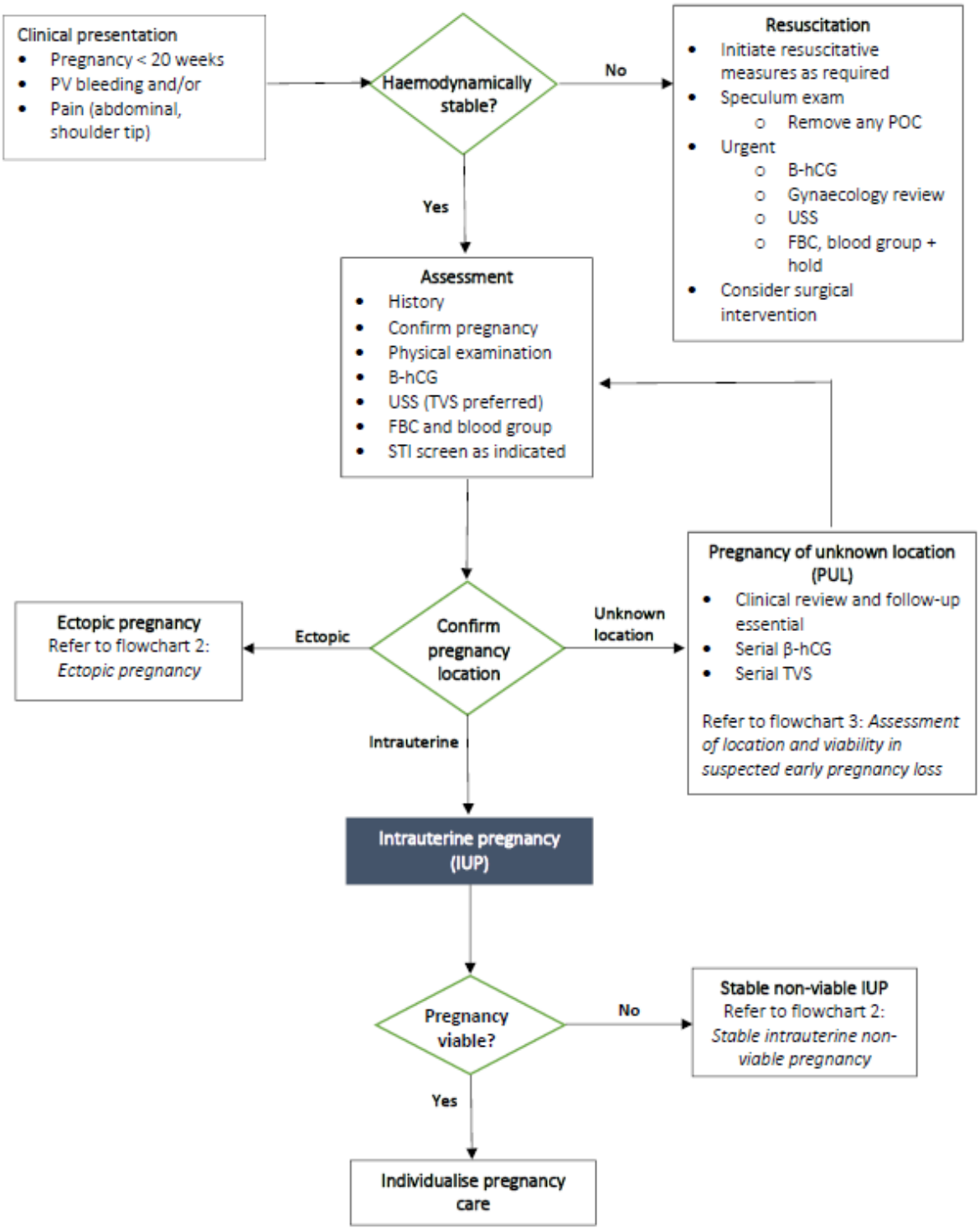
Primary Recurrent Pregnancy Loss	Recurrent pregnancy losses in a woman who has never given birth to a live infant
RCOG	Royal College of Obstetricians and Gynaecologists (United Kingdom)
RCT	Randomised controlled trial
Rh D status	Whether someone is Rh D positive or Rh D negative, determined by the presence of the rhesus D (Rh D) antigen in their blood cells
RPL	Recurrent Pregnancy Loss
Standard deviation	A measure of how dispersed the data is in relation to the mean.
Sublingual (medication administration route)	Medication is placed under the tongue to dissolve and absorb into the blood through the tissue
Systematic review	A study design that attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.
Trimester	The 3-month periods of time in pregnancy. They are referred to as first, second, or third. For the purpose of this guideline the first trimester was up to 14 weeks pregnant, and second trimester was from 14 weeks pregnant.
TSH	Thyroid-Stimulating Hormone
T4	Thyroxine
UACE	Uterine artery chemoembolisation
UAE	Uterine artery embolisation
WHO	World Health Organization

Appendix F: Flowcharts for key aspects of clinical care in miscarriage

Flowchart 1: Early pregnancy loss assessment

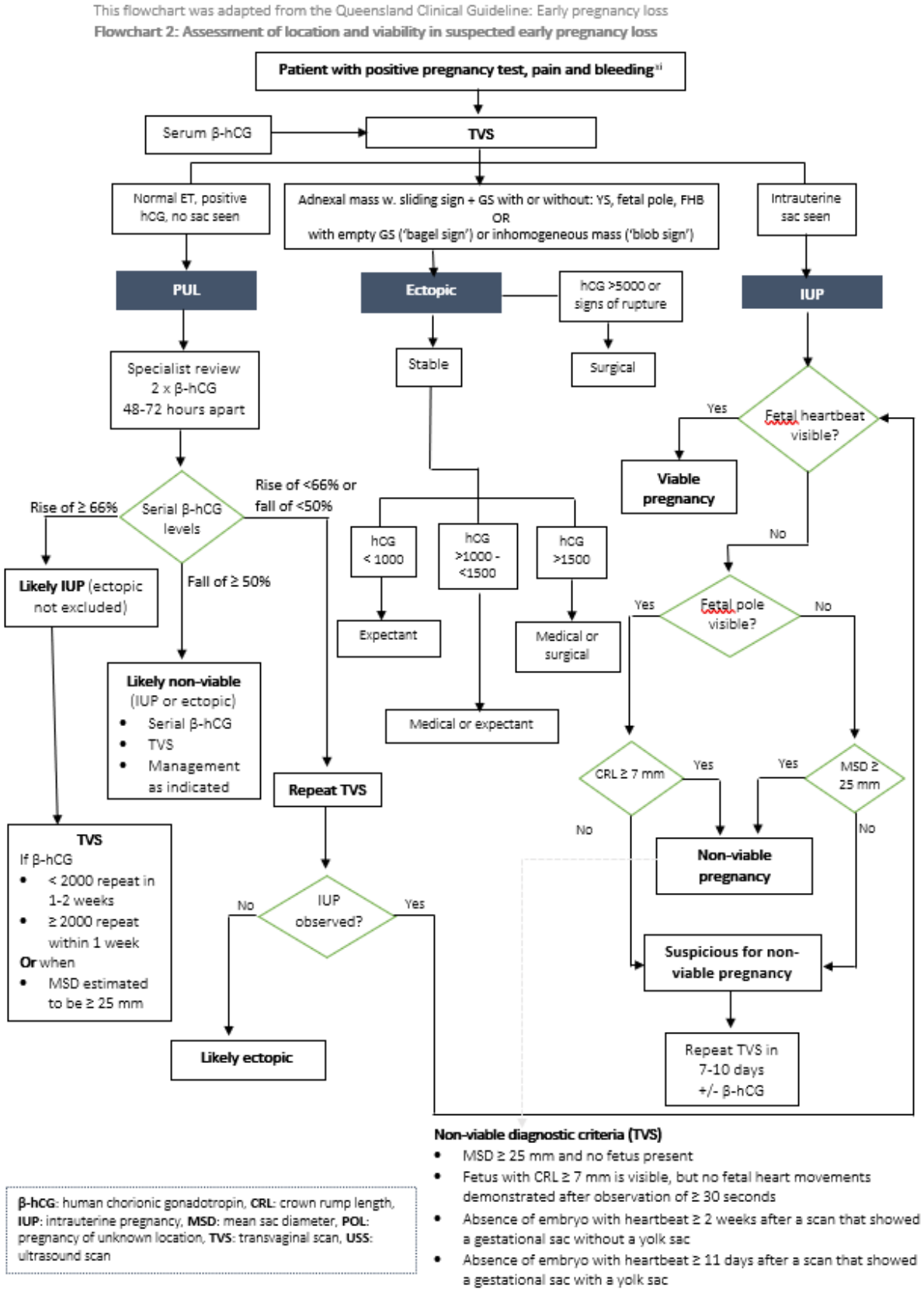
This is a reproduction of the Queensland Clinical Guideline: Early pregnancy loss' flowchart

Flowchart: Assessment of suspected early pregnancy loss



B-hCG: human chorionic gonadotropin, **FBC**: full blood count, **POC**: products of conception, **PV**: per vaginam, **STI**: sexually transmitted infection, **TVS**: transvaginal scan, **USS**: ultrasound scan, >: greater than

Flowchart 2: Assessment of location and viability in suspected early pregnancy loss

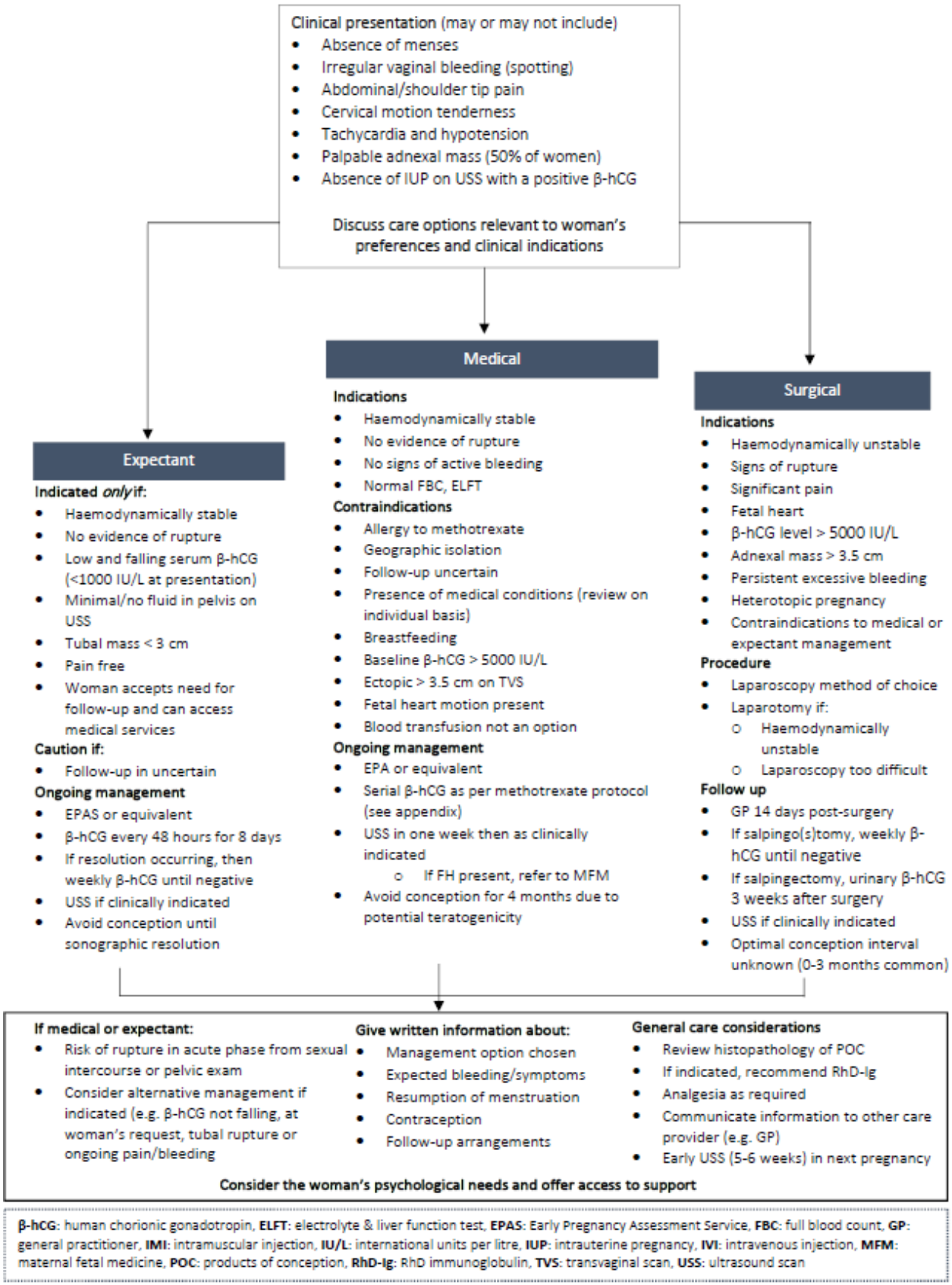


[xi] In cases which include a prior confirmed IUP, a TVS showing an empty uterus with opposed endometrium, or a small amount of heterogeneous material (e.g., clotted blood), may signify pregnancy loss by complete or incomplete miscarriage.

Flowchart 3: Management of ectopic pregnancy

This is a reproduction of the Queensland Clinical Guideline: Early pregnancy loss' flowchart

Flowchart 3: Management of ectopic pregnancy



β-hCG: human chorionic gonadotropin, **ELFT**: electrolyte & liver function test, **EPAS**: Early Pregnancy Assessment Service, **FBC**: full blood count, **GP**: general practitioner, **IMI**: intramuscular injection, **IU/L**: international units per litre, **IUP**: intrauterine pregnancy, **IVI**: intravenous injection, **MFM**: maternal fetal medicine, **POC**: products of conception, **RhD-Ig**: RhD immunoglobulin, **TVS**: transvaginal scan, **USS**: ultrasound scan

Appendix G: Evidence profiles and evidence to decision tables

- Part 1: Miscarriage (up to 14 weeks)
- Part 2: Recurrent miscarriage
- Part 3: Tubal ectopic pregnancy
- Part 4: Non-tubal ectopic pregnancy
- Part 5: Rh (D) Immunoglobulin (Anti-D)

Part 1: Miscarriage (up to 14 weeks)

Clinical Question 1 - Incomplete miscarriage

What are the benefits and harms of different treatment options (surgical/medical/expectant management) for incomplete miscarriage?

PICO (1.1)

Population: Pregnant women up to 14 weeks with an incomplete miscarriage

Intervention: Active management (surgical evacuation of the uterus, medical management with misoprostol [± mifepristone])

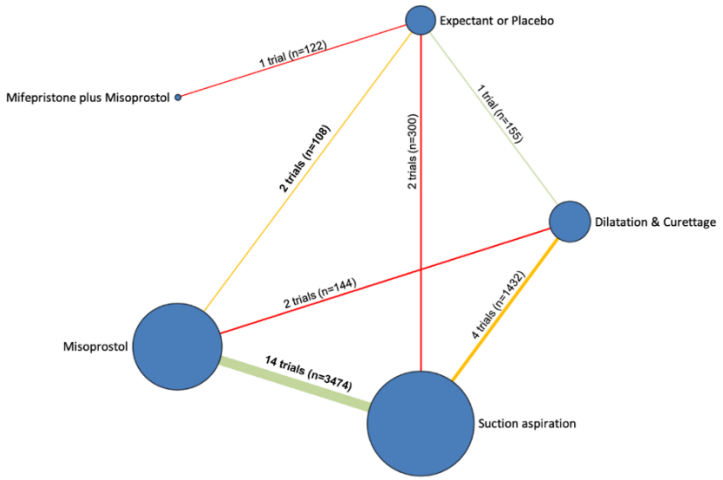
Comparator: Expectant management or placebo

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Summary
		Expectant management or placebo	Active management (surgical or medical)		
Achieving a complete miscarriage (Participants with incomplete miscarriage) (Ghosh 2021)	36 studies[2] Follow up network meta-analysis for incomplete miscarriage				See attached figure for Network diagram and SUCRA graph
Suction aspiration versus expectant management or placebo for achieving complete miscarriage	Relative risk: 1.19 (95% CI 1.09 - 1.31)	**767** per 1000	**913** per 1000 Difference: **146 more per 1000** (95% CI 69 more - 238 more)	**Moderate** Due to serious imprecision in the indirect evidence[2]	Suction aspiration probably improves the likelihood of achieving complete miscarriage compared to expectant management or placebo SUCRA 83.6%
D&C versus expectant management or placebo for achieving complete miscarriage	Relative risk: 1.19 (95% CI 1.08 - 1.31)	**767** per 1000	**913** per 1000 Difference: **146 more per 1000** (95% CI 61 more - 238 more)	**Moderate** Network evidence downgraded one level due to moderate certainty direct evidence (no intransitivity, incoherence, or imprecision)	D&C probably improves the likelihood of achieving a complete miscarriage compared to expectant management or placebo SUCRA 79.4%
Mifepristone + Misoprostol versus	Relative risk: 1.08 (95% CI 0.87 - 1.34)	**767** per 1000	**828** per 1000	**Very low**	We are uncertain whether mifepristone+ misoprostol increases or

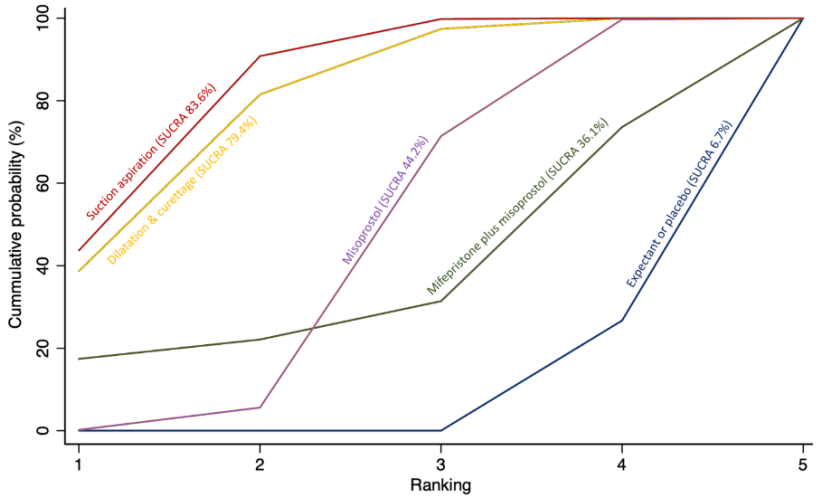
expectant management or placebo for achieving complete miscarriage		Difference: **61 more per 1000** (95% CI 100 fewer - 261 more)	Network evidence downgraded three levels due to very low certainty direct evidence (no intransitivity, incoherence, or imprecision)	decreases the likelihood of achieving a complete miscarriage, due to very low certainty evidence
Misoprostol versus expectant management or placebo for achieving complete miscarriage	Relative risk: 1.14 (95% CI 1.03 - 1.25)	**767** per 1000 **874** per 1000 Difference: **107 more per 1000** (95% CI 23 more - 192 more)	**Moderate** Network evidence downgraded one level due to low certainty direct evidence upgraded by one level as network evidence is precise	Misoprostol probably improves the likelihood of achieving complete miscarriage compared to expectant management or placebo, SUCRA 44%
Days of bleeding (Participants with incomplete miscarriage) (Ghosh 2021)	Lower better 11 studies Follow up NMA for incomplete miscarriage		See attached figure for Network diagram and SUCRA graph	We are uncertain whether active management (surgical or medical) increases or decreases days of bleeding (participants with incomplete miscarriage), very low certainty evidence (Ghosh 2021)
Suction aspiration versus expectant management or placebo for days of bleeding	Lower better	Mean Mean Difference: **MD 0.86 lower** (95% CI 2.51 lower - 0.79 higher)	**Very low** Due to very low certainty evidence for direct evidence	
D&C versus expectant management or placebo for days of bleeding	Lower better	Mean Mean Difference: **MD 1.26 fewer** (95% CI 2.56 fewer - 0.04 fewer)	**Very low** Due to very low certainty evidence for direct evidence	
Mifepristone + Misoprostol versus expectant management or placebo for days of bleeding	Lower better	Mean Mean Difference: **MD 0.70 fewer** (95% CI 2.51 fewer - 2.7 more)	**Very low** Due to very low certainty evidence for direct evidence	

Misoprostol versus expectant management or placebo for days of bleeding	Lower better	Mean Mean Difference: **MD 0.3 lower** (95% CI 1.38 lower - 1.99 higher)	**Very low** Due to very low certainty evidence for direct evidence	

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Ghosh 2021].
2. **Imprecision: serious.**



Network diagram for achieving a complete miscarriage for incomplete miscarriage



SUCRA graph for achieving complete miscarriage for incomplete miscarriage

PICO (1.2) – this table is for CQ1 and CQ2

Population: Pregnant women up to 14 weeks with miscarriage (incomplete or missed)

Intervention: Active management (surgical evacuation of the uterus, medical management with misoprostol [± mifepristone])

Comparator: Expectant management or placebo

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Summary**
		Expectant management or placebo	Active management (surgical or medical)		
Serious complication (Combines participants with incomplete and missed miscarriage) (Ghosh 2021)	71 studies Follow up network meta-analysis for serious complications				
Suction aspiration versus expectant management for serious complications	Relative risk: 0.55 (95% CI 0.23 - 1.32)	**19** per 1000	**10** per 1000 Difference: **9 fewer per 1000** (95% CI 15 fewer - 6 more)	**Low** Network evidence downgraded two levels due to low certainty direct evidence (no intransitivity or incoherence)	Suction aspiration may have little or no difference for serious complications versus expectant management.
D&C versus expectant management for serious complications	Relative risk: 0.43 (95% CI 0.17 - 1.06)	**19** per 1000	**8** per 1000 Difference: **11 fewer per 1000** (95% CI 16 fewer - 1 more)	**Low** Network evidence downgraded two levels due to low certainty indirect evidence	D&C may make little or no difference for serious complications compared to expectant management.
Mifepristone + misoprostol versus expectant management for serious complications	Relative risk: 0.76 (95% CI 0.31 - 1.84)	**19** per 1000	**14** per 1000 Difference: **5 fewer per 1000** (95% CI 13 fewer - 16 more)	**Low** Network downgraded two level due to low certainty direct evidence	Mifepristone + misoprostol may make little or no difference for serious complications compared to expectant management.
Misoprostol versus expectant	Relative risk: 0.5 (95% CI 0.22 - 1.15)	**19** per 1000	**10** per 1000	**Low**	

management for serious complications		Difference: **9 fewer per 1000** (95% CI 15 fewer - 3 more)	Network evidence downgraded two levels due to low certainty indirect evidence	Misoprostol may make little or no difference for serious complications compared to expectant management.
Need for unplanned/emergency surgical procedure to complete evacuation of retained products of conception (Ghosh 2021)	28 studies[1] Follow up network meta-analysis for need for unplanned/emergency surgical procedures			
Suction aspiration versus expectant management or placebo for need for unplanned/emergency surgical procedure	Relative risk: 0.37 (95% CI 0.22 - 0.65)	**120** per 1000 **44** per 1000 Difference: **76 fewer per 1000** (95% CI 94 fewer - 42 fewer)	**Moderate** Network evidence downgraded one level due to direct evidence incoherence	Suction aspiration probably decreases the need for unplanned/emergency surgical procedure compared to expectant management or placebo
D&C versus expectant management or placebo for need for unplanned/emergency surgical procedure	Relative risk: 0.8 (95% CI 0.09 - 7.02)	**120** per 1000 **96** per 1000 Difference: **24 fewer per 1000** (95% CI 109 fewer - 722 more)	**Very low** Network evidence downgraded one level due to low certainty indirect and one due to imprecision	We are uncertain whether D&C increases or decreases the need for unplanned/emergency surgical procedure compared to expectant management or placebo, due to very low certainty evidence
Mifepristone + misoprostol versus expectant management or placebo for need for unplanned/emergency surgical procedure	Relative risk: 0.64 (95% CI 0.33 - 1.23)	**120** per 1000 **77** per 1000 Difference: **43 fewer per 1000** (95% CI 80 fewer - 28 more)	**Low** Network evidence downgraded one level due to moderate certainty direct evidence downgraded due to incoherence	Mifepristone +misoprostol may have little or no difference for need for unplanned/emergency surgical procedure compared to expectant management or placebo
Misoprostol versus expectant management or placebo for need for	Relative risk: 1.04 (95% CI 0.56 - 1.95)	**120** per 1000 **125** per 1000 Difference: **5 more per 1000**	**Low** Network evidence downgraded due to low certainty indirect evidence with imprecision but	Misoprostol may have little or no difference for need for unplanned/emergency surgical

unplanned/emergency surgical procedure		(95% CI 53 fewer - 114 more)	not further downgraded as indirect evidence previously downgraded for imprecision	procedure compared to expectant management or placebo
Pelvic inflammatory disease, sepsis or endometritis (combined incomplete and missed) (Ghosh 2021)	Follow up network meta-analysis for incomplete and missed miscarriage combined			
Suction aspiration for pelvic inflammatory disease, sepsis or endometritis for miscarriage (combined incomplete and missed)	Relative risk: 1.42 (95% CI 0.88 - 2.28)	**36** per 1000 **51** per 1000 Difference: **15 more per 1000** (95% CI 4 fewer - 46 more)	**Moderate** Network evidence downgraded one level due to moderate certainty direct evidence	Suction and aspiration probably has little or no difference for pelvic inflammatory disease, sepsis or endometritis compared to expectant management or placebo
D&C for pelvic inflammatory disease, sepsis or endometritis for miscarriage (combined incomplete and missed)	Relative risk: 1.85 (95% CI 1.05 - 3.25)	**36** per 1000 **67** per 1000 Difference: **31 more per 1000** (95% CI 2 more - 81 more)	**Very low** Network evidence downgraded three levels due to very low certainty indirect evidence, further downgraded one level for incoherence but upgraded one as network is precise	We are uncertain whether D&C increases or decreases pelvic inflammatory disease, sepsis or endometritis for miscarriage (combined incomplete and missed) compared to expectant management or placebo due to very low certainty evidence
Mifepristone + misoprostol for pelvic inflammatory disease, sepsis or endometritis for miscarriage (combined incomplete and missed)	Relative risk: 0.9 (95% CI 0.48 - 1.68)	**36** per 1000 **32** per 1000 Difference: **4 fewer per 1000** (95% CI 19 fewer - 24 more)	**Low** Network evidence downgraded two levels due to low certainty direct evidence	Mifepristone + misoprostol may have little or no difference on pelvic inflammatory disease, sepsis or endometritis for miscarriage (combined incomplete and missed) compared to expectant management or placebo

Misoprostol for pelvic inflammatory disease, sepsis or endometritis for miscarriage (combined incomplete and missed)	Relative risk: 1.08 (95% CI 0.62 - 1.88)	36 per 1000 — 39 per 1000 Difference: **3 more per 1000** (95% CI 14 fewer - 32 more)	**Moderate** Network evidence downgraded one level due to moderate certainty direct evidence	Misoprostol probably has little or no difference on pelvic inflammatory disease, sepsis or endometritis for miscarriage (combined incomplete and missed) compared to expectant management or placebo
Readmission to hospital (combines participants with incomplete and missed miscarriage) (Ghosh 2021)	10 studies Follow up network meta-analysis for incomplete and missed miscarriage			
Suction aspiration for readmission to hospital for miscarriage (combined incomplete and missed)	Relative risk: 0.5 (95% CI 0.21 - 1.15)		**Low**	Suction and aspiration may have little or no difference on readmission to hospital for miscarriage (combined incomplete and missed) compared to expectant management or placebo
D&C for readmission to hospital for miscarriage (combined incomplete and missed)	Relative risk: 0.32 (95% CI 0.08 - 1.24)		**Very low**	We are uncertain whether D&C increases or decreases the readmission to hospital for miscarriage (combined incomplete and missed) compared to expectant management or placebo
Mifepristone + misoprostol for readmission to hospital for miscarriage (combined incomplete and missed)	Relative risk: 0.56 (95% CI 0.13 - 2.48)		**Low**	Mifepristone + misoprostol may have little or no difference on readmission to hospital for miscarriage (combined incomplete and missed) compared to expectant management or placebo
Misoprostol for readmission to hospital for miscarriage (combined incomplete and missed)	Relative risk: 1.08 (95% CI 0.4 - 2.96)		**Very low**	We are uncertain whether misoprostol increases or decreases the readmission to hospital for miscarriage (combined incomplete and missed) compared to expectant management or placebo

Nausea (combined participants with incomplete and missed miscarriage (Ghosh 2021)	21 studies			
Suction aspiration versus expectant management for nausea	Relative risk: 0.68 (95% CI 0.31 - 1.52)		**Very low**	We are uncertain whether suction and aspiration increases or decreases the rate of nausea compared to expectant management
D&C versus expectant management for nausea	Relative risk: 4.12 (95% CI 0.13 - 129.62)		**Low**	D&C may have little or no difference on nausea compared to expectant management
Mifepristone + misoprostol versus expectant management for nausea	Relative risk: 1.89 (95% CI 0.62 - 5.72)		**Moderate**	Mifepristone + misoprostol probably has little or no difference on nausea compared to expectant management
Misoprostol versus expectant management for nausea	Relative risk: 1.37 (95% CI 0.7 - 2.69)		**Moderate**	Misoprostol probably has little or no difference on nausea compared to expectant management
Vomiting (combined participants with incomplete and missed miscarriage (Ghosh 2021)	21 studies			
Suction aspiration versus expectant management for vomiting	Relative risk: 0.71 (95% CI 0.37 - 1.39)		**Low**	Active management (surgical or medical) may have little or no difference versus expectant management for vomiting

D&C versus expectant management for vomiting	Relative risk: 0.48 (95% CI 0.11 - 2.13)		Low	Active management (surgical or medical) may have little or no difference versus expectant management for vomiting
Mifepristone + misoprostol versus expectant management for vomiting	Relative risk: 2.32 (95% CI 0.91 - 5.91)		Low	Active management (surgical or medical) may have little or no difference versus expectant management for vomiting
Misoprostol versus expectant management for vomiting	Relative risk: 1.31 (95% CI 0.76 - 2.3)		Low	Active management (surgical or medical) may have little or no difference versus expectant management for vomiting
Diarrhoea (combined participants with incomplete and missed miscarriage (Ghosh 2021)	18 studies			
Suction aspiration versus expectant management for diarrhoea	Relative risk: 0.69 (95% CI 0.42 - 1.12)		Low	Suction aspiration may have little or no difference compared expectant management for diarrhoea
D&C versus expectant management for diarrhoea	Relative risk: 0.54 (95% CI 0.02 - 13.12)		Low	D&C may have little or no difference compared expectant management for diarrhoea
Mifepristone + misoprostol versus expectant management for diarrhoea	Relative risk: 1.47 (95% CI 0.93 - 2.33)		Low	Mifepristone + misoprostol may have little or no difference compared expectant management for diarrhoea

Misoprostol versus expectant management for diarrhoea	Relative risk: 1.61 (95% CI 1.11 - 2.32)		Low	Misoprostol may increase the rate of diarrhoea compared to expectant management
Pyrexia (combined participants with incomplete and missed miscarriage) (Ghosh 2021)	26 studies			
Suction and aspiration compared to expectant management for pyrexia (Ghosh 2021)	Relative risk: 1.36 (95% CI 0.37 - 5.06		Very low	We are uncertain whether suction and aspiration increases or decreases the rate of pyrexia compared to expectant management
D&C compared to expectant management for pyrexia (Ghosh 2021)	Relative risk: 1.1 (95% CI 0.23 - 5.19)		Low	D&C may have little or no difference on pyrexia rate compared to expectant management
Mifepristone + misoprostol compared to expectant management for pyrexia (Ghosh 2021)	Relative risk: 4.15 (95% CI 0.88 - 19.59)		Very low	We are uncertain whether mifepristone + misoprostol increases or decreases the rate of pyrexia compared to expectant management
Misoprostol compared to expectant management for pyrexia (Ghosh 2021	Relative risk: 3.51 (95% CI 0.98 - 12.53)		Moderate	Misoprostol probably has little or no difference on pyrexia rate compared to expectant management
Pain score (VAS) for miscarriage (combined incomplete and missed) (Ghosh 2021) Suction aspiration and D&C not reported	Lower better Follow up network meta-analysis for miscarriage (combined incomplete and missed)			

Mifepristone + misoprostol pain score for miscarriage (combined incomplete and missed)	Lower better 1 study	Difference: **MD 0.14 higher** (95% CI 0.21 lower - 0.5 higher)	**Low** Downgraded one level as patient reported outcome and one level due to imprecision	Mifepristone + misoprostol may have little or no difference on pain score for miscarriage (combined incomplete and missed) compared to expectant management or placebo
Misoprostol for pain score for miscarriage (combined incomplete and missed)	Lower better 3 studies	Difference: **MD 0.33 lower** (95% CI 0.08 lower - 0.57 higher)	**Low** Downgraded one level as patient reported outcome and one level for imprecision	Misoprostol may have little or no difference on pain score for miscarriage (combined incomplete and missed) compared to expectant management or placebo
Days of bleeding (combined incomplete and missed miscarriage) (Ghosh 2021)	Lower better 18 studies Follow up NMA for incomplete and missed miscarriage combined			
Suction aspiration versus expectant management or placebo for miscarriage (combined incomplete and missed)	Lower better	**10** Mean **8** Mean Difference: **MD 2.0 lower** (95% CI 3.01 lower - 0.99 lower)	**Very low** Downgraded due to low certainty direct evidence further downgraded due to incoherence and not upgraded as direct grade not downgraded for imprecision	We are uncertain whether suction and aspiration increases or decreases the days of bleeding compared to expectant management or placebo for miscarriage (combined incomplete and missed)
D&C versus expectant management or placebo for days of bleeding for miscarriage (combined incomplete and missed)	Lower better	**10** Mean **8.04** Mean Difference: **MD 1.95 fewer** (95% CI 3.48 fewer - 0.45 fewer)	**Low** Direct and indirect evidence downgraded due to patient reported outcome and imprecision.	D&C may decrease the days of bleeding compared to expectant management or placebo for miscarriage (combined incomplete and missed)
Mifepristone + misoprostol versus expectant management or	Lower better	**10** Mean **9.86** Mean Difference: **MD 0.14 lower** (95% CI 1.71 lower - 1.43 higher)	**Very low** Downgraded as direct evidence was very low certainty evidence	We are uncertain whether mifepristone + misoprostol increases or decreases days of bleeding for miscarriage (combined incomplete and missed)

placebo for days of bleeding for miscarriage (combined incomplete and missed)			and further downgraded for incoherence	versus expectant management or placebo
Misoprostol versus expectant management or placebo for miscarriage (combined incomplete and missed)	Lower better	10 Mean 9.53 Mean Difference: **MD 0.47 lower** (95% CI 153 lower - 0.6 higher)	**Very low** Downgraded due to low certainty indirect evidence and imprecision	We are uncertain whether misoprostol increases or decreases days of bleeding for miscarriage (combined incomplete and missed) versus expectant management or placebo
Satisfaction for miscarriage (combined incomplete and missed) (Ghosh 2021)		There was significant heterogeneity in the methods of reporting women's views or satisfaction across all the studies. Meta-analysis was not possible. Overall, all methods of managing a miscarriage were found to be acceptable. In general satisfaction was similar (satisfied or very satisfied in a scale of four) with misoprostol and suction aspiration.		
Anxiety score for miscarriage (combined incomplete and missed) (Ghosh 2021)		There was no difference shown between suction aspiration and misoprostol		

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. WE used the base line from the NMA as risk with standard care. Supporting references [Ghosh 2021].

Clinical Question 2 – Missed miscarriage

What are the benefits and harms of different treatment options (surgical/medical/expectant management) for missed miscarriage?

PICO (2.1)

Population: Pregnant women up to 14 weeks with missed miscarriage

Intervention: Active management (surgical evacuation of the uterus, medical management with misoprostol [± mifepristone])

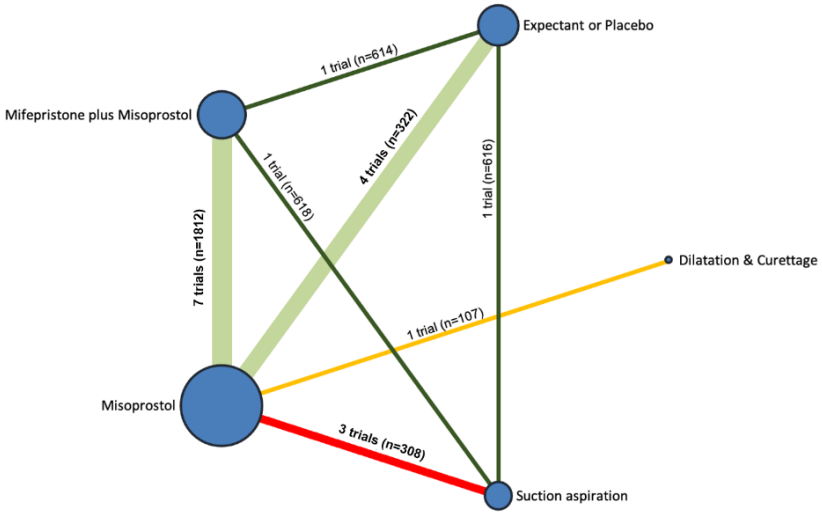
Comparator: Expectant management or placebo

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Summary
		Any of the above listed interventions	Active management (surgical evacuation of		
Achieving a complete miscarriage (Participants with missed miscarriage) (Ghosh 2021)	16 studies[1] Follow up network meta-analysis for missed miscarriage				See figure attached for network and SUCRA graph
Suction aspiration versus expectant management or placebo for achieving complete miscarriage for missed miscarriage	Relative risk: 2.43 (95% CI 1.69 - 3.49)	**455** per 1000 Difference: **487 more per 1000** (95% CI 402 more - 580 more)	**942** per 1000	**Moderate** Network evidence downgraded one level due to high certainty direct evidence and incoherence between direct and indirect estimates (no intransitivity, or imprecision)	Suction aspiration probably increases the rates for achieving complete miscarriage for missed miscarriage compared to expectant management or placebo
D&C versus expectant management or placebo for achieving complete miscarriage for missed miscarriage	Relative risk: 2.07 (95% CI 1.19 - 3.59)	**455** per 1000 Difference: **545 more per 1000** (95% CI 313 more - 847 more)	**1000** per 1000	**High**	D&C increases the rates for achieving complete miscarriage for missed miscarriage compared to expectant management or placebo

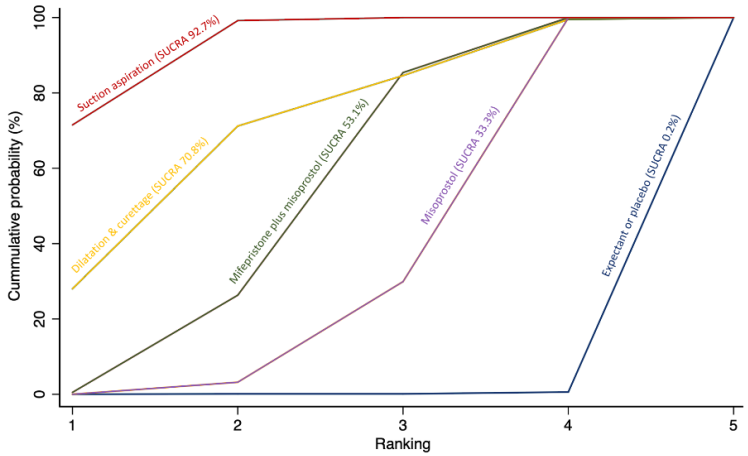
Mifepristone+ misoprostol versus expectant management or placebo for achieving complete miscarriage for missed miscarriage	Relative risk: 1.82 (95% CI 1.28 - 2.58)	**455** per 1000 **828** per 1000 Difference: **373 more per 1000** (95% CI 127 more - 719 more)	**Moderate** Indirect evidence downgraded one level due to severe unexplained statistical heterogeneity	Mifepristone+ misoprostol probably increases the rates for achieving complete miscarriage for missed miscarriage versus expectant management or placebo
Misoprostol versus expectant management or placebo for achieving complete miscarriage for missed miscarriage	Relative risk: 1.67 (95% CI 1.18 - 2.37)	**455** per 1000 **760** per 1000 Difference: **305 more per 1000** (95% CI 82 more - 623 more)	**Low** Network evidence downgraded two levels due to moderate certainty indirect evidence and incoherence between direct and indirect estimates (no intransitivity, or imprecision)	Misoprostol may increase the rate for achieving complete miscarriage for missed miscarriage compared to expectant management or placebo
Failure to achieve complete miscarriage Mifepristone + Misoprostol, versus misoprostol alone at 7 days (Chu 2020)	Relative risk: 0.73 (95% CI 0.54 - 0.99) Based on data from 696 participants in 1 studies[2]	**240** per 1000 **124** per 1000 Difference: **46 fewer per 1000** (95% CI 78 fewer - 2 fewer)	**Moderate**	Mifepristone + misoprostol Active probably reduces the failure rate of achieving complete miscarriage compared to misoprostol alone for missed miscarriage
Requirement of surgery to achieve complete miscarriage Mifepristone + Misoprostol, versus misoprostol alone (Chu 2020)	Relative risk: 0.71 (95% CI 0.53 - 0.95) Based on data from 696 participants in 1 studies[3]	**250** per 1000 **178** per 1000 Difference: **72 fewer per 1000** (95% CI 117 fewer - 12 fewer)	**Moderate**	Mifepristone + misoprostol probably reduces requirement of surgery to achieve complete miscarriage compared to misoprostol
Days of bleeding (Participants with missed miscarriage) (Ghosh 2021)	Lower better[4]		5	

Suction aspiration versus expectant management or placebo for days of bleeding for missed miscarriage	Lower better		Very low Due to serious inconsistency and low certainty of the direct evidence	We are uncertain whether active management increases or decreases the days of bleeding for missed miscarriage compared to expectant management or placebo.
Mifepristone+ Misoprostol versus expectant management or placebo for days of bleeding for missed miscarriage	Higher better		Very low Due to serious inconsistency and low certainty of the direct evidence	We are uncertain whether active management increases or decreases the days of bleeding for missed miscarriage compared to expectant management or placebo.
Misoprostol versus expectant management or placebo for days of bleeding for missed miscarriage	Higher better		Very low Due to serious inconsistency and low certainty of the direct evidence	We are uncertain whether active management increases or decreases the days of bleeding for missed miscarriage compared to expectant management or placebo.

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Ghosh 2021].
2. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Chu 2020].
3. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Chu 2020].
4. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Ghosh 2021].
5. **Inconsistency: serious. Imprecision: serious.** Wide confidence intervals.



Network for achieving complete miscarriage for missed miscarriage



SUCRA graph for achieving complete miscarriage for missed miscarriage

Other considerations

Intrauterine adhesions (IUAs)

Hooker 2014 AMSTAR Moderate (no protocol but used PRISMA). *Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome.*

- Included one RCT where participants were randomised to doxycycline, doxycycline + conjugated equine estrogen or no treatment for adhesion prevention. Other prospective cohort studies included women with a miscarriage that were subjected to a D&C and assessed after surgery for adhesions. Hysteroscopies were performed between 1 and 12 months after miscarriage.
    - Reporting a pooled estimate of 19% adhesions (95% CI 12.8 t 27.5%) post miscarriage
    - Women with more than one miscarriage were more likely to have IUAs (OR 1.99, 95% CI: 1.32 to 3.00), I^2=0%
    - More than one D&C also increases the rates of IUAs detected (OR 2.05, 95% CI: 1.35 to 3.12), I^2=0% in follow up. No difference with only one D&C
    - Recurrent curettage procedures were identified as the most important risk factor for IUA formation
- Also searched for future fertility: included 1770 participants from eight prospective studies. The relationship between IUAs following a miscarriage and subsequent fertility and reproductive outcome could not be assessed, as the presence of IUAs was not studied in the included eight studies. Also, in general included studies were old, and did not consider all the interventions currently available.

Antibiotic prophylaxis

Islam et al published a systematic review in the BJOG 2021, *Prophylactic antibiotics for preventing genital tract infection in women undergoing surgical procedures for incomplete abortion: a systematic review and meta-analysis of randomised controlled trials*.

- Included 24 trials that included terminations and incomplete miscarriages. The author was contacted, and the subgroup analysis of incomplete miscarriage reported a similar finding, concluding that the study provides evidence that antibiotic prophylaxis is beneficial in reducing post-abortion GTI among women undergoing surgical procedures for incomplete abortion.

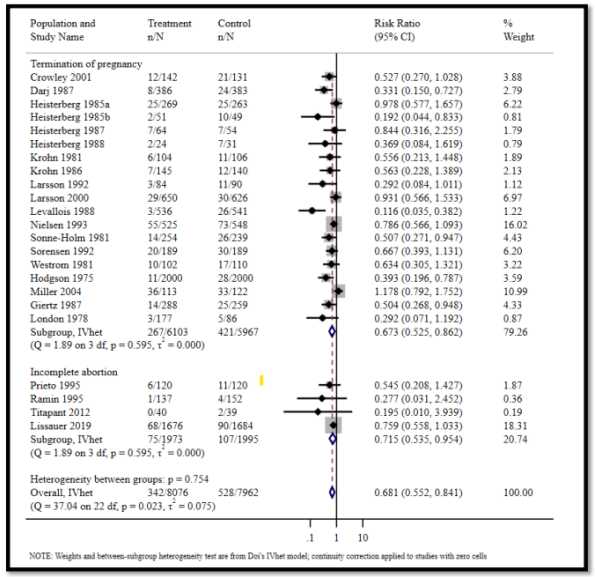


Figure-1: Forest plot by population examining the effect of prophylactic antibiotic use and post-abortion GTI.

- The trial contributing the majority of women for the meta-analysis (and the most recent) was Lissauer 2019. 3412 patients in Malawi, Pakistan, Tanzania and Uganda randomly assigned to a single preoperative dose of 400 mg of oral doxycycline and 400 mg of oral metronidazole or identical placebos 2 hours before the surgery.
  They had a protocol change for the primary outcome making the diagnosis of infection a pragmatic broad criterion of infection "if the symptoms were of sufficient severity the clinicians judged that there was pelvic infection and that treatment was required. There was concern that the original criteria, although highly specific, could lead to missed diagnoses in some patients with infection. This was potentially a patient safety issue, particularly where patient access to care was limited. These changes were made before data were unblinded."
- Using the pragmatic data there was no clear evidence of difference (RR 0.759, 95%CI 0.558 to 1.033); Still, they reported the strict criteria as secondary outcome reporting (RR 0.60, 95% CI 0.37 to 0.96)

Evidence to decision – Clinical Questions 1 & 2, Incomplete and missed miscarriage

Domain	Summary of judgement	Comments
Certainty of evidence	Moderate	Ranged from moderate GRADE for network meta-analysis, low GRADE for intrauterine adhesions to moderate GRADE for antibiotics.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	Trials comparing different managements for miscarriage that assessed the psychological impact, did not find a clear evidence difference between groups.
Additional considerations		
One study (Petrou 2009) suggests that women with first-trimester miscarriage would value being offered alternatives to expectant management. Considering the level of pain, time to return to normal activities, number of days of bleeding after treatment, the chance of complications requiring more time or readmission and time spent at the hospital receiving treatment.		
Domain	**Summary of judgement**	**Comments**
Resources	N/A	
Domain	**Summary of judgement**	**Comments**
Equity	Probably no equity impact	No specific equity issues were identified.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	There are different options and the acceptability may vary.
Domain	**Summary of judgement**	**Comments**
Feasibility	Probably feasible	All options are probably feasible.

Clinical Question 3 - Progesterone treatment for bleeding in early pregnancy

What are the harms and benefits of treatment with progesterone in pregnant women with no history of recurrent miscarriage and present with bleeding?

PICO (3.1)

Population: Pregnant women up to 14 weeks with with bleeding and no history of recurrent miscarriage

Intervention: Progesterone (any route) or NMA

Comparator: Placebo, no treatment

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Summary**
		Placebo, no treatment	Progesterone (any route) or specified in the outcome for NMA		
Miscarriage (Zhao 2022) included up to 28 weeks	59 studies[1] Follow up network meta-analysis Zhao 2022				See graphs attached
Oral dydrogesterone versus placebo for miscarriage	Odds ratio: 0.43 (95% CI 0.29 - 0.64)	**10** per 100	**4** per 100 Difference: **6 fewer per 100** (95% CI 7 fewer - 4 fewer)	**Low** Due to serious indirectness[2]	Oral dydrogesterone probably decreases the miscarriage rate in pregnancies' up to 28 weeks
Vaginal progesterone versus placebo for miscarriage	Odds ratio: 0.87 (95% CI 0.75 - 1.0)	**10** per 100	**9** per 100 Difference: **1 fewer per 100** (95% CI 2 fewer - 0 fewer)	**Low** Due to serious indirectness[3]	Vaginal progesterone probably has little or no difference on miscarriage rate up to 28 weeks
Oral micronized progesterone versus placebo for miscarriage	Odds ratio: 0.85 (95% CI 0.53 - 1.35)	**10** per 100	**9** per 100 Difference: **1 fewer per 100** (95% CI 5 fewer - 3 more)	**Low** Due to serious indirectness[4]	Oral micronized progesterone probably has little or no difference on miscarriage rate up to 28 weeks

Intramuscular progesterone versus placebo for miscarriage	Odds ratio: 0.94 (95% CI 0.62 - 1.42)	10 per 100 9 per 100 Difference: **1 fewer per 100** (95% CI 4 fewer - 4 more)	**Low** Due to serious indirectness[5]	Intramuscular progesterone probably has little or no difference on miscarriage rate up to 28 weeks
Miscarriage (Yan 2020)	Relative risk: 0.7 (95% CI 0.52 - 0.94) Based on data from 4833 participants in 8 studies[6]	10 per 100 7 per 100 Difference: **3 fewer per 100** (95% CI 5 fewer - 1 fewer)	**Low** Due to serious risk of bias and low certainty systematic review[7]	Progesterone (any route) may reduce the miscarriage rate compared to placebo.
Preterm birth (Yan 2020)	Relative risk: 0.87 (95% CI 0.43 - 1.72) Based on data from 579 participants in 5 studies[8]	100 per 1000 87 per 1000 Difference: **13 fewer per 1000** (95% CI 57 fewer - 72 more)	**Low** Due to serious risk of bias and serious imprecision[9]	We are uncertain whether progesterone (any route) increases or decreases preterm birth (Yan 2020)
Live birth (Yan 2020)	Relative risk: 1.02 (95% CI 0.98 - 1.07) Based on data from 4094 participants in 2 studies[10]		**Low**	Progesterone (any route) may have little or no difference on live birth (Yan 2020)

1. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Zhao 2022].
2. **Indirectness: serious.** Differences between the population of interest and those studied.
3. **Indirectness: serious.** Differences between the population of interest and those studied.
4. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the outcomes of interest and those reported (e.g., short-term/surrogate not patient-important).
5. **Indirectness: serious.** Differences between the population of interest and those studied.
6. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Yan 2020].
7. **Risk of Bias: serious.** Unknown or inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias.
8. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. We used 10%. An average of WHO data Across countries, the rate of preterm birth ranges from 4–16% of babies born in 2020. Supporting references [27].
9. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals.
10. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Yan 2020].

PICO (3.2)

Population: Pregnant women up to 14 weeks with bleeding and no history of recurrent miscarriage

Intervention: Micronized progesterone

Comparator: Placebo, no treatment

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Placebo, no treatment	Micronized progesterone		
Live birth (Devall 2021) no history of previous miscarriage	Relative risk: 0.99 (95% CI 0.95 - 1.04) Based on data from 4090 participants in 2 studies[1] Follow up Subgroup analysis	**747** per 1000	**740** per 1000 Difference: **7 fewer per 1000** (95% CI 37 fewer - 30 more)	**High**	Vaginal micronized progesterone has little or no difference on live birth rate for women with early pregnancy bleeding and NO previous miscarriage (Devall 2021)
Live birth for women with early pregnancy bleeding and one or more previous miscarriages (Devall 2021)	Relative risk: 1.08 (95% CI 1.02 - 1.14) Based on data from 4090 participants in 2 studies[2] Follow up Subgroup analysis	**747** per 1000	**807** per 1000 Difference: **60 more per 1000** (95% CI 15 more - 105 more)	**Moderate**	Vaginal micronized progesterone increases live birth rate for women with early pregnancy bleeding and ONE OR MORE previous miscarriage (Devall 2021)
Miscarriage (delivery < 24w) (Dewall 2021)	Relative risk: 0.9 (95% CI 0.8 - 1.01) Based on data from 4090 participants in 2 studies[3]	**100** per 1000	**90** per 1000 Difference: **10 fewer per 1000** (95% CI 20 fewer - 1 more)	**High**	"We cannot rule out a substantial reduction in the miscarriage rate with vaginal micronized progesterone compared to placebo" I am confused by this result!!! these are exact words

Preterm birth (< 37W) (Dewall 2021)	Relative risk: 1.08 (95% CI 0.92 - 1.27) Based on data from 3154 participants in 2 studies[4]	**100** per 1000 **108** per 1000 Difference: **8 more per 1000** (95% CI 8 fewer - 27 more)	**Moderate** Direct evidence downgraded one level for serious imprecision (wide 95% CIs).	Micronized progesterone probably has little or no difference on preterm birth (<37w) compared to placebo for women with threatened miscarriage (Dewall 2021)
Stillbirth (Dewall 2021)	Relative risk: 0.89 (95% CI 0.25 - 2.71) Based on data from 4038 participants in 1 studies[5]	**14** per 1000 **12** per 1000 Difference: **2 fewer per 1000** (95% CI 10 fewer - 24 more)	**Low** Due to very serious imprecision[6]	Micronized progesterone may have little or no difference on stillbirth compared to placebo for women with threatened miscarriage (Dewall 2021)
Congenital anomalies (Dewall 2021)	Relative risk: 1.0 (95% CI 0.68 - 1.46) Based on data from 3085 participants in 1 studies[7] Follow up no baseline risk		**Moderate** Due to serious imprecision[8]	Micronized progesterone probably has little or no difference on congenital anomalies compared to placebo for women with threatened miscarriage (Dewall 2021)

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dewall 2021].
2. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dewall 2021].
3. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. We used a 10% general estimate of miscarriage. Supporting references [Dewall 2021].
4. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dewall 2021].
5. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. We used an estimated of the overall worldwide stillbirth according to WHO (14/1000). Supporting references [Dewall 2021].
6. **Imprecision: very serious**. Only data from one study, Wide confidence intervals.
7. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dewall 2021].
8. **Imprecision: serious**. Wide confidence intervals.

PICO (3.3)

Population: Pregnant women up to 14 weeks with bleeding and no history of recurrent miscarriage

Intervention: Dydrogesterone

Comparator: Placebo, no treatment

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Placebo, no treatment	Dydrogesterone		
Miscarriage (delivery < 24w) (Dewall 2021)	Relative risk: 0.9 (95% CI 0.55 - 1.47) Based on data from 406 participant in 1 study[1]	**100** per 1000	**90** per 1000 Difference: **10 fewer per 1000** (95% CI 45 fewer - 47 more)	**Moderate** Direct evidence downgraded one level due to serious limitations in study design.	Dydrogesterone probably has little or no difference on miscarriage (delivery,24w) rate compared to placebo for women with threatened miscarriage (Dewall 2021)
Stillbirth (Dewall 2021)	Relative risk: 0.33 (95% CI 0.01 - 8.13) Based on data from 406 participants in 1 study[2]	**14** per 1000	**5** per 1000 Difference: **9 fewer per 1000** (95% CI 14 fewer - 100 more)	**Very low** Due to serious indirectness, due to very serious imprecision[3]	We are uncertain whether dydrogesterone increases or decreases the stillbirth rate compared to placebo for women with threatened miscarriage (Dewall 2021)
Live birth	Follow up was not reported for threatened miscarriage, only for recurrent				
Congenital anomalies (Dewall 2021)	Relative risk: 0.71 (95% CI 0.23 - 2.21) Based on data from 406 participants in 1 study[4] Follow up: no baseline risk			**Very low** Due to serious inconsistency, due to very serious imprecision[5]	We are uncertain whether dydrogesterone increases or decreases congenital anomalies compared to placebo for women with threatened miscarriage due to very low certainty evidence (Dewall 2021)

Major congenital anomalies (Katalinic 2024)	Relative risk: 1.11 (95% CI 0.73 - 1.68) Based on data from 5070 participants in 9 studies[6] Follow up Australia, Austria, Belgium, China (including Hong Kong), Finland, Germany, India, Israel, Jordan, Malaysia, Russian Federation, Singapore, Spain, Thailand, Ukraine, Vietnam		**Low** Combined RCT and OS.	Dydrogesterone may have little or no difference on major congenital anomalies (Katalinic 2024)
Preterm birth (< 37W) (Dewall 2021)	Relative risk: 0.87 (95% CI 0.4 - 1.88) Based on data from 334 participants in 1 study[7]	**100** per 1000 **87** per 1000 Difference: **13 fewer per 1000** (95% CI 60 fewer - 88 more)	**Low** Direct evidence downgraded one level for serious limitations in study design and one level for serious imprecision (wide 95% CIs).	Dydrogesterone may have little or no difference on preterm birth (< 37w) rate compared to placebo for women with threatened miscarriage (Dewall 2021)

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dewall 2021].
2. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. We used an estimated of the overall worldwide stillbirth according to WHO. Supporting references [Dewall 2021].
3. **Indirectness: serious.** Due to study design limitations; **Imprecision: very serious.** Wide confidence intervals, only data from one study.
4. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dewall 2021].
5. **Inconsistency: serious.** due to study design limitation; **Imprecision: very serious.** Wide confidence intervals, due to number of events less than 30.
6. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Katalinic 2024].
7. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dewall 2021].

Evidence to decision – Clinical Question 3, Progesterone treatment for bleeding in early pregnancy

Domain	Summary of judgement	Comments
Certainty of evidence	Low to Moderate	Varied from Low GRADE to Moderate GRADE
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	Early pregnancy bleeding is likely to lead to high levels of stress. People likely may want to receive treatment to improve the outcome.
Additional considerations		
• Knowing and empathizing with the uncertainty and anxiety associated with threatened miscarriage, may lead to offering treatments even with no clear evidence of benefit.		
Domain	**Summary of judgement**	**Comments**
Resources	N/A	
Domain	**Summary of judgement**	**Comments**
Equity	Probably no impact	No equity issues were identified as no intervention is recommended.
Domain	**Summary of judgement**	**Comments**
Acceptability	Varies	Acceptability may vary as, for some people, the lack of treatment for early pregnancy bleeding may be unacceptable despite the lack of evidence.
Domain	**Summary of judgement**	**Comments**
Feasibility	N/A	No feasibility issues, as no treatment is recommended.

Part 2: Recurrent miscarriage

Clinical Question 4 - Screening tests

What tests should be offered to investigate recurrent miscarriage?

PICO (4.1)

Population: People with recurrent miscarriage

Intervention: Acquired thrombophilia: anti-beta-2-glycoprotein-I antibodies (aβ2GPI)

Comparator: No test

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		No test	Anti-beta-2-glycoprotein-I antibodies (aβ2GPI)		
aβ2GPI and RPL (Opanttrny 2006)	Odds ratio: 2.12 (95% CI 0.69 - 6.53) Based on data from 1788 participants in 5 studies Follow up Recurrent was defined as 2 or more miscarriages	20 per 1000	41 per 1000 Difference: **21 more per 1000** (95% CI 6 fewer - 98 more)	**Very low** Due to serious imprecision[1]	We are uncertain whether anti-beta-2-glycoprotein-i antibodies (aβ2gpi) is related to recurrent pregnancy loss
aβ2GPI and RLP (Santos 2017)		SR provided a narrative result "Of three studies that analysed the association between aβ2GPI and RM, only one article found a significant association on their analysis. The other included in the present study did not observe this association"			
anti-B2GPI and adverse pregnancy outcomes (not RPL)		SR included one study including healthy pregnant women who were tested for aPL and then followed for obstetric events; two studies			

		followed a cohort of known aPL positive pregnant women, and 1 examined outcomes of a second pregnancy among women who had a history of prior miscarriage and aPL positivity. They found no association between anti-B2GPI positivity and adverse pregnancy outcomes including fetal loss, placental abruption and intrauterine growth restriction. Only one study reported an association with pre-eclampsia.		

1. **Indirectness: no serious.** Differences between the intervention/comparator of interest and those studied the test used to measure it differed, but subgroup analysis showed no difference; **Imprecision: serious.** Wide confidence intervals.

PICO (4.2)

Population: People with recurrent miscarriage/ RPL (recurrent pregnancy loss)/ EPL (early pregnancy loss)

Intervention: Factor V Leiden, prothrombin gene mutation, protein S deficiency

Comparator: No test

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Summary**
		No test	Factor V Leiden, prothrombin gene mutation, protein S deficiency		
Factor V Leiden and RPL (LIU 2021)	Odds ratio: 2.44 (95% CI 1.96 - 3.03) Based on data from participants in 81 studies Follow up Europe, Middle east, Asia, Africa, Latina America, North America	20 per 1000	47 per 1000 Difference: **27 more per 1000** (95% CI 18 more - 38 more)	**Low** Upgraded due to large magnitude of effect, Downgraded due to serious inconsistency[1]	Women with recurrent pregnancy loss maybe more likely to have a mutation of the factor V Leiden

Factor V Leiden and RPL with 2 or more EPL (Liu 2021)[2]	Odds ratio: 2.15 (95% CI 1.66 - 2.79) Based on data from participants in 45 studies Follow up from 1998-2020	**20** per 1000 **42** per 1000 Difference: **22 more per 1000** (95% CI 13 more - 34 more)		Subgroup analysis of Liu 2021
Factor V Leiden and RPL with 3 or more EPL (Liu 2021)[3]	Odds ratio: 2.78 (95% CI 1.97 - 3.91) Based on data from participants in 36 studies	**20** per 1000 **54** per 1000 Difference: **34 more per 1000** (95% CI 19 more - 54 more)		Subgroup analysis of Liu 2021
(PGM) Mutation of prothrombin gene and RPL (Liu 2021)	Odds ratio: 2.08 (95% CI 1.61 - 2.68) Based on data from participants in 64 studies	**20** per 1000 **41** per 1000 Difference: **21 more per 1000** (95% CI 12 more - 32 more)	**Moderate** Upgraded due to large magnitude of effect[4]	Women with recurrent pregnancy loss are probably more likely to have a mutation of the prothrombin gene
(PGM) Mutation of prothrombin gene and 2 or more RPL (Liu 2021)	Odds ratio: 2.23 (95% CI 1.54 - 3.22) Based on data from participants in 33 studies	**20** per 1000 **44** per 1000 Difference: **24 more per 1000** (95% CI 10 more - 42 more)		Subgroup analysis of Liu 2021
(PGM) Mutation of prothrombin gene and RPL3 or more miscarriages (Liu 2021)	Relative risk: 1.89 (95% CI 1.34 - 2.68) Based on data from participants in 31 studies	**20** per 1000 **38** per 1000 Difference: **18 more per 1000** (95% CI 7 more - 34 more)		Subgroup analysis of Liu 2021
Protein S deficiency and RPL (Liu 2021)	Odds ratio: 3.45 (95% CI 1.15 - 10.35) Based on data from participants in 10 studies	**20** per 1000 **66** per 1000 Difference: **46 more per 1000** (95% CI 3 more - 154 more)	**Moderate** Due to serious inconsistency, Upgraded due to Very large magnitude of effect[5]	Women with recurrent pregnancy loss are probably more likely to have a protein S deficiency
LMWH for inherited thrombophilia and live birth (Quenby 2023)	Odds ratio: 1.08 (95% CI 0.65 - 1.78)	**20** per 1000 **22** per 1000 Difference: **2 more per 1000**	**High**	LMWH does not increase the livebirth rate in women who had two or more

	Based on data from 326 participants in studies Follow up absolute risk difference, 0·7%, 95% CI –9·2% to 10·6%	(95% CI 7 fewer - 15 more)		pregnancy losses and confirmed inherited thrombophilia.

1. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:70 %.; **Upgrade: large magnitude of effect.**
2. undefined
3. undefined
4. **Upgrade: large magnitude of effect.**
5. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:59 %.; **Upgrade: very large magnitude of effect.**

PICO (4.3)

Population: People with recurrent miscarriage

Intervention: Male partner: Sperm DNA fragmentation

Comparator: No test

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		No test	Male partner: Sperm DNA fragmentation		
Sperm DNA fragmentation and RPL (Dai 2022)	17 studies[1]	Difference: **MD 8.45 higher** (95% CI 1.48 higher - 15.42 higher)		**Low** Due to very serious inconsistency, Upgraded due to Very large magnitude of effect[2]	Male partner: sperm DNA fragmentation may be increased in couples with RPL (Dai 2022)
Sperm DNA fragmentation and RPL (McQueen 2019) using TUNEL assay	Based on data from 280 participants in 6 studies	Difference: **MD 14.25 higher** (95% CI 4.86 higher - 23.64 higher)		**Low** Due to very serious inconsistency, Upgraded due to Very large magnitude of effect[3]	Male partner: sperm DNA fragmentation measured using TUNEL assay may be increased in couples with RPL (McQueen 2019)

Sperm DNA fragmentation and RPL (McQueen 2019) using SCD assay	Based on data from 316 participants in 5 studies	Difference: **MD 3.54 higher** (95% CI 3.30 lower - 10.38 higher)	**Very low** Due to very serious inconsistency[4]	We are uncertain whether male partner: sperm DNA fragmentation measured using SCD assay is increased or decreased in couples with RPL due to very low certainty evidence (McQueen 2019)
Sperm DNA fragmentation and RPL (McQueen 2019) using SCSA assay	Based on data from 165 participants in 3 studies	Difference: **MD 5.18 higher** (95% CI 0.31 higher - 10.05 higher)	**Low** Due to serious inconsistency, Upgraded due to large magnitude of effect[5]	Male partner: sperm DNA fragmentation measured using SCSA assay may be increased in couples with RPL (McQueen 2019)
Sperm DNA fragmentation and RPL (McQueen 2019) using COMET assay	Based on data from 45 participants in 1 studies[6]	Difference: **MD 10.10 higher** (95% CI 2.10 higher - 18.10 higher)	**Low** Due to serious imprecision, Upgraded due to large magnitude of effect[7]	Male partner: sperm DNA fragmentation measured using comet assay may be increased in couples with RPL (McQueen 2019)

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Dai 2022].
2. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2:98 %.; **Upgrade: very large magnitude of effect.**
3. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2:.98%.; **Upgrade: very large magnitude of effect.**
4. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2: 99%.
5. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:.80%.; **Upgrade: large magnitude of effect.**
6. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [McQueen 2019].
7. **Imprecision: serious.** Low number of patients; **Upgrade: large magnitude of effect.**

PICO (4.4)
Population: People with recurrent miscarriage
Intervention: Antinuclear antibodies (ANA)
Comparator: No test

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		No test	Antinuclear antibodies (ANA)		
ANA (+) and RPL (Ticconi 2022)	Odds ratio: 3.22 (95% CI 2.12 - 4.88) Based on data from participants in 22 studies[1]	20 per 1000	62 per 1000 Difference: **42 more per 1000** (95% CI 21 more - 71 more)	**Low** Due to serious inconsistency, upgraded due to large magnitude of effect[2]	Antinuclear antibodies (ANA) may be increased in women with RPL (Ticconi 2022)
ANA (+) subgroup analysis (titres 1: 40 ≤ ANA ≤ 1: 80) (Chen 2020)[3]	Odds ratio: 2.44 (95% CI 0.42 - 14.06) Based on data from 1859 participants in 3 studies[4]	20 per 1000	47 per 1000 Difference: **27 more per 1000** (95% CI 12 fewer - 203 more)	**Very low** Due to serious inconsistency[5]	We are uncertain whether antinuclear antibodies (1: 40 ≤ ANA ≤ 1: 80) are increased or decreased in women with RPL (Chen 2020)
ANA (+) subgroup analysis (titres ANA ≥ 1: 160) (Chen 2020)	Odds ratio: 45.89 (95% CI 8.44 - 249.45) Based on data from 1859 participants in 3 studies	20 per 1000	484 per 1000 Difference: **464 more per 1000** (95% CI 127 more - 816 more)	**Low** Due to serious inconsistency, Upgraded due to large magnitude of effect[6]	Antinuclear antibodies titres ≥ 160 may be increased in women with RPL (Chen 2020)

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Ticconi 2022].
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:75 %.; **Upgrade: large magnitude of effect.**
3. undefined
4. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. We used 2% as an estimate of RPL. Supporting references [Chen 2020].
5. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:86 %.
6. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2 %.; **Upgrade: large magnitude of effect.**

Evidence to decision – Clinical Question 4, Screening tests

Domain	Summary of judgement	Comments
Certainty of evidence	Low	GRADE varied across tests considered from Very Low to Moderate
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	People having RPL may be more likely to rate a care experience as good if they have a healthcare professional to talk to about their worries/fears for RM investigations.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	
Domain	**Summary of judgement**	**Comments**
Equity	Probably reduced equity	Some investigations for recurrent miscarriage, such as sperm DNA fragmentation, may not be publicly funded. Decisions regarding which tests to undertake should consider the associated costs and likelihood of improved outcomes for the couple
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	In general couples with recurrent pregnancy loss consider testing for possible causes as beneficial.
Domain	**Summary of judgement**	**Comments**
Feasibility	Feasibility varies for different tests	We recognise that not all the tests recommended are available nationwide and that the need to travel to get them done will add costs and stress.

Clinical Question 5 – Cytogenetic analysis of pregnancy tissue

What is the benefit of cytogenetic analysis of pregnancy tissue and when should it be offered?

Evidence to decision – Clinical Question 5, Cytogenetic analysis of pregnancy tissue

Domain	Summary of judgement	Comments
Certainty of evidence	Low	Indirect evidence to the clinical question only was identified and thus downgraded for this. Evidence in systematic reviews were from observational studies but were generally noted to be of moderate quality on quality assessment.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	Cytogenetic testing of pregnancy tissue following miscarriage allows women/couples to gain more insight into the cause of the miscarriage and may help them to process their grief. However, women should be made aware of the unclear relationship of the outcome of testing to the likelihood of a further miscarriage.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Formal economic evaluation is outside of the scope of this clinical question
Additional considerations		
Cytogenetic testing of pregnancy tissue following a miscarriage is usually publicly funded when conducted through hospital miscarriage services.		
Domain	**Summary of judgement**	**Comments**
Equity	Substantial variability is expected or uncertain	Pregnancy tissue has important meaning for Māori which may mean that cytogenetic testing is not preferred for cultural reasons. Return of pregnancy tissue after testing may help mitigate these concerns. Geographical distance may make cytogenetic evaluation by techniques that require tissue culture more challenging because of transfer times and as a result there is a higher chance of test failure for rural and remote women. New testing techniques using CMA may help to mitigate this as cells are not required to be cultured.

Domain	Summary of judgement	Comments
Acceptability	Probably acceptable	The role of cytogenetic testing of pregnancy tissues in guiding clinicians as to whether further investigations or treatments are required is unclear. If women are offered testing of pregnancy tissue by their clinician, they should be made aware of the limitations of testing and the unclear relationship to prognosis in future pregnancies.

Domain	Summary of judgement	Comments
Feasibility	Substantial variability is expected or uncertain	Routine cytogenetic testing of all pregnancy tissue may be difficult to implement in clinical practice, particularly techniques that require cell culture such as conventional karyotyping. Women having medical miscarriage need to be informed how to collect the tissue and arrange transfer to the laboratory for testing.

Clinical Question 6 – Antiphospholipid syndrome

What are the benefits and harms of treatment for antiphospholipid syndrome?

PICO (6.1)

Population: Pregnant women with a history of recurrent miscarriage and antiphospholipid syndrome

Intervention: Aspirin

Comparator: Placebo, no treatment

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Placebo, no treatment	Aspirin		
Live birth (Yang 2021 - Systematic Review)[1]	Odds ratio: 1.42 (95% CI 0.77 - 2.63) Based on data from 214 participants in 5 studies			**Low** Downgraded two levels due to serious risk of bias and indirectness[2]	Aspirin may not increase live birth

1. undefined
2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomisation process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up, Selective outcome reporting.

PICO (6.2)

Population: Pregnant women with a history of recurrent miscarriage and antiphospholipid syndrome

Intervention: Low-molecular weight heparin + aspirin

Comparator: Aspirin

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Aspirin	LMWH + aspirin		
Live birth (Hamulyák 2020; Cochrane Review)[1]	Relative risk: 1.2 (95% CI 1.04 - 1.38) Based on data from 1155 participants in 3 studies	**704** per 1000	**845** per 1000 Difference: **141 more per 1000** (95% CI 28 more - 268 more)	**High** Neither upgraded nor downgraded[2]	LMWH + aspirin results in a slight increase in live birth

Live birth (Yang 2021; Systematic Review)	Odds ratio: 3.2 (95% CI 2.54 - 4.04) Based on data from 1984 participants in 14 studies		**Moderate** Downgraded two levels due to serious risk of bias and indirectness; upgraded due to large magnitude of effect[3]	LMWH + aspirin likely results in a large increase in live birth
Pregnancy loss (Hamulyák 2020; Cochrane Review)[4]	Relative risk: 0.55 (95% CI 0.26 - 1.16) Based on data from 1155 participants in 3 studies	**296** per 1000 **163** per 1000 Difference: **133 fewer per 1000** (95% CI 219 fewer - 47 more)	**High** Neither upgraded nor downgraded[5]	LMWH + aspirin results in little or no difference in pregnancy loss

1. undefined
2. **Publication bias: no serious.** Laskin reported sponsorship from a pharmaceutical study; other studies were funded by research grants.
3. **Risk of Bias: serious.** overall - all studies were judged to be at unclear risk of bias; **Indirectness: serious.** Differences between the population of interest and those studied; may include some women without APS; **Upgrade: large magnitude of effect.**
4. undefined
5. **Risk of Bias: no serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias.

PICO (6.3)

Population: Pregnant women with a history of recurrent miscarriage and antiphospholipid syndrome

Intervention: Unfractionated heparin + aspirin

Comparator: Aspirin

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Aspirin	UFH + aspirin		
Live birth (Hamulyák 2020; Cochrane Review)	Relative risk: 1.74 (95% CI 1.28 - 2.35) Based on data from 140 participants in 2 studies	**428** per 1000	**745** per 1000 Difference: **317 more per 1000** (95% CI 120 more - 578 more)	**High** Neither downgraded nor upgraded	UFH + aspirin results in a slight increase in live birth

Live birth (Yang 2021; systematic review)	Odds ratio: 4.99 (95% CI 3.18 - 7.84) Based on data from 492 participants in 5 studies		**Moderate** Downgraded two levels due to serious risk of bias and indirectness; upgraded due to large magnitude of effect[1]	UFH + aspirin likely results in a large increase in live birth
Pregnancy loss (Hamulyák 2020; Cochrane Review)	Relative risk: 0.46 (95% CI 0.29 - 0.71) Based on data from 140 participants in 2 studies	**570** per 1000 **262** per 1000 Difference: **308 fewer per 1000** (95% CI 405 fewer - 165 fewer)	**Moderate** Downgraded due to serious risk of bias[2]	UFH + aspirin probably reduces the risk of pregnancy loss

1. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomisation process, resulting in potential for selection bias, Selective outcome reporting, Incomplete data and/or large loss to follow up; **Indirectness: serious.** Differences between the population of interest and those studied; **Upgrade: large magnitude of effect.**
2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias (1 quasi-randomised trial).

Evidence to decision – Clinical Question 6, Antiphospholipid syndrome

Domain	Summary of judgement	Comments
Certainty of evidence	Moderate	One Cochrane review and a second systematic review judged most included studies as being at low risk of bias; both reviews, however, were downgraded to moderate quality due to the inclusion of quasi-randomised studies.
Domain	**Summary of judgement**	**Comments**
Values and preferences	No substantial variability expected	Women with antiphospholipid syndrome and a history of recurrent miscarriage who are either expecting to conceive or who are already pregnant may prefer low-molecular weight heparin + aspirin over aspirin alone.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Formal economic evaluation is outside of the scope of this clinical question.
Additional considerations		
Qualitative evidence regarding the decision to take low-molecular weight heparin in combination with aspirin or aspirin alone suggests that women with recurrent miscarriage wished to do anything they could to prevent another miscarriage and so were willing to inject low-molecular weight heparin daily. Any concerns around taking low-molecular weight heparin during pregnancy were focused on the safety of the medication for their unborn child.		
Domain	**Summary of judgement**	**Comments**
Equity	Probably will lead to equitable outcomes	Low-molecular weight heparin and low-dose aspirin are subsidised in Aotearoa New Zealand and Australia and are both widely available. Aspirin in particular, is widely available for purchase in both countries without a prescription and is cheap.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	Aspirin + low-molecular weight heparin are both generally deemed safe and can be administered at home.
Domain	**Summary of judgement**	**Comments**
Feasibility	Substantial variability is expected or uncertain	Low-molecular weight heparin and low-dose aspirin can both be administered at home, are subsidised in Aotearoa New Zealand and Australia and are widely available.

Clinical Question 7 – Genetic/chromosome factors

What are the benefits and harms of investigations for genetic/chromosome factors?

PICO (7.1)

Population: People with unexplained recurrent miscarriage

Intervention: Pre-implantation genetic testing (PGT-A)

Comparator: No treatment (expectant management)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		No treatment (expectant management)	Pre-implantation genetic testing (PGT-A)		
Live birth rate per person - PGT-A (FISH) vs natural conception [SR: Musters 2011][1]	Based on data from 442 participants in 11 studies	**420** per 1000	**350** per 1000	**Very low** Due to serious inconsistency, Due to serious risk of bias[2]	No comparative studies identified. Live birth rate per couple among PGT-A studies varied between 19% and 46%. Live birth rate per couple among studies of natural conception with a history of recurrent miscarriage ranged from 11% to 61%.
Miscarriage rate per person - PGT-A (FISH) vs natural conception [SR: Musters 2011][3]	Based on data from 442 participants in 11 studies	**280** per 1000	**90** per 1000	**Very low** Due to serious inconsistency, Due to serious risk of bias[4]	No comparative studies identified. The miscarriage rate per couple among PGT-A studies varied between 0% and 10%. Miscarriage rate per couple among studies of natural conception with a history of recurrent miscarriage ranged from 14% to 52%.
Live birth rate per embryo transfer - PGT-A (CMA) vs expectant management [cohort: Murugappan 2016]	Based on data from 300 participants in 1 study	**340** per 1000	**320** per 1000	**Very low** Due to serious risk of bias[5]	IVF with PGT-A may have little or no difference on live birth rate per embryo transfer compared to expectant management (p value 0.75)

Miscarriage rate - PGT-A (CMA) vs expectant management [cohort: Murugappan 2016]	Based on data from 300 participants in 1 study	**240** per 1000 **200** per 1000	**Very low** Due to serious risk of bias[6]	IVF with PGT-A may have little or no difference on miscarriage rate compared to expectant management (p value 0.61)
Euploid embryo transfer rate - PGT-A (CMA) [cohort: Murugappan 2016]	Based on data from 198 participants in 1 study	**790** per 1000		Among cycles that completed PGT-A 21% did not have a euploid embryo to transfer. The risk of not having a euploid embryo to transfer was 25% in those under 35yrs and 37% in those over 35yrs.
Live birth rate per embryo transfer - PGT-A (CMA) vs IVF with no PGT-A [cohort: Sato 2019]	Odds ratio: 3.89 (95% CI 1.16 - 13.1) Based on data from 79 participants in 1 study	**216** per 1000 **524** per 1000 Difference: **308 more per 1000** (95% CI 26 more - 567 more)	**Very low** Due to serious imprecision[7]	IVF with PGT-A may improve live birth rate per embryo transfer compared to IVF without PGT-A (p value 0.028)
Live birth rate per person - PGT-A (CMA) vs IVF with no PGT-A [cohort: Sato 2019]	Odds ratio: 1.33 (95% CI 0.45 - 3.91) Based on data from 79 participants in 1 study	**211** per 1000 **268** per 1000 Difference: **57 more per 1000** (95% CI 104 fewer - 300 more)	**Very low** Due to serious imprecision[8]	IVF with PGT-A may have little or no difference on live birth rate per person compared to IVF without PGT-A (p value 0.60)
Miscarriage rate - PGT-A (CMA) vs IVF with no PGT-A [cohort: Sato 2019][9]	Odds ratio: 0.68 (95% CI 0.06 - 6.51) Based on data from 79 participants in 1 study	**200** per 1000 **143** per 1000 Difference: **57 fewer per 1000** (95% CI 185 fewer - 419 more)	**Very low** Due to serious imprecision[10]	IVF with PGT-A may have little or no difference on miscarriage rate compared to IVF without PGT-A (p value 0.68)
Euploid embryo transfer rate - PGT-A (CMA) [cohort: Sato 2019]	Based on data from 79 participants in 1 study	**708** per 1000		Among cycles that completed PGT-A 29.9% did not have a euploid embryo to transfer. 92.5% of embryos were able to be biopsied.
Live birth rate per embryo transfer - PGT-	Odds ratio: 7.0 (95% CI 1.19 - 26.1)	**125** per 1000 **500** per 1000	**Very low** Due to serious imprecision[11]	

A (CMA) vs IVF with no PGT-A [cohort: Pantou 2022]	Based on data from 65 participants in 1 study	Difference: **375 more per 1000** (95% CI 20 more - 664 more)		IVF with PGT-A may improve live birth rate per embryo transfer compared to IVF without PGT-A (p value 0.0038)
Live birth rate per person - PGT-A (CMA) vs IVF with no PGT-A [cohort: Pantou 2022]	Odds ratio: 4.92 (95% CI 1.32 - 18.39) Based on data from 65 participants in 1 study	**125** per 1000 **360** per 1000 Difference: **235 more per 1000** (95% CI 34 more - 599 more)	**Very low** Due to serious imprecision[12]	IVF with PGT-A may improve live birth rate per person compared to IVF without PGT-A (p value 0.0178)
Miscarriage rate - PGT-A (CMA) vs IVF with no PGT-A [cohort: Pantou 2022][13]	Odds ratio: 0.07 (95% CI 0.01 - 0.43) Based on data from 65 participants in 1 study	**750** per 1000 **181** per 1000 Difference: **569 fewer per 1000** (95% CI 721 fewer - 187 fewer)	**Very low** Due to serious imprecision[14]	IVF with PGT-A may improve miscarriage rate compared to IVF without PGT-A (p value 0.0036)
Euploid embryo transfer rate - PGT-A (CMA) [cohort: Pantou 2022]	Based on data from 65 participants in 1 study	**720** per 1000		94.6% of embryos were able to be biopsied.
Live birth rate per embryo transfer - PGT-A (CMA) vs IVF with no PGT-A [cohort: Kato 2023]	Based on data from 321 participants in 1 study	**192** per 1000 **646** per 1000	**Low**	IVF with PGT-A may improve live birth rate per embryo transfer compared to IVF without PGT-A (p value <0.0001)
Live birth rate per person - PGT-A (CMA) vs IVF with no PGT-A [cohort: Kato 2023]	Based on data from 321 participants in 1 study	**288** per 1000 **396** per 1000	**Low**	IVF with PGT-A may improve live birth rate per embryo transfer compared to IVF without PGT-A (p value 0.0123)
Miscarriage rate - PGT-A (CMA) vs IVF with no PGT-A [cohort: Kato 2023]	Based on data from 300 participants in 1 study	**405** per 1000 **78** per 1000	**Low**	IVF with PGT-A may improve miscarriage rate compared to IVF without PGT-A (p value <0.0001)

Preterm birth - PGT-A (CMA) vs IVF with no PGT-A [cohort: Kato 2023]	Based on data from 164 participants in 1 study	**87** per 1000	**42** per 1000	**Low**	IVF with PGT-A may have little or no difference on preterm birth compared to IVF without PGT-A (p value 0.2360)
Small for gestational age - PGT-A (CMA) vs IVF with no PGT-A [cohort: Kato 2023]	Based on data from 164 participants in 1 study	**21** per 1000	**44** per 1000	**Low**	IVF with PGT-A may have little or no difference on SGA compared to IVF without PGT-A (p value 0.4096)
Congenital anomalies - PGT-A (CMA) vs IVF with no PGT-A [cohort: Kato 2023]	Based on data from 164 participants in 1 study	**15** per 1000	**11** per 1000	**Low**	IVF with PGT-A may have little or no difference on rate of congenital anomalies compared to IVF without PGT-A (p value 0.8193)
Median time to pregnancy - PGT-A (CMS) vs expectant management [cohort: Murugappan 2016]	Measured by: Months Lower better Based on data from 300 participants in 1 study	**3.0** Months Median	**6.5** Months Median		

1. undefined
2. **Risk of Bias: serious.** due to no comparative studies so intervention and control groups drawn from different studies; **Inconsistency: serious.** Heterogeneity between studies groups in age (10y difference), number of previous miscarriages, technique used for PGT-A.
3. undefined
4. **Risk of Bias: serious.** due to no comparative studies so intervention and control groups drawn from different studies; **Inconsistency: serious.** Heterogeneity between studies groups in age (10y difference), number of previous miscarriages, technique used for PGT-A.
5. **Risk of Bias: serious.** due to selection bias (2yr difference in mean age between groups), and only good quality embryos tested (21% had no euploid embryo to replace).
6. **Risk of Bias: serious.** due to selection bias (2yr difference in mean age between groups), and only good quality embryos tested (21% had no euploid embryo to replace).
7. **Imprecision: serious.** Wide confidence intervals.
8. **Imprecision: serious.** Wide confidence intervals.
9. Miscarriage rate = miscarriages/ clinical pregnancies
10. **Imprecision: serious.** Wide confidence intervals.
11. **Imprecision: serious.** Wide confidence intervals.
12. **Imprecision: serious.** Wide confidence intervals.
13. Miscarriage rate = miscarriages/ clinical pregnancies
14. **Imprecision: serious.** Wide confidence intervals.

PICO (7.2)

Population: Recurrent miscarriage with known genetic abnormalities

Intervention: Pre-implantation genetic testing (PGT-M or PGT-SR)

Comparator: No treatment (expectant management)

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		No treatment (expectant management)	Pre-implantation genetic testing (PGT-M or PGT-SR)		
Live birth rate per person - PGT-SR (FISH) vs natural conception [SR: Franssen 2011][1]	Based on data from 425 participants in 23 studies	**735** per 1000	**310** per 1000		No comparative studies identified. Live birth rate in PGT-SR group ranged from 0–100%, median 31%. Live birth rate in natural conception group ranged from 64–83%, median 73.5%.
Miscarriage rate per person - PGT-SR (FISH) vs natural conception [SR: Franssen 2011][2]	Based on data from 425 participants in 23 studies	**350** per 1000	**0** per 1000		No comparative studies identified. The miscarriage rate in PGT-SR group ranged from 0–50%, median 0%. Miscarriage rate in natural conception group ranged from 21–49%, median 35%.
Live birth rate - PGT-SR vs expectant management [SR: Li 2022][3]	Odds ratio: 0.55 (95% CI 0.11 - 2.62) Based on data from 125 participants in 2 studies	**680** per 1000	**600** per 1000 Difference: **80 fewer per 1000** (95% CI 491 fewer - 168 more)	**Very low** Due to serious inconsistency[4]	IVF with PGT-SR may have little or no difference on live birth rate compared to expectant management
Miscarriage rate - PGT-SR vs expectant management [SR: Li 2022][5]	Odds ratio: 0.15 (95% CI 0.04 - 0.51) Based on data from 125 participants in 2 studies	**653** per 1000	**240** per 1000 Difference: **413 fewer per 1000** (95% CI 583 fewer - 163 fewer)	**Low** [6]	IVF with PGT-SR may improve miscarriage rates compared to expectant management

1. RPL with a carrier status of a structural chromosomal anomaly
2. RPL with a carrier status of a structural chromosomal anomaly
3. undefined
4. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 71%.;
5. undefined
6. **Inconsistency: no serious.** I2 = 45%.

Evidence to decision – Clinical Question 7, Genetic/chromosome factors

Domain	Summary of judgement	Comments
Certainty of evidence	Very low	Significant limitations to the evidence: • Largely observational data currently; no RCTs were identified • Conclusions limited by differences in techniques used to conduct PGT Systematic reviews were evaluated as being of critically low quality by AMSTAR-2. Outcomes were downgraded for risk of bias (intervention and comparator data drawn from different studies), and imprecision (wide confidence intervals).
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	Formal economic evaluation is out of scope of this clinical question. One included study (Murugappan 2016) conducted a CEA of comparative cohort. PGT-A was not cost effective for increasing live birth.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	
Additional considerations		
In New Zealand: IVF with PGT-SR is funded for selected chromosomal translocations e.g., Robertsonian translocations. If IVF with PGT-M is appropriate for a woman/couple based on the recommendation of the Clinical Genetics service this is usually funded. After 5 years of no live birth with recurrent miscarriage IVF is funded but PGT-A is not. In Australia: MBS funding exists for PGT-M for selected disorders following recommendation for testing from a clinical genetics service. This is not specific to those with recurrent miscarriage. It appears that PGT-A remains a privately funded addition to IVF treatment as no MBS item number was identified for this treatment		
Domain	**Summary of judgement**	**Comments**
Equity	Probably reduced equity	Equity concerns exist around access issues. • Cost of treatment, particularly for PGT-A which is not publicly funded in either Australia or New Zealand, presents are barrier to access for lower socioeconomic status women/couples. Access to public funding for the IVF cycle may remove some of the cost burden but genetic testing of embryos is required to be paid privately and is a significant barrier for many. Access to public

		funding in NZ for couples with no identified genetic issue is dependent on having been trying for a baby for 5 years, and waitlists are approximately 18 months once a patient is accepted for public funding. • Geographic location of IVF clinics for treatment also presents an access barrier. Clinics tend to be located in main centres posing challenges and extra transport and accommodation costs for those who live in rural and remote locations further adding to the cost burden of treatment.

Domain	Summary of judgement	Comments
Acceptability	Substantial variability is expected or uncertain	The views of women/couples regarding the use of PGT in recurrent miscarriage are unclear and at times conflicting.

Additional considerations

For PGT-A:
A cross-sectional survey of patients with recurrent pregnancy loss in Japan (Takeda 2020) found that most patients were not aware of PGT-A. Only a quarter of patients expressed that they wanted to have PGT-A. Most patients who reported wanting PGT-A and who self-assessed as knowing well or knowing a little about PGT-A, stated their reason for wanting PGT-A was “to have a live birth” and not the "to avoid miscarriage” option.
For PGT-SR:
Evidence of patient acceptability was mixed. In a cohort of 268 couples (De Krom 2015), 77% with a translocation were reported to have opted for PGT-SR following genetic counselling. However, in another cohort couples seen in a specialized recurrent miscarriage clinic were reportedly twice as likely to pursue natural conception than PGT-SR (Maithripala 2018).

Domain	Summary of judgement	Comments
Feasibility	Substantial variability is expected or uncertain	Long wait lists for IVF exist in New Zealand (approximately 18 months) reduce access for patients. The requirement to self-fund PGT-A also reduces access. Implementation of PGT techniques for women and couples with recurrent miscarriage would require training of embryologists to undertake biopsy of embryos and ongoing quality auditing. Embryo biopsy tissue would need to be transferred to a central laboratory for testing as genetic testing is often not able to be conducted at clinic sites.

Additional considerations

Access to public funding for PGT-M/PGT-SR often requires genetic counselling. Feasibility of implementing a recommendation for PGT-M/PGT-SR would be dependent on a sufficient genetic counsellor workforce to ensure availability of this service.

Clinical Question 8 – Anatomical factors

What are the benefits and harms of treatment for women who are wanting to become pregnant and who have identified anatomical factors (septum/septa, scars, adhesions, polyps and submucosal fibroids)?

PICO (8.1)

Population: Women with identified anatomical factors/uterine structural differences, with or without recurrent miscarriage

Intervention: Surgical management of septum

Comparator: Expectant management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Expectant management	Surgical management of septum		
Miscarriage rate in patients with complete septum undergoing hysteroscopic metroplasty compared to expectant management (SR Carrera 2022)[1]	Odds ratio: 0.16 (95% CI 0.03 - 0.78) Based on data from 74 participants in 2 studies	**265** per 1000	**55** per 1000 Difference: **210 fewer per 1000** (95% CI 254 fewer - 46 fewer)	**Very low** Due to serious imprecision[2]	We are uncertain whether hysteroscopic metroplasty in patients with complete septum increases or decreases miscarriage rate compared to expectant management
Miscarriage rate in patients with incomplete septum undergoing hysteroscopic metroplasty compared to expectant management (SR Carrera 2022)	Odds ratio: 0.36 (95% CI 0.19 - 0.71) Based on data from 226 participants in 2 studies	**311** per 1000	**140** per 1000 Difference: **171 fewer per 1000** (95% CI 232 fewer - 68 fewer)	**Very low** Due to serious imprecision[3]	We are uncertain whether hysteroscopic metroplasty in patients with incomplete septum increases or decreases miscarriage rate compared to expectant management

Live birth in patients with complete septum undergoing hysteroscopic metroplasty compared to expectant management (SR Carrera 2022)	Odds ratio: 1.61 (95% CI 0.72 - 3.57) Based on data from 144 participants in 3 studies	**317** per 1000 **428** per 1000 Difference: **111 more per 1000** (95% CI 67 fewer - 307 more)	**Very low** Due to serious imprecision[4]	We are uncertain whether hysteroscopic metroplasty in patients with complete septum increases or decreases the odds of a live birth compared to expectant management
Live birth in patients with incomplete septum undergoing hysteroscopic metroplasty compared to expectant management (SR Carrera 2022)	Odds ratio: 2.6 (95% CI 0.84 - 8.05) Based on data from 285 participants in 3 studies	**414** per 1000 **647** per 1000 Difference: **233 more per 1000** (95% CI 42 fewer - 436 more)	**Very low** Due to serious inconsistency and serious imprecision[5]	We are uncertain whether hysteroscopic metroplasty in patients with incomplete septum increases or decreases the odds of a live birth compared to expectant management
Preterm birth in patients with complete septum undergoing hysteroscopic metroplasty compared to expectant management (SR Carrera 2022)	Odds ratio: 0.43 (95% CI 0.02 - 10.6) Based on data from 118 participants in 3 studies	**71** per 1000 **32** per 1000 Difference: **39 fewer per 1000** (95% CI 69 fewer - 377 more)	**Very low** Due to serious imprecision[6]	We are uncertain whether hysteroscopic metroplasty in patients with complete septum increases or decreases the odds of preterm birth compared to expectant management
Preterm birth in patients with incomplete septum undergoing hysteroscopic metroplasty compared to expectant management (SR Carrera 2022)	Odds ratio: 0.3 (95% CI 0.11 - 0.79) Based on data from 227 participants in 3 studies	**144** per 1000 **48** per 1000 Difference: **96 fewer per 1000** (95% CI 126 fewer - 27 fewer)	**Very low** Due to very serious imprecision[7]	We are uncertain whether hysteroscopic metroplasty in patients with incomplete septum increases or decreases the odds of preterm birth compared to expectant management

Live birth rate after resection of septate uterus in patients with RPL* compared to expectant management (SR Jiang 2023)[8]	Relative risk: 1.77 (95% CI 1.26 - 2.49) Based on data from 254 participants in 3 studies	**355** per 1000 **628** per 1000 Difference: **273 more per 1000** (95% CI 92 more - 529 more)	**Very low** Due to serious imprecision[9]	We are uncertain whether resection of septate uterus in patients with RPL increases or decreases live birth rate compared to expectant management
Preterm birth after resection of septate uterus in patients with RPL* compared to expectant management (SR Jiang 2023)	Relative risk: 0.15 (95% CI 0.04 - 0.53) Based on data from 61 participants in 2 studies	**429** per 1000 **64** per 1000 Difference: **365 fewer per 1000** (95% CI 412 fewer - 202 fewer)	**Very low** Due to serious imprecision[10]	We are uncertain whether resection of septate uterus in patients with RPL increases or decreases preterm birth rate compared to expectant management
Miscarriage rate after resection of septate uterus in patients with RPL* compared to expectant management (SR Jiang 2023)	Relative risk: 0.36 (95% CI 0.2 - 0.66) Based on data from 91 participants in 2 studies	**562** per 1000 **202** per 1000 Difference: **360 fewer per 1000** (95% CI 450 fewer - 191 fewer)	**Very low** Downgraded for serious imprecision and serious risk of bias[11]	We are uncertain whether resection of septate uterus in patients with RPL increases or decreases miscarriage rate compared to expectant management
Live birth rate (Rikken 2021)[12] 12 months	Relative risk: 0.88 (95% CI 0.47 - 1.7) Based on data from 80 participants in 1 study	**350** per 1000 **308** per 1000 Difference: **42 fewer per 1000** (95% CI 185 fewer - 245 more)	**Low** Due to serious imprecision and serious risk of bias[13]	Resection of septum may have little or no difference on live birth rate
Pregnancy loss (Rikken 2021)[14] 12 months	Relative risk: 2.3 (95% CI 0.86 - 5.9) Based on data from 80 participants in 1 study	**130** per 1000 **299** per 1000 Difference: **169 more per 1000** (95% CI 18 fewer - 637 more)	**Low** Due to serious imprecision and serious risk of bias[15]	Resection of septum may have little or no difference on pregnancy loss rate
Preterm birth (Rikken 2021)[16]	Relative risk: 1.3 (95% CI 0.37 - 4.4)	**100** per 1000 **130** per 1000	**Low**	Resection of septum may have little or no difference on preterm birth rate

12 months	Based on data from 80 participants in 1 study	Difference: **30 more per 1000** (95% CI 63 fewer - 340 more)	Due to very imprecision and serious risk of bias[17]	

1. undefined
2. **Risk of Bias: no serious.** Inclusion of patients graded with different classification systems of the uterine anomalies, patients diagnosed by different methods (ultrasonography, hysterosalpingography, 3D ultrasound, or hysteroscopy), and patients included without a postoperative control of their surgery. Surgery evolution not accounted for: included studies published between 1997 and 2021.; **Imprecision: serious.** Low number of patients.
3. **Risk of Bias: no serious.** Inclusion of patients graded with different classification systems of the uterine anomalies, patients diagnosed by different methods (ultrasonography, hysterosalpingography, 3D ultrasound, or hysteroscopy), and patients included without a postoperative control of their surgery. Surgery evolution not accounted for: included studies published between 1997 and 2021.; **Imprecision: serious.** Low number of patients.
4. **Risk of Bias: no serious.** Inclusion of patients graded with different classification systems of the uterine anomalies, patients diagnosed by different methods (ultrasonography, hysterosalpingography, 3D ultrasound, or hysteroscopy), and patients included without a postoperative control of their surgery. Surgery evolution not accounted for: included studies published between 1997 and 2021.; **Imprecision: serious.** Wide confidence intervals.
5. **Risk of Bias: no serious.** Inclusion of patients graded with different classification systems of the uterine anomalies, patients diagnosed by different methods (ultrasonography, hysterosalpingography, 3D ultrasound, or hysteroscopy), and patients included without a postoperative control of their surgery. Surgery evolution not accounted for: included studies published between 1997 and 2021.; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 72%.; **Imprecision: serious.** Wide confidence intervals.
6. **Risk of Bias: no serious.** Inclusion of patients graded with different classification systems of the uterine anomalies, patients diagnosed by different methods (ultrasonography, hysterosalpingography, 3D ultrasound, or hysteroscopy), and patients included without a postoperative control of their surgery. Surgery evolution not accounted for: included studies published between 1997 and 2021.; **Imprecision: serious.** Wide confidence intervals.
7. **Risk of Bias: no serious.** Inclusion of patients graded with different classification systems of the uterine anomalies, patients diagnosed by different methods (ultrasonography, hysterosalpingography, 3D ultrasound, or hysteroscopy), and patients included without a postoperative control of their surgery. Surgery evolution not accounted for: included studies published between 1997 and 2021.; **Imprecision: very serious.** Low number of patients, due to inconsistency in data provided (btw miscarriage, live term birth and preterm birth: 0 miscarriage but 6 term birth and 0 preterm out of 10 pregnancies).
8. RPL: ≥2 clinical pregnancies before 22 completed weeks' gestation,
9. **Imprecision: serious.** Low number of patients, Wide confidence intervals.
10. **Imprecision: serious.** Low number of patients.
11. **Risk of Bias: serious.** due to lack of outcome data for the largest study; **Imprecision: serious.** Low number of patients; **Upgrade: large magnitude of effect.**
12. undefined
13. **Risk of Bias: serious.** due to not differencing between women with complete or incomplete septa, mix of women with RPL, primary infertility, preterm birth and one miscarriage; **Imprecision: serious.** Low number of patients, only data from one study.
14. undefined
15. **Risk of Bias: serious.** due to not differencing between women with complete or incomplete septa, mix of women with RPL, primary infertility, preterm birth and one miscarriage; **Imprecision: serious.** Low number of patients, only data from one study, Wide confidence intervals.
16. undefined
17. **Risk of Bias: serious.** due to not differencing between women with complete or incomplete septa, mix of women with RPL, primary infertility, preterm birth and one miscarriage; **Imprecision: serious.** Low number of patients, only data from one study, Wide confidence intervals.

PICO (8.2)

Population: Women with identified anatomical factors/uterine structural differences, with or without recurrent miscarriage

Intervention: Presence of congenital uterine malformation

Comparator: No congenital uterine malformation

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		No congenital uterine malformation	Presence of congenital uterine malformation		
First or second trimester miscarriage - women with arcuate uterus (SR Caballero Campo 2024)	Odds ratio: 1.14 (95% CI 0.77 - 1.68) Based on data from 1778 participants in 4 studies	**364** per 1000	**395** per 1000 Difference: **31 more per 1000** (95% CI 58 fewer - 126 more)	**Very low** Due to serious imprecision[1]	We are uncertain whether the presence of an arcuate uterus increases or decreases the odds of a miscarriage
First or second trimester miscarriage - women with bicornuate uterus (SR Caballero Campo 2024)	Odds ratio: 2.09 (95% CI 1.47 - 2.97) Based on data from 3709 participants in 6 studies	**340** per 1000	**518** per 1000 Difference: **178 more per 1000** (95% CI 91 more - 265 more)	**Low** Downgraded for serious imprecision, Upgraded for large magnitude of effect[2]	The presence of a bicornuate uterus may increase the odds of a miscarriage
First or second trimester miscarriage - women with unicornuate uterus (SR Caballero Campo 2024)	Odds ratio: 0.83 (95% CI 0.45 - 1.56) Based on data from participants in 7 studies	**289** per 1000	**252** per 1000 Difference: **37 fewer per 1000** (95% CI 134 fewer - 99 more)	**Very low** Due to serious imprecision[3]	We are uncertain whether the presence of an unicornuate uterus increases or decreases the odds of a miscarriage
First or second trimester miscarriage - women with didelphys uterus (SR Caballero Campo 2024)	Odds ratio: 1.48 (95% CI 0.91 - 2.39) Based on data from 1690 participants in 4 studies	**395** per 1000	**491** per 1000 Difference: **96 more per 1000** (95% CI 22 fewer - 214 more)	**Very low** Due to serious imprecision[4]	We are uncertain whether the presence of a didelphys uterus increases or decreases the odds of a miscarriage
Preterm delivery - women with arcuate uterus (SR Caballero Campo 2024)	Odds ratio: 8.91 (95% CI 3.1 - 25.63) Based on data from 6159 participants in 2 studies	**49** per 1000	**315** per 1000 Difference: **266 more per 1000** (95% CI 89 more - 520 more)	**Very low** Due to very serious imprecision[5]	We are uncertain whether the presence of an arcuate uterus increases or decreases the odds of a preterm delivery

Preterm delivery - women with bicornuate uterus, aOR (SR Caballero Campo 2024)	Odds ratio: 4.9 (95% CI 3.93 - 6.11) Based on data from 287733 participants in 7 studies	**78** per 1000 **293** per 1000 Difference: **215 more per 1000** (95% CI 172 more - 263 more)	**Low** Downgraded for serious imprecision, Upgraded for large magnitude of effect[6]	The presence of a bicornuate uterus may increase the odds of a preterm delivery
aOR Preterm delivery - women with **unicornuate uterus** (SR Caballero Campo 2024)	Odds ratio: 3.85 (95% CI 1.84 - 8.16) Based on data from 8763 participants in 8 studies	**64** per 1000 **208** per 1000 Difference: **144 more per 1000** (95% CI 48 more - 294 more)	**Low** Downgraded for serious imprecision, Upgraded for large magnitude of effect[7]	The presence of an unicornuate uterus may increase the odds of a preterm delivery
Preterm delivery - women with **didelphys uterus** (SR Caballero Campo 2024)	Odds ratio: 4.62 (95% CI 2.43 - 8.8) Based on data from 262577 participants in 7 studies	**72** per 1000 **264** per 1000 Difference: **192 more per 1000** (95% CI 87 more - 334 more)	**Very low** Due to serious inconsistency and serious imprecision[8]	We are uncertain whether the presence of a didelphys uterus increases or decreases the odds of a preterm delivery

1. **Imprecision: serious.** Wide confidence intervals.
2. **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
3. **Imprecision: serious.** Wide confidence intervals.
4. **Imprecision: serious.** Wide confidence intervals.
5. **Imprecision: very serious.** Wide confidence intervals, due to low number of events in the exposed group.
6. **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
7. **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
8. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 74%.; **Imprecision: serious.** Wide confidence intervals.

PICO (8.3)

Population: Women with identified anatomical factors/uterine structural differences, with or without recurrent miscarriage

Intervention: Surgical management of caesarean scar

Comparator: Expectant management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Expectant management	Surgical management		
Live birth rate after hysteroscopic niche resection compared with expectant management - 47m follow up (He 2023)	Relative risk: 1.48 (95% CI 0.8 - 2.75) Based on data from 166 participants in 1 study	**457** per 1000	**676** per 1000 Difference: **219 more per 1000** (95% CI 91 fewer - 800 more)	**Very low** Due to serious imprecision[1]	We are uncertain whether hysteroscopic niche resection increases or decreases live birth rate compared with expectant management
Preterm birth after hysteroscopic niche resection compared with expectant management - 47m follow up (He, 2023)	Relative risk: 1.66 (95% CI 0.26 - 10.5) Based on data from 166 participants in 1 study	**46** per 1000	**76** per 1000 Difference: **30 more per 1000** (95% CI 34 fewer - 437 more)	**Very low** Due to serious imprecision[2]	We are uncertain whether hysteroscopic niche resection increases or decreases preterm birth compared with expectant management
Live birth subsequent to FET for women with large size [1] CSD compared to women with small size [2] CSD, adjusted* OR (Wang 2022)[3]	Odds ratio: 0.42 (95% CI 0.19 - 0.9) Based on data from 307 participants in 1 study	**263** per 1000	**130** per 1000 Difference: **133 fewer per 1000** (95% CI 200 fewer - 20 fewer)	**Low** Downgraded for serious indirectness, Upgraded for Large magnitude of effect[4]	Large size CSD may decrease the live birth rate subsequent to a FET compared to small size CSD
Miscarriage subsequent to FET for women with large size [1] CSD compared to women with small size	Odds ratio: 1.01 (95% CI 0.45 - 2.28) Based on data from 307 participants in 1 study	**312** per 1000	**314** per 1000 Difference: **2 more per 1000** (95% CI 143 fewer - 196 more)	**Very low** Due to serious indirectness[6]	We are uncertain whether large CSD increases or decreases the miscarriage rate subsequent to a FE compared to small size CSD

[2] CSD, adjusted* OR (Wang 2022)[5]				
Live birth subsequent to FET for women with medium size [3] CSD compared to women with small size [2] CSD, adjusted* OR (Wang 2022)[7]	Odds ratio: 0.83 (95% CI 0.52 - 1.33) Based on data from 434 participants in 1 study	**263** per 1000 **229** per 1000 Difference: **34 fewer per 1000** (95% CI 106 fewer - 59 more)	**Very low** Due to serious indirectness[8]	We are uncertain whether medium CSD increases or decreases the live birth rate subsequent to a FE compared to small size CSD
Miscarriage subsequent to FET for women with medium size [3] CSD compared to women with small size [2] CSD, adjusted* OR (Wang 2022)[9]	Odds ratio: 1.1 (95% CI 0.62 - 1.97) Based on data from 434 participants in 1 study	**312** per 1000 **333** per 1000 Difference: **21 more per 1000** (95% CI 93 fewer - 160 more)	**Very low** Due to serious indirectness[10]	We are uncertain whether medium CSD increases or decreases the miscarriage rate subsequent to a FE compared to small size CSD
Live birth rate after IVF cycle - patients with isthmocele vs previous CS without isthmocele, adjusted (SR Vitagliano 2023)	Odds ratio: 0.62 (95% CI 0.53 - 0.72) Based on data from 7544 participants in 6 studies	**339** per 1000 **241** per 1000 Difference: **98 fewer per 1000** (95% CI 125 fewer - 69 fewer)	**Low** Downgraded for serious indirectness, Upgraded for large magnitude of effect[11]	Isthmocele may decrease live birth rate after an IVF cycle compared to previous CS without isthmocele
Miscarriage rate after IVF cycle - patients with isthmocele vs previous CS without isthmocele, adjusted (SR Vitagliano 2023)	Odds ratio: 1.38 (95% CI 1.09 - 1.76) Based on data from 3247 participants in 6 studies	**210** per 1000 **268** per 1000 Difference: **58 more per 1000** (95% CI 15 more - 109 more)	**Low** Downgraded for serious indirectness, Upgraded for large magnitude of effect[12]	Isthmocele may increase miscarriage rate after an IVF cycle compared to previous CS without isthmocele
Live birth rate after IVF cycle - patients with isthmocele vs previous vaginal birth, adjusted (SR Vitagliano 2023)[13]	Odds ratio: 0.55 (95% CI 0.42 - 0.71) Based on data from 897 participants in 2 studies	**382** per 1000 **254** per 1000 Difference: **128 fewer per 1000** (95% CI 176 fewer - 77 fewer)	**Low** Downgraded for serious indirectness, Upgraded for large magnitude of effect[14]	Isthmocele may decrease live birth rate after an IVF cycle compared to previous vaginal birth

1. **Imprecision: serious.** Wide confidence intervals, only data from one study, Low number of patients.
2. **Imprecision: serious.** Wide confidence intervals, Low number of patients, only data from one study.
3. * Adjusted for age, BMI, fresh or frozen-thawed cycle, the stage of embryo transferred, endometrial thickness. [1] large CSD estimated as residual myometrial thickness (RMT) <3mm [2] small size CSD defined as RMT > 6mm
4. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied; **Upgrade: large magnitude of effect.**
5. * Adjusted for age, BMI, fresh or frozen-thawed cycle, the stage of embryo transferred, endometrial thickness. [1] large CSD estimated as residual myometrial thickness (RMT) <3mm [2] small size CSD defined as RMT > 6mm
6. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied.
7. * Adjusted for age, BMI, fresh or frozen-thawed cycle, the stage of embryo transferred, endometrial thickness. [3] medium CSD estimated as residual myometrial thickness (RMT) in a range of 3-6 mm [2] small size CSD defined as RMT > 6mm
8. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied.
9. * Adjusted for age, BMI, fresh or frozen-thawed cycle, the stage of embryo transferred, endometrial thickness. [3] medium CSD estimated as residual myometrial thickness (RMT) in a range of 3-6 mm [2] small size CSD defined as RMT > 6mm
10. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied.
11. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied; **Upgrade: large magnitude of effect.**
12. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied; **Upgrade: large magnitude of effect.**
13. undefined
14. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied; **Upgrade: large magnitude of effect**

PICO (8.4)

Population: Women with identified anatomical factors/uterine structural differences, with or without recurrent miscarriage

Intervention: Surgical management of adhesions

Comparator: Expectant management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Expectant management	Surgical management		
Miscarriage after hysteroscopic	10.0 (95% CI 2.0 - 26.0)			Very low	N/A

adhesiolysis of mild IUA compared to the general population, pooled proportion (%) (SR Hooker 2022)[1]	Based on data from 130 participants in 4 studies		Due to serious indirectness, serious inconsistency and serious risk of bias[2]	
Live birth after hysteroscopic adhesiolysis of mild IUA compared to the general population, pooled proportion (%) (SR Hooker 2022)[3]	86.6 (95% CI 71.0 - 97.0) Based on data from 142 participants in 5 studies		**Very low** Due to serious indirectness and serious risk of bias[4]	N/A
Term delivery after hysteroscopic adhesiolysis of mild IUA compared to the general population, pooled proportion (%) (SR Hooker 2022)	83.0 (95% CI 53.0 - 95.0) Based on data from 130 participants in 4 studies		**Very low** Due to serious inconsistency, serious indirectness and serious risk of bias[5]	N/A
Live birth after hysteroscopic adhesiolysis in women with Asherman syndrome, percentage (grade 1 to 5) (Hanstede 2021)	67.4 Based on data from 500 participants in 1 study		**Very low** Due to serious risk of bias, serious inconsistency and serious indirectness[6]	N/A
Live birth rate after adhesiolysis - severe Asherman compared to mild (Hanstede 2021)	Odds ratio: 0.31 (95% CI 0.12 - 0.84) Based on data from 500 participants in 1 study		**Low** Downgraded for serious risk of bias and serious indirectness, Upgraded for large magnitude of effect[7]	Severe Asherman treated with adhesiolysis may decrease live birth rate compared to mild, treated, Asherman

1. undefined

2. **Risk of Bias: serious.** due to not adjusting for confounders; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 66.82%.; **Indirectness: serious.** Differences between the intervention/comparator of interest and those studied: comparison was general population (not expectant management of adhesions), due to follow up time ranged between 24.5 months and 3.9 years.
3. undefined
4. **Risk of Bias: serious.** due to not adjusting for confounders; **Indirectness: serious.** Differences between the intervention/comparator of interest and those studied: comparison was general population (not expectant management of adhesions), due to follow up time ranged between 24.5 months and 3.9 years.
5. **Risk of Bias: serious.** due to not adjusting for confounders; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 83.6%.; **Indirectness: serious.** Differences between the intervention/comparator of interest and those studied: comparison was general population (not expectant management of adhesions), due to follow up time ranged between 24.5 months and 3.9 years.
6. **Risk of Bias: serious.** 2 to 7years post-surgery follow up timeframe, confounders (age from 23 to 49, BMI from 17.9 to 40), Asherman from grade 1 to grade 5; **Inconsistency: serious.** due to no CI provided; **Indirectness: serious.** Differences between the intervention/comparator of interest and those studied.
7. **Risk of Bias: serious.** 2 to 7years post-surgery follow up timeframe, confounders (age from 23 to 49, BMI from 17.9 to 40); **Indirectness: serious.** Differences between the intervention/comparator of interest and those studied; **Upgrade: large magnitude of effect.**

PICO (8.5)

Population: Women with identified anatomical factors/uterine structural differences, with or without recurrent miscarriage

Intervention: Surgical management of polyp

Comparator: Expectant management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Expectant management	Surgical management		
Clinical pregnancy after 4 IUI cycles in infertile women who underwent hysteroscopic polypectomy of endometrial polyp compared to women who underwent diagnostic hysteroscopy and polyp biopsy only (Cochrane review Bosteels 2018)	Odds ratio: 4.41 (95% CI 2.45 - 7.96) Based on data from 204 participants in 1 study	**282** per 1000 Difference: **352 more per 1000** (95% CI 208 more - 476 more)	**634** per 1000	**Low** Downgraded for serious risk of bias, serious indirectness and serious imprecision, Upgraded for large magnitude of effect[1]	Surgical management of endometrial polyp may increase clinical pregnancy rates after 4 IUI cycles

Live birth rate from IVF/ICSI after hysteroscopic resection of endometrial polyp vs no treatment of polyp (SR Zhang 2019)	Odds ratio: 1.37 (95% CI 0.9 - 2.09) Based on data from 761 participants in 4 studies		**Very low** Due to serious indirectness and serious imprecision[2]	We are uncertain whether hysteroscopic resection of endometrial polyp increases or decreases live birth rate after IVF/ICSI, compared to no treatment
Miscarriage after IVF/ICSI after hysteroscopic resection of endometrial polyp vs no treatment of polyp (SR Zhang 2019)	Odds ratio: 0.84 (95% CI 0.4 - 1.75) Based on data from 1772 participants in 5 studies		**Very low** Due to serious indirectness and serious imprecision[3]	We are uncertain whether hysteroscopic resection of endometrial polyp increases or decreases miscarriage rate after IVF/ICSI, compared to no treatment

1. **Risk of Bias: serious.** Selective outcome reporting; **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied; **Imprecision: serious.** Wide confidence intervals, Low number of patients, only data from one study; **Upgrade: large magnitude of effect.**
2. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied (no treatment= women without polyp in 3/4 studies); **Imprecision: serious.** Wide confidence intervals.
3. **Indirectness: serious.** Differences between the population of interest and those studied, Differences between the intervention/comparator of interest and those studied (no treatment= women without polyp in 3/5 studies); **Imprecision: serious.** Wide confidence intervals.

PICO (8.6)

Population: Women with identified anatomical factors/uterine structural differences, with or without recurrent miscarriage

Intervention: Surgical management of submucosal fibroid

Comparator: Expectant management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Expectant management	Surgical management		
Myomectomy for submucous fibroid versus no intervention - **Clinical pregnancy** rate in women seeking infertility treatment	Odds ratio: 2.04 (95% CI 0.62 - 6.66) Based on data from 52 participants in 1 study	**273** per 1000	**434** per 1000 Difference: **161 more per 1000** (95% CI 84 fewer - 441 more)	**Very low** Due to serious indirectness and very serious imprecision[1]	We are uncertain whether myomectomy of submucous fibroid increases or decreases clinical pregnancy rates in women seeking infertility treatment

(Cochrane review Metwally 2020)				
Myomectomy for submucous fibroid versus no intervention - **Miscarriage** rate in women seeking infertility treatment (Cochrane review Metwally 2020)	Odds ratio: 1.27 (95% CI 0.27 - 5.97) Based on data from 52 participants in 1 study	**136** per 1000 **167** per 1000 Difference: **31 more per 1000** (95% CI 95 fewer - 348 more)	**Very low** Due to serious indirectness and very serious imprecision[2]	We are uncertain whether myomectomy of submucous fibroid increases or decreases miscarriage rates in women seeking infertility treatment

1. **Indirectness: serious.** population sampled limited (single fibroid of max. 4 cm diameter); **Imprecision: very serious.** no sample size calculation, there is only one study and small number of events, Wide confidence intervals.
2. **Indirectness: serious.** population sampled limited (single fibroid of max. 4 cm diameter); **Imprecision: very serious.** No sample size calculation, there is only one study and small number of events, Wide confidence intervals.

Evidence to decision – Clinical Question 8, Congenital uterine/anatomical factors

Domain	Summary of judgement	Comments
Certainty of evidence	Very Low	The evidence for septate uterus relies on systematic reviews of mostly observational study: the evidence therefore started at low. The evidence was downgraded for imprecision (low number of patients, wide confidence intervals, inconsistent data) and high heterogeneity. It could not be upgraded as it consisted of observational studies. The evidence was therefore very low. The evidence for other congenital uterine malformation (didelphys, bicornuate, arcuate and unicornuate uterus) relies on systematic reviews of mostly observational study: the evidence therefore started at low. Some of the evidence was upgraded for large magnitude of effect. Some of the evidence was downgraded for imprecision (low number of patients, wide confidence intervals, inconsistent data) and high heterogeneity.
Domain	**Summary of judgement**	**Comments**
Values and preferences	No substantial variability expected	Women with a congenital uterine malformation, seeking to become pregnant, may be open to undergo septum resection, especially if they experience recurrent pregnancy loss.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Resources are out of scope.
Domain	**Summary of judgement**	**Comments**
Equity	Varies	Rates of congenital genital anomalies appear to be similar in Indigenous and non-Indigenous, although this statistic covers all genital anomalies, for males and females, rather than just rates of septate uterus. Remote areas in Australia have more cases of congenital genital anomalies compared to cities and inner regions. Even though rates of congenital genital anomalies may be similar between Indigenous and non-Indigenous, length to diagnosis and access to surgical management may vary. No data could be found for equity issues in New Zealand. Inequity may exist between remote and non-remote areas, in term of accessing surgery. Travel to the city where septate resection is more likely to be performed may be necessary.
Domain	**Summary of judgement**	**Comments**

Acceptability	Probably acceptable	Surgical management of septate is already being done.
Domain	**Summary of judgement**	**Comments**
Feasibility	Feasible	Surgical management of congenital uterine anomalies is already being done although it is a specialist skill - waiting list for the procedure may be long.

Evidence to decision – Clinical Question 8, Acquired uterine/anatomical factors

Domain	Summary of judgement	Comments
Certainty of evidence	Low	The evidence for caesarean scar defect (CSD) relies on two high quality systematic reviews and two moderate quality cohort studies. Being observational studies, the evidence started at low. The evidence was further downgraded for indirectness and imprecision (wide confidence intervals, few patients). Some outcomes were upgraded from very low to low certainty due to large magnitude of effect. The evidence for adhesions and Asherman syndrome relies on a low-quality systematic review (due to not registering a protocol) of observational studies, as well as one cohort study. The evidence was of very low certainty due to indirectness, not adjusting for confounders, high heterogeneity, and variation in follow up timeframes. The evidence for polyp relies on one 2018 Cochrane review that included one RCT: the evidence was downgraded for imprecision, wide confidence interval and indirectness. A low-quality systematic review (due to not registering a protocol) of observational studies was also identified: it was downgraded to very low due to indirectness and imprecision. The evidence for submucosal fibroid relies on one Cochrane review from 2020 that included one RCT. The evidence was downgraded for imprecision, wide confidence interval and indirectness.
Domain	**Summary of judgement**	**Comments**
Values and preferences	No substantial variability expected	Despite low evidence of effectiveness of surgical management over expectant management, women with acquired uterine abnormalities may wish to address the issue, especially if those abnormalities cause symptoms such as pain, menstrual irregularities, bleeding. In women with RPL where

		uterine abnormality is suspected to play a role in the aetiology of their condition, surgical management may be preferred - whether or not the evidence is there to confirm effectiveness of an intervention. Availability of surgical techniques (accessibility of hysteroscopic surgery rather than abdominal for instance) may also influence patients' decision and preferences.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Resources are out of scope.
Domain	**Summary of judgement**	**Comments**
Equity	Important issues or potential issues not investigated	We are uncertain of the effect our recommendations may have on equity, due to a lack of research conducted on the topic of acquired uterine abnormalities. However, it is noted that First Nations women in Australia have a higher rate of caesarean section than non-Indigenous women. This could therefore mean an increased risk of developing a niche. In Aotearoa New Zealand, Māori women have a lower rate of caesarean section compared to European/other women. This could therefore mean a decreased risk of developing a niche.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	The lack of evidence around the added value of surgical management over expectant management may not be acceptable to all - more studies are recommended to bridge the knowledge gap.
Domain	**Summary of judgement**	**Comments**
Feasibility	Feasible	Surgical management of acquired uterine anomalies is already being done - no feasibility issue is expected from our recommendation.

Clinical Question 9 – Hypothyroidism

What are the benefits and harms of treatment for hypothyroidism in women with recurrent miscarriage?

PICO (9.1)

Population: Pregnant women with a history of recurrent miscarriage who have abnormally low thyroid function (including subclinical hypothyroidism and those with TPO antibodies)

Intervention: Levothyroxine

Comparator: Placebo

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Placebo	Levothyroxine		
Live birth rate - Subclinical hypothyroidism (Yu 2023)	Relative risk: 1.2 (95% CI 1.01 - 1.42) Based on data from 367 participants in 3 studies			**Low** Observational study design[1]	Levothyroxine may slightly increase the live birth rate however we are limited in our conclusion due to very low certainty evidence
Preterm birth < 37 weeks - Subclinical hypothyroidism (Yu 2023)[2]	Relative risk: 0.58 (95% CI 0.19 - 1.78) Based on data from 328 participants in 2 studies			**Very low** Observational study design, downgraded one level each for selection bias (randomisation) and imprecision (low number of participants)[3]	We are uncertain whether levothyroxine reduces the rate of preterm birth < 37 weeks
Miscarriage - Subclinical hypothyroidism (Yu 2023)	Relative risk: 0.65 (95% CI 0.44 - 0.97) Based on data from 883 participants in 4 studies			**Very low** Observational study design, downgraded one level each for selection bias (randomisation) and inconsistency (heterogeneity)[4]	Levothyroxine may slightly reduce the risk of pregnancy loss however we are limited in our conclusion due to very low certainty evidence
Live birth rate - TPOAb+ (Yu 2023)	Relative risk: 1.14 (95% CI 0.93 - 1.39)			**Very low**	Levothyroxine may have little or no difference on live birth rate

	Based on data from 343 participants in 5 studies		Observational studies; downgraded one level each for selection bias (no randomisation) and inconsistency (low study numbers)[5]	
Preterm birth < 37 weeks - TPOAb+ (Yu 2023)	Relative risk: 0.48 (95% CI 0.32 - 0.72) Based on data from 663 participants in 6 studies		**Low** Downgraded one level each for selection bias (no randomisation in one cohort study) and inconsistency (low study numbers)[6]	Levothyroxine may decrease the risk of preterm birth < 37 weeks
Miscarriage - TPOAb+ (Yu 2023)	Relative risk: 0.59 (95% CI 0.44 - 0.79) Based on data from 579 participants in 8 studies		**Very low** Downgraded two levels for selection bias (no randomisation for two cohort studies) and inconsistency (low study numbers)[7]	Levothyroxine probably reduces the risk of pregnancy loss however we are limited in our conclusion due to very low certainty evidence
Live birth rate - TPOAb+ (Dhillion-Smith 2019)	Relative risk: 1.04 (95% CI 0.72 - 1.51) Based on data from 196 participants in 1 study		**Moderate** Due to serious imprecision[8]	Levothyroxine probably has little or no difference on live birth rate
Live birth rate - TPOAb+ (van Dijk 2022)	Relative risk: 1.03 (95% CI 0.77 - 1.38) Based on data from 187 participants in 1 study	**480** per 1000 **494** per 1000 Difference: **14 more per 1000** (95% CI 110 fewer - 182 more)	**Moderate** Due to serious imprecision[9]	Levothyroxine probably has little or no difference on live birth rate
Miscarriage rate - TPOAb+ (van Dijk 2022)	Relative risk: 0.83 (95% CI 0.56 - 1.25) Based on data from 187 participants in 1 study	**330** per 1000 **274** per 1000 Difference: **56 fewer per 1000** (95% CI 145 fewer - 83 more)	**Moderate** Due to serious imprecision[10]	Levothyroxine probably has little or no difference on miscarriage rate
Preterm birth rate - TPOAb+ (van Dijk 2022)	Relative risk: 1.39 (95% CI 0.3 - 6.49)	**40** per 1000 **56** per 1000	**Low** Due to very serious imprecision[11]	Levothyroxine may have little or no difference on preterm birth rate

	Based on data from 187 participants in 1 study	Difference: **16 more per 1000** (95% CI 28 fewer - 220 more)		
Birth weight (g) - TPOAb+ (Yu 2023)	High better	Difference: **MD 4.8 lower** (95% CI 55.57 lower - 45.96 higher)	**Low** Downgraded two levels for inconsistency (low study numbers and only two studies) [12]	Levothyroxine may have little or no difference on birth weight (g)

1. **Risk of Bias: serious. Imprecision: serious.**
2. undefined
3. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: serious.**
4. **Risk of Bias: serious.** No randomisation: may include participants who are TPOAb+; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2 = 60.4 %.
5. **Risk of Bias: serious.** no randomisation; **Imprecision: serious.** Low number of patients.
6. **Risk of Bias: serious.** 5 of 6 studies are RCT, includes one cohort study; **Imprecision: serious.** Low number of patients.
7. **Risk of Bias: very serious.** 2 of 8 studies were cohort studies, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias; **Imprecision: serious.** Low number of patients.
8. **Indirectness: no serious.** >3 miscarriages subgroup used; **Imprecision: serious.** Low number of patients, due to secondary analysis of a subgroup.
9. **Imprecision: serious.** Low number of patients.
10. **Imprecision: serious.** Low number of patients.
11. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
12. **Imprecision: very serious.** Low number of patients, only data from two studies.

Evidence to decision – Clinical Question 9, Hypothyroidism

Domain	Summary of judgement	Comments
Certainty of evidence	Low to Moderate	For overt hypothyroidism, the evidence was judged as moderate quality as was obtained from cohort studies. For subclinical hypothyroidism or thyroid antibodies, the evidence was judged as low, as was obtained from a systematic review that had no registered protocol and included both RCTs and cohort studies.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	Women with recurrent miscarriage have a strong desire to prevent miscarriage and may be open to levothyroxine even when benefits are uncertain given the low risk of harm. Conversely, women may be reluctant to take a medication whilst pregnant if the benefits are also uncertain and may feel like this treatment offers 'false' hope in preventing another miscarriage.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Formal economic evaluation is outside of the scope of this clinical question
Domain	**Summary of judgement**	**Comments**
Equity	Probably will lead to equitable outcomes	Levothyroxine is subsidised in Aotearoa New Zealand and Australia and is widely available.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	Clinicians may be open to prescribing levothyroxine given the low risk of harm.
Domain	**Summary of judgement**	**Comments**
Feasibility	Probably feasible	Levothyroxine is subsidised in Aotearoa New Zealand and Australia and is widely available. There are no practical treatment alternatives to levothyroxine for hypothyroidism. Prescription of levothyroxine is outside of the scope of practice of midwives, thus would require prescription and monitoring by a woman's general practitioner, an obstetrician or another healthcare professional.

Clinical Question 10 – Intravenous immunoglobulin

What are the benefits of harms of intravenous immunoglobulin treatment for recurrent miscarriage?

PICO (10.1)

Population: Pregnant women with unexplained recurrent miscarriage

Intervention: Immunotherapy intravenous immunoglobulin (IVIg)

Comparator: Placebo, treatment as usual

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the evidence** (Quality of evidence)	**Summary**
		Placebo, treatment as usual	Immunotherapy intravenous immunoglobulin (IVIg)		
Live birth (Wong 2014; Cochrane review)	Odds ratio: 0.98 (95% CI 0.61 - 1.58) Based on data from 303 participants in 8 studies	**590** per 1000	**585** per 1000 Difference: **5 fewer per 1000** (95% CI 123 fewer - 105 more)	**High**	IVIg has little or no difference on live birth
Live birth (Yamada 2022)	Odds ratio: 2.6 (95% CI 1.15 - 5.86) Based on data from 99 participants in 1 study	**347** per 1000	**580** per 1000 Difference: **233 more per 1000** (95% CI 32 more - 410 more)	**Moderate** Downgraded one level for risk of bias; study funded by IVIg manufacturer[1]	High dose IVIg likely results in an increase in live birth in women with 4 or more miscarriages

1. **Risk of Bias: no serious.** due to funding provided by producer of IVIg.

Evidence to decision – Clinical Question 10, Intravenous immunoglobulin

Domain	Summary of judgement	Comments
Certainty of evidence	Moderate	Evidence overall was high, as in part, was obtained from a Cochrane review and a second systematic review but was downgraded to moderate as more evidence is needed in specific groups of patients, such as women with ≥ 4 miscarriages and in respect of dosing.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	Given concerns around the cost and lack of established efficacy of IVIg for unexplained recurrent miscarriage, women may have concerns around IVIg. This must be balanced against IVIg being recommended for women who have had ≥ 4 unexplained miscarriages and for whom this treatment may offer their last hope of a baby.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Formal economic evaluation is outside of the scope of this clinical question.
Additional considerations		
IVIg is not approved in Aotearoa New Zealand and Australia, is expensive, and is unlikely to be approved for use in recurrent miscarriage in the future by either the New Zealand Blood Service or the Australian National Blood Authority.		
Domain	**Summary of judgement**	**Comments**
Equity	Probably will lead to inequitable outcomes	IVIg is expensive and is not publicly funded in Aotearoa New Zealand and Australia; hence access is less likely to be an option for people with lower socio-economic status. Given global shortages of IVIg, the use of IVIg for recurrent miscarriage, where efficacy is yet to be established may result in IVIg not being available for a condition where there is an established therapeutic role such as immune thrombocytopenia, Kawaskai disease, Guillian-Barré syndrome, lupus or to prevent infection in people who have received a bone marrow transplant.
Domain	**Summary of judgement**	**Comments**
Acceptability	Substantial variability is expected or uncertain	Given concerns around, cost, equity, and the lack of established efficacy of IVIg for unexplained recurrent miscarriage, clinicians may have concerns around IVIg. This must be balanced against IVIg being recommended for women who have had ≥ 4 unexplained miscarriages and for those women who are willing to pay for the treatment.

Domain	Summary of judgement	Comments
Feasibility	Probably unfeasible	IVIg is not approved in Aotearoa New Zealand and Australia for recurrent miscarriage and is unlikely to be provided by the New Zealand Blood Service or the national blood donor service in Australia (Lifeblood). The cost of the IVIg may affect its feasibility as a treatment for recurrent miscarriage as may global shortages of IVIg.

Clinical Question 11 – Progesterone treatment for recurrent miscarriage

What are the harms and benefits of treatment with progesterone in pregnant women with a history of recurrent miscarriage (with or without bleeding)?

PICO (11.1)

Population: Pregnant women up to 14 weeks without bleeding and a history of recurrent miscarriage

Intervention: Progesterone (any route) for RPL asymptomatic

Comparator: Placebo, no treatment

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Placebo, no treatment	Progesterone (any route)		
Live birth in women with RPL (≥ 2) asymptomatic without threatened miscarriage (Zhao 2024)	Relative risk: 1.08 (95% CI 0.98 - 1.19) Based on data from 1006 participants in 3 studies	**708** per 1000	**765** per 1000 Difference: **57 more per 1000** (95% CI 14 fewer - 135 more)	**Low** Due to serious imprecision and indirectness[1]	Progestogens may have little or no difference on live birth in women with recurrent miscarriage (≥ 2) without threatened miscarriage (asymptomatic) (Zhao 2024)
Miscarriage in women with RPL asymptomatic sensitivity analysis (*) EtD for details (Haas 2019-RANZCOG 2024)[2]	Relative risk: 0.98 (95% CI 0.82 - 1.18) Based on data from 1684 participants in 10 studies	**275** per 1000	**270** per 1000 Difference: **5 fewer per 1000** (95% CI 49 fewer - 50 more)	**Moderate** Due to serious indirectness[3]	Progesterone (any route) probably has little or no difference on miscarriage in women with RPL asymptomatic

1. **Inconsistency: no serious.** heterogeneity 0%; **Indirectness: no serious.** Differences between the intervention of interest and those studied; **Imprecision: serious.** Wide confidence intervals.
2. undefined
3. **Risk of Bias: no serious.** The sensitivity analysis removed the ones with high risk of bias for allocation (selection bias); **Indirectness: serious.** Differences between the intervention of interest and those studied.

PICO (11.2)

Population: Pregnant women up to 14 weeks with threatened (bleeding) and a history of recurrent miscarriage

Intervention: Progesterone (any route) for RPL and threatened miscarriage

Comparator: Placebo, no treatment

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Placebo, no treatment	Progesterone (any route)		
Live birth for women with early pregnancy bleeding and one or more previous miscarriage (Zhao 2024)	Relative risk: 1.06 (95% CI 0.97 - 1.16) Based on data from 1973 participants in 3 studies[1]	**733** per 1000	**777** per 1000 Difference: **44 more per 1000** (95% CI 22 fewer - 117 more)	**Low** Due to serious imprecision, Due to serious risk of bias[2]	Progesterone (any route) may have little or no difference on live birth for women with early pregnancy bleeding and one or more previous miscarriage (Zhao 2024)
Live birth for women with early pregnancy bleeding and two or more previous miscarriages (RANZCOG 2024)[3]	Relative risk: 1.14 (95% CI 1.04 - 1.24) Based on data from 730 participants in 2 studies	**747** per 1000	**852** per 1000 Difference: **105 more per 1000** (95% CI 30 more - 179 more)	**Moderate** Due to serious imprecision[4]	Progesterone (any route) probably improve on live birth for women with early pregnancy bleeding and TWO or more previous miscarriage
Congenital abnormalities and progesterone use for threatened miscarriage or recurrent miscarriage (Zhao 2024)	Relative risk: 1.06 (95% CI 0.76 - 1.48) Based on data from 6015 participants in 7 studies[5]	**22** per 1000	**23** per 1000 Difference: **1 more per 1000** (95% CI 5 fewer - 11 more)	**Moderate** Due to serious imprecision[6]	Progesterone use for threatened miscarriage or recurrent miscarriage probably has little or no difference on congenital abnormalities (Zhao 2024)
Serious adverse events using progesterone for threatened miscarriage (El-Zibdeh 2005 – Coomarasamy 2020)	Relative risk: 1.07 (95% CI 0.83 - 1.4) Based on data from 4648 participants in 2 studies	**27** per 1000	**29** per 1000 Difference: **2 more per 1000** (95% CI 5 fewer - 11 more)	**Moderate** Due to serious imprecision[7]	Progesterone probably has little or no difference on serious adverse events for threatened miscarriage

1. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Zhao 2024].

2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomisation process, resulting in potential for selection bias; **Imprecision: serious.** Wide confidence intervals.
3. undefined
4. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was 0%; **Imprecision: serious.** Low number of patients; **Publication bias: no serious.** one was funded by United Kingdom National Institute for Health Research Health Technology Assessment program and the other Mothers and babies Golden Casket Clinical Fellowship (L.A.M.). Progesterone and placebo pessaries were provided by Perrigo Australia.
5. Systematic review. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [20].
6. **Imprecision: serious.**
7. **Imprecision: serious.**

Evidence to decision – Clinical Question 11, Progesterone treatment for recurrent miscarriage

Domain	Summary of judgement	Comments
Certainty of evidence	Moderate	Evidence comes from two high-quality systematic reviews,
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	We anticipate that people with two or more previous miscarriages are likely to prefer treatment for early pregnancy bleeding, although this may vary.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	
Domain	**Summary of judgement**	**Comments**
Equity	Probably increase equity	For people with two or more previous miscarriages and early pregnancy bleeding the use of progesterone may increase equity, as it is widely available and funded in Australia and New Zealand.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	Acceptability may vary as, for some pregnant people with no early pregnancy bleeding, and have had two or more previous miscarriages the lack of treatment may be unacceptable despite the lack of evidence. The use of progestogen for people with two or more previous miscarriages and early pregnancy bleeding is probably acceptable.
Domain	**Summary of judgement**	**Comments**
Feasibility	Probably feasible	Progesterone is available and funded in NZ and Australia.

Part 3: Tubal ectopic pregnancy

Clinical Question 12 - Ultrasound features diagnostic of a tubal ectopic pregnancy

What ultrasound features are diagnostic of a tubal ectopic pregnancy?

PICO (12.1)

Population: Pregnant women presenting in early pregnancy with pain and/or bleeding or asymptomatic with pregnancy of unknown location (PUL)

Intervention: Ultrasonography with any of the following features, singularly or in combination:

- Uterus:
  - Empty uterus/no evidence of intrauterine pregnancy
  - Cystic areas/sacs (including pseudo-gestational sac/decidual cyst, cystic area inside the uterus, or pseudo sac)
  - Fluid inside the uterus
  - Heterotopic pregnancy (co-existing intrauterine and ectopic pregnancies)
- Tube and ovary
  - Adnexal mass (yolk sac, fetal pole, fetal heartbeat)
  - Tubal ring sign (also known as bagel sign, donut sign or blob sign)
  - Adnexal cyst (simple)
  - Complex extra-adnexal mass
- Peritoneal cavity
  - Identification of fluid/blood (including free fluid, haemoperitoneum, or free blood in the pelvis)

Comparator: Confirmation of diagnosis of ectopic pregnancy by one or more of the following index tests:

- Surgical/histological confirmation of ectopic pregnancy
- Confirmation of ectopic pregnancy on follow up ultrasound scan
- Rising hCG levels with no evidence of chorionic villi on evacuation of retained products of conception (ERPC)
- Suspected/confirmed ectopic pregnancy which resolved after medical treatment.

Evidence to decision – Clinical Question 12, Ultrasound features diagnostic of a tubal ectopic pregnancy.

Domain	Summary of judgement	Comments
Certainty of evidence	Moderate	The certainty of the evidence is based on NICE's grading of the evidence. NICE's evidence included ten observational studies. One outcome was graded as very low, ten outcomes were graded low, four were graded as moderate and two were graded as high.
Domain	**Summary of judgement**	**Comments**
Values and preferences	N/A	Domain N/A
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Resources are out of scope

Domain	Summary of judgement	Comments
Equity	Important issues or potential issues not investigated	Women living remotely may not benefit from early diagnosis if ultrasound is not easily accessible
Domain	**Summary of judgement**	**Comments**
Acceptability	No important issues with the recommended alternative	No change to diagnosis criteria has been introduced; we do not foresee any acceptability issue
Domain	**Summary of judgement**	**Comments**
Feasibility	No important issues with the recommended alternative	No change to diagnosis criteria has been introduced - we do not foresee any feasibility issue

Clinical Question 13 – Management of tubal ectopic pregnancy

What are the benefits and harms of different treatment options (surgical/medical/expectant management) for tubal ectopic pregnancy?

PICO (13.1)

Population: Pregnant women with suspected ectopic pregnancy who meet local policy criteria for methotrexate (MTX)

Intervention: Active management

Comparator: Expectant management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Expectant management	Active management		
Resolution of the ectopic pregnancy (NMA Al Wattar 2023)	Based on data from 2938 participants in 31 studies Follow up network				
Single dose MTX + mifepristone versus expectant	Relative risk: 1.09 (95% CI 0.89 - 1.33)			**Moderate** Due to serious risk of bias[1]	Single dose MTX + mifepristone probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to expectant management
Single dose MTX versus expectant	Relative risk: 0.97 (95% CI 0.85 - 1.1)			**Moderate** Due to serious risk of bias[2]	Single dose MTX probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to expectant management
Salpingotomy + MTX versus expectant	Relative risk: 1.16 (95% CI 0.98 - 1.38)			**Moderate** Due to serious risk of bias[3]	Salpingotomy + MTX probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to expectant management
Salpingotomy versus expectant	Relative risk: 0.99 (95% CI 0.84 - 1.16)			**Moderate** Due to serious risk of bias[4]	Salpingotomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to expectant management

Salpingectomy versus expectant	Relative risk: 1.05 (95% CI 0.87 - 1.28)		**Moderate** Due to serious risk of bias[5]	Salpingectomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to expectant management
Multi-dose MTX versus expectant	Relative risk: 1.0 (95% CI 0.88 - 1.15)		**Moderate** Due to serious risk of bias[6]	Multi-dose MTX probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to expectant management
Treatment failure (NMA Al Wattar 2023)	Based on data from 2938 participants in 31 studies Follow up network			
Single dose MTX + mifepristone versus expectant	Relative risk: 0.61 (95% CI 0.28 - 1.35)		**Low** Due to serious imprecision and serious risk of bias[7]	Single dose MTX + mifepristone may have little or no difference on the risk of treatment failure compared to expectant management
Single dose MTX versus expectant	Relative risk: 0.77 (95% CI 0.42 - 1.44)		**Low** Due to serious imprecision and serious risk of bias[8]	Single dose MTX may have little or no difference on the risk of treatment failure compared to expectant management
Salpingotomy + MTX versus expectant	Relative risk: 1.53 (95% CI 0.14 - 16.68)		**Low** Due to serious imprecision and serious risk of bias[9]	Salpingotomy + MTX may have little or no difference on the risk of treatment failure compared to expectant management
Salpingotomy versus expectant	Relative risk: 1.12 (95% CI 0.49 - 2.56)		**Low** Due to serious imprecision and serious risk of bias[10]	Salpingotomy may have little or no difference on the risk of treatment failure compared to expectant management
Salpingectomy versus expectant	Relative risk: 0.09 (95% CI 0.03 - 0.3)		**Moderate** Due to serious risk of bias[11]	Salpingectomy probably decreases the risk of treatment failure compared to expectant management

Multi-dose MTX versus expectant	Relative risk: 0.75 (95% CI 0.39 - 1.43)		**Low** Due to serious imprecision and serious risk of bias[12]	Multi dose MTX may have little or no difference on the risk of treatment failure compared to expectant management
Intrauterine pregnancy (IUP) after tubal ectopic pregnancy (EP) - MTX versus expectant management (SR Hao 2023)	Odds ratio: 1.25 (95% CI 0.64 - 2.45) Based on data from 337 participants in 5 studies	**656** per 1000 **704** per 1000 Difference: **48 more per 1000** (95% CI 106 fewer - 168 more)	**Very low** Due to serious imprecision[13]	We are uncertain whether MTX increases or decreases the likelihood of an intrauterine pregnancy after a tubal ectopic pregnancy compared to expectant management
Recurrent EP after EP - MTX versus expectant management (SR Hao 2023)	Odds ratio: 0.69 (95% CI 0.09 - 5.55) Based on data from 255 participants in 3 studies	**67** per 1000 **47** per 1000 Difference: **20 fewer per 1000** (95% CI 61 fewer - 218 more)	**Very low** Due to very serious imprecision[14]	We are uncertain whether MTX increases or decreases the likelihood of recurrent ectopic pregnancy after a tubal ectopic pregnancy compared to expectant management

1. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
2. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
3. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
4. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
5. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
6. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
7. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
8. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
9. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
10. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
11. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
12. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
13. **Imprecision: serious.** Wide confidence intervals, Low number of patients.
14. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.

PICO (13.2)

Population: Pregnant women with suspected ectopic pregnancy who meet local policy criteria for methotrexate (MTX)

Intervention: Salpingectomy
Comparator: Other active management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Other active management	Salpingectomy		
Treatment failure (NMA Al Wattar 2023)	Based on data from 2938 participants in 31 studies Follow up network				
Single dose MTX + mifepristone versus salpingectomy	Relative risk: 6.82 (95% CI 2.17 - 21.47)			**Moderate** Downgraded for serious imprecision and serious risk of bias, Upgraded for large magnitude of effect[1]	Single dose MTX + mifepristone probably increases the risk of treatment failure compared to salpingectomy
Single dose MTX versus salpingectomy	Relative risk: 8.59 (95% CI 3.03 - 24.36)			**Moderate** Downgraded for serious imprecision and serious risk of bias, Upgraded for large magnitude of effect[2]	Single dose MTX probably increases the risk of treatment failure compared to salpingectomy
Salpingotomy + MTX versus salpingectomy[3]	Relative risk: 16.96 (95% CI 1.52 - 189.9)			**Moderate** Downgraded for serious imprecision and serious risk of bias, Upgraded for large magnitude of effect[4]	Salpingotomy + MTX probably increases the risk of treatment failure compared to salpingectomy
Salpingotomy versus salpingectomy	Relative risk: 12.46 (95% CI 5.1 - 30.48)			**Moderate** Downgraded for serious imprecision and serious risk of bias, Upgraded for large magnitude of effect[5]	Salpingotomy probably increases the risk of treatment failure compared to salpingectomy
Salpingectomy versus multi-dose MTX	Relative risk: 0.12 (95% CI 0.04 - 0.38)			**High**	

			Downgraded for serious risk of bias, Upgraded for large magnitude of effect[6]	Salpingectomy decreases the risk of treatment failure compared to multi-dose MTX
Resolution of the ectopic pregnancy (NMA Al Wattar 2023)	Based on data from 2938 participants in 31 studies Follow up network			
Salpingectomy versus single dose MTX + mifepristone	Relative risk: 0.96 (95% CI 0.76 - 1.22)		**Moderate** Due to serious risk of bias[7]	Salpingectomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to single dose MTX + mifepristone
Salpingectomy versus single dose MTX	Relative risk: 1.09 (95% CI 0.93 - 1.27)		**Moderate** Due to serious risk of bias[8]	Salpingectomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to single dose MTX
Salpingectomy versus salpingotomy + MTX	Relative risk: 0.91 (95% CI 0.78 - 1.05)		**Moderate** Due to serious risk of bias[9]	Salpingectomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to salpingotomy + MTX
Salpingectomy versus salpingotomy	Relative risk: 1.07 (95% CI 0.96 - 1.18)		**Moderate** Due to serious risk of bias[10]	Salpingectomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to salpingotomy
Salpingectomy versus multi-dose MTX	Relative risk: 1.05 (95% CI 0.9 - 1.23)		**Moderate** Due to serious risk of bias[11]	Salpingectomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to multi-dose MTX
Anti-Mullerian hormone (AMH) **levels**	High better		**Low**	

between unilateral salpingectomy and control group (SR Kobayashi 2022)	Based on data from 373 participants in 3 studies	Difference: **MD 0.28 fewer** (95% CI 0.50 fewer - 0.06 fewer)	Downgrade for serious imprecision, Upgraded for large magnitude of effect[12]	Unilateral salpingectomy may decrease AMH levels compared to controls (no ectopic pregnancy, no salpingectomy)

1. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
2. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
3. undefined
4. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
5. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
6. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Upgrade: large magnitude of effect.**
7. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
8. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
9. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
10. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
11. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
12. **Imprecision: serious.** Low number of patients; **Upgrade: large magnitude of effect.**

PICO (13.3)

Population: Pregnant women with suspected ectopic pregnancy who meet local policy criteria for methotrexate (MTX)

Intervention: Salpingotomy + methotrexate

Comparator: Other active management

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Other active management	Salpingotomy + methotrexate		
Resolution of the ectopic pregnancy (NMA Al Wattar 2023)	Based on data from 2938 participants in 31 studies Follow up network				

Salpingotomy + methotrexate versus single dose MTX + mifepristone	Relative risk: 1.06 (95% CI 0.86 - 1.31)		**Moderate** Due to serious risk of bias[1]	Salpingotomy + methotrexate probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to single dose MTX + mifepristone
Salpingotomy + methotrexate versus single dose MTX	Relative risk: 1.2 (95% CI 1.06 - 1.36)		**Moderate** Due to serious risk of bias[2]	Salpingotomy + methotrexate probably increases the likelihood of resolution of the ectopic pregnancy compared to single dose MTX
Salpingotomy + methotrexate versus salpingotomy	Relative risk: 1.18 (95% CI 1.07 - 1.3)		**Moderate** Due to serious risk of bias[3]	Salpingotomy + methotrexate probably increases the likelihood of resolution of the ectopic pregnancy compared to salpingotomy
Salpingotomy + methotrexate versus salpingectomy	Relative risk: 1.1 (95% CI 0.96 - 1.28)		**Moderate** Due to serious risk of bias[4]	Salpingotomy + methotrexate probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to salpingectomy
Salpingotomy + methotrexate versus multi-dose MTX	Relative risk: 1.16 (95% CI 1.02 - 1.31)		**Moderate** Due to serious risk of bias[5]	Salpingotomy + methotrexate probably increases the likelihood of resolution of the ectopic pregnancy compared to multi-dose MTX
Treatment failure (NMA Al Wattar 2023)	Based on data from 2938 participants in 31 studies Follow up network			
Single dose MTX + mifepristone versus salpingotomy + methotrexate[6]	Relative risk: 0.4 (95% CI 0.04 - 4.24)		**Low** Due to serious risk of bias and serious imprecision[7]	Single dose MTX + mifepristone may have little or no difference on the risk of treatment failure compared to salpingotomy + MTX
	Relative risk: 0.51 (95% CI 0.05 - 5.08)		**Low**	Single dose MTX may have little or no difference on the risk of treatment

Single dose MTX versus salpingotomy + methotrexate[8]			Due to serious risk of bias and serious imprecision[9]	failure compared to salpingotomy + MTX
Salpingotomy + methotrexate versus salpingotomy	Relative risk: 1.36 (95% CI 0.14 - 12.83)		**Low** Due to serious imprecision and serious risk of bias[10]	Salpingotomy + methotrexate may have little or no difference on the risk of treatment failure compared to salpingotomy
Salpingotomy + methotrexate versus salpingectomy	Relative risk: 16.96 (95% CI 1.52 - 189.9)		**Moderate** Downgraded for serious imprecision and serious risk of bias, Upgraded for large magnitude of effect[11]	Salpingotomy + methotrexate probably increases the risk of treatment failure compared to salpingectomy
Salpingotomy + methotrexate versus multi-dose MTX	Relative risk: 2.05 (95% CI 0.2 - 21.49)		**Low** Due to serious imprecision and serious risk of bias[12]	Salpingotomy + methotrexate may have little or no difference on the risk of treatment failure compared to multi-dose MTX

1. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
2. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
3. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
4. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
5. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
6. undefined
7. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
8. undefined
9. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
10. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.
11. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
12. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals.

PICO (13.4)

Population: Pregnant women with suspected ectopic pregnancy who meet local policy criteria for methotrexate (MTX)

Intervention: Two doses MTX or multi-doses

Comparator: Single dose MTX

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Single dose MTX	Two doses MTX		
Treatment success - two doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 1.84 (95% CI 1.13 - 3.0) Based on data from 485 participants in 4 studies	**789** per 1000	**873** per 1000 Difference: **84 more per 1000** (95% CI 20 more - 129 more)	**Moderate** Downgraded for very serious imprecision, Upgraded for large magnitude of effect[1]	Two doses MTX probably increases treatment success compared to single dose
Treatment success in high hCG group (>3000-5500 IU/L) - two doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 3.23 (95% CI 1.53 - 6.84) Based on data from 133 participants in 4 studies	**500** per 1000	**764** per 1000 Difference: **264 more per 1000** (95% CI 105 more - 372 more)	**Moderate** Downgraded for very serious imprecision, Upgraded for large magnitude of effect[2]	Two doses MTX probably increases treatment success in patients with a high ß-hCG (> 3000-5500 IU/L) compared to single dose
Treatment success in large size adnexal mass (>20-35 mm) - two doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 2.92 (95% CI 1.23 - 6.93) Based on data from 104 participants in 3 studies	**547** per 1000	**779** per 1000 Difference: **232 more per 1000** (95% CI 51 more - 346 more)	**Moderate** Downgraded for very serious imprecision, Upgraded for large magnitude of effect[3]	Two doses MTX probably increases treatment success in patients with a large size adnexal mass (> 20-35 mm) compared to single dose
Treatment failure - two doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 0.54 (95% CI 0.33 - 0.89) Based on data from 485 participants in 4 studies	**211** per 1000	**126** per 1000 Difference: **85 fewer per 1000** (95% CI 130 fewer - 19 fewer)	**Moderate** Due to serious imprecision[4]	Two doses MTX probably decreases treatment failure compared to single dose
Side effects - two doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 1.53 (95% CI 1.01 - 2.3)	**227** per 1000	**310** per 1000 Difference: **83 more per 1000**	**Moderate**	Two doses MTX probably increases side effects compared to single dose

	Based on data from 485 participants in 4 studies	(95% CI 2 more - 176 more)	Downgraded for very serious imprecision, Upgraded for large magnitude of effect[5]	
Tubal rupture - two doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 0.65 (95% CI 0.26 - 1.63) Based on data from 409 participants in 3 studies	**59** per 1000 **39** per 1000 Difference: **20 fewer per 1000** (95% CI 43 fewer - 34 more)	**Low** Due to very serious imprecision[6]	Two doses MTX may have little or no difference on the odds of tubal rupture compared to single dose
Treatment success - multiple doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 1.79 (95% CI 0.89 - 3.62) Based on data from 409 participants in 3 studies		**Low** Due to very serious imprecision[7]	Multiple doses MTX may have little or no difference on treatment success compared to single dose
Treatment success in high hCG group (>800 IU/L) - multiple doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 2.0 (95% CI 0.54 - 7.44) Based on data from 66 participants in 1 study	**771** per 1000 **871** per 1000 Difference: **100 more per 1000** (95% CI 126 fewer - 191 more)	**Low** Due to very serious imprecision[8]	Multiple doses MTX may have little or no difference on treatment success in patient with high hCG (> 800 IU/L) compared to single dose
Treatment success in large size adnexal mass (>20 mm) - multiple doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 1.63 (95% CI 0.38 - 6.96) Based on data from 86 participants in 1 study	**825** per 1000 **885** per 1000 Difference: **60 more per 1000** (95% CI 183 fewer - 145 more)	**Low** Due to very serious imprecision[9]	Multiple doses MTX may have little or no difference on treatment success in patient with a large size adnexal mass (> 2 cm) compared to single dose
Treatment failure - multiple doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 0.56 (95% CI 0.28 - 1.13) Based on data from 298 participants in 3 studies	**159** per 1000 **96** per 1000 Difference: **63 fewer per 1000** (95% CI 109 fewer - 17 more)	**Low** Due to very serious imprecision[10]	Multi doses MTX may have little or no difference on treatment failure compared to single dose
Side effects - multiple doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 2.1 (95% CI 1.24 - 3.54) Based on data from participants in 3 studies		**Low** Due to very serious imprecision[11]	Multiple doses MTX may increase side effects compared to single dose

Tubal rupture - multiple doses vs single dose (SR Alur-Gupta 2020)	Odds ratio: 1.62 (95% CI 0.41 - 6.49) Based on data from 178 participants in 3 studies	**34** per 1000 **54** per 1000 Difference: **20 more per 1000** (95% CI 20 fewer - 152 more)	**Low** Due to very serious imprecision[12]	Multiple doses MTX may have little or no difference on the odds of tubal rupture compared to single dose

1. **Imprecision: very serious.** Wide confidence intervals, Low number of patients; **Upgrade: large magnitude of effect.**
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients; **Upgrade: large magnitude of effect.**
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients; **Upgrade: large magnitude of effect.**
4. **Imprecision: serious.** Low number of patients.
5. **Imprecision: very serious.** Low number of patients, Wide confidence intervals; **Upgrade: large magnitude of effect.**
6. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
7. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
8. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, only data from one study.
9. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, only data from one study.
10. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
11. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
12. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.

PICO (13.5)

Population: Pregnant women with suspected ectopic pregnancy who meet local policy criteria for methotrexate (MTX)

Intervention: MTX

Comparator: Surgery

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Surgery	MTX		
Intrauterine pregnancy (IUP) after tubal ectopic pregnancy (EP) - MTX versus surgery (SR Hao 2023)[1]	Odds ratio: 1.52 (95% CI 1.2 - 1.92) Based on data from 3530 participants in 20 studies	**654** per 1000	**742** per 1000 Difference: **88 more per 1000** (95% CI 40 more - 130 more)	**Low**	MTX may increase the likelihood of an intrauterine pregnancy after a tubal ectopic pregnancy compared to surgery
	Odds ratio: 1.12 (95% CI 0.84 - 1.51)	**113** per 1000	**125** per 1000	**Very low** Due to serious imprecision[2]	

Recurrent EP after EP - MTX versus surgery (SR Hao 2023)	Based on data from 2888 participants in 14 studies	Difference: **12 more per 1000** (95% CI 16 fewer - 48 more)		We are uncertain whether MTX increases or decreases recurrent ectopic pregnancy compared to surgery
IUP after EP - MTX versus salpingectomy (SR Hao 2023)	Odds ratio: 2.11 (95% CI 1.52 - 2.93) Based on data from 1564 participants in 10 studies	**604** per 1000 **763** per 1000 Difference: **159 more per 1000** (95% CI 95 more - 213 more)	**Low** Due to very serious imprecision, Upgraded due to Large magnitude of effect[3]	MTX may increase the likelihood of an intrauterine pregnancy after a tubal ectopic pregnancy compared to salpingectomy
Recurrent EP after EP - MTX versus salpingectomy (SR Hao 2023)	Odds ratio: 0.98 (95% CI 0.57 - 1.71) Based on data from 740 participants in 6 studies	**100** per 1000 **98** per 1000 Difference: **2 fewer per 1000** (95% CI 40 fewer - 60 more)	**Very low** Due to very serious imprecision[4]	We are uncertain whether MTX increases or decreases recurrent ectopic pregnancy compared to salpingectomy
Treatment success - fixed multidose IM MTX versus laparoscopic salpingostomy (Cochrane review Hajenius 2007)	Relative risk: 1.84 (95% CI 0.73 - 4.65) Based on data from 100 participants in 1 study	**714** per 1000 **1314** per 1000 Difference: **600 more per 1000** (95% CI 193 fewer - 2606 more)	**Very low** Due to very serious imprecision and serious risk of bias[5]	We are uncertain whether fixed multidose MTX increases or decreases treatment success compared to laparoscopic salpingostomy
Treatment success - variable dose IM MTX versus laparoscopic salpingostomy (Cochrane review Hajenius 2007)	Relative risk: 1.11 (95% CI 0.52 - 2.34) Based on data from 265 participants in 4 studies	**876** per 1000 **972** per 1000 Difference: **96 more per 1000** (95% CI 420 fewer - 1174 more)	**Low** Due to serious imprecision and serious risk of bias[6]	Variable dose MTX may have little or no difference on treatment success compared to laparoscopic salpingostomy
Treatment success - single dose IM MTX versus laparoscopic salpingostomy (Cochrane review Hajenius 2007)	Relative risk: 0.38 (95% CI 0.2 - 0.71) Based on data from 265 participants in 4 studies	**876** per 1000 **333** per 1000 Difference: **543 fewer per 1000** (95% CI 701 fewer - 254 fewer)	**Low** Due to serious risk of bias and serious imprecision[7]	Single dose MTX may decrease treatment success compared to laparoscopic salpingostomy

Initial hCG levels <3,393.78 IU/L - prediction for treatment success (Zhang 2020)	Based on data from 238 participants in 1 study	Sensitivity 78.9% Specificity 62.5% Positive predictive value 67.78 Negative predictive value 74.76%	**Low**	

1. undefined
2. **Imprecision: serious.** Wide confidence intervals.
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients; **Upgrade: large magnitude of effect.**
4. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: very serious.** Wide confidence intervals, only data from one study.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Wide confidence intervals, Low number of patients.
7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Low number of patients.

Evidence to decision – Clinical Question 13, Management of tubal ectopic pregnancy

Domain	Summary of judgement	Comments
Certainty of evidence	Moderate	In Al Wattar's systematic review, all outcomes were downgraded for high risk of performance bias and for high risk of bias for randomisation. Some outcomes were downgraded for wide confidence intervals. Some outcomes were upgraded for large magnitude of effect. The certainty of the evidence was low to moderate. In Alur Gupta's systematic review, most outcomes were downgraded for low numbers of participants. Some outcomes were downgraded for wide confidence intervals. Some outcomes were upgraded for large magnitude of effect. The certainty of the evidence was therefore low to moderate. In Hao's systematic review, some outcomes were downgraded for imprecision (wide confidence intervals), and some were upgraded for large magnitude of effect. The certainty of the evidence was therefore very low to low. In Kobayashi's systematic review, one outcome was reported (AMH levels after salpingectomy): it was downgraded for low number of patient and upgraded for large magnitude of effect. The certainty of the evidence was therefore low.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	In women with a stable EP, expectant, medical and surgical management and their associated risks should be discussed. A study conducted in New Zealand in 2001 did not find a significant difference in psychological scores between women treated with MTX and women treated by surgery. However, other considerations should also be taken into account. This includes family planning (does the woman wish to become pregnant?), patency of the other fallopian tube, ability to access and afford assisted reproductive treatment if needed. Management also depends on the woman's availability and willingness for long follow up and bloods (in the case of expectant and medical management) and her ability to reach the emergency department in adequate time if needed. This may be a concern for patients living in remote areas.
Domain	**Summary of judgement**	**Comments**

Resources	N/A	Resources are out of scope. However, a 2003 economic evaluation done in New Zealand compared the cost of MTX treatment with that of laparoscopic surgery for unruptured ectopic pregnancy. It found a significant reduction in direct costs when using MTX. Indirect costs were also decreased in women with a hCG < 1500 IU/L treated with MTX.
Domain	**Summary of judgement**	**Comments**
Equity	Likely increases inequity	No equity issues specifically related to the impact and treatment of ectopic pregnancy were identified. However, equity issues related to access to care for First Nations women remain. In the context of an ectopic pregnancy, this may present as a decreased likelihood of the ectopic pregnancy being identified early. This may mean an increased risk of an emergency procedure. There may also be challenges to accessing medical or expectant management for women living remotely, as frequent monitoring and blood tests are needed. Living remotely may also be an issue if medical or expectant management fails and urgent surgical care is needed, leading to an increased risk of maternal death for those living in remote or very remote areas. In New Zealand, data on ectopic pregnancy are sparse. However, Māori women are more at risk of maternal death than non-Māori women.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	Some practitioners may be wary of expectant management despite evidence of some effectiveness in stable EP. Medical management may seem more acceptable. The rates of medical management of EP have risen in the last decades and we do not foresee any acceptability issue with our recommendation. Salpingectomy remains common and we do not foresee any acceptability issue with a surgical management.
Domain	**Summary of judgement**	**Comments**
Feasibility	Probably feasible	The rates of medical management of EP have risen in the last decades. Despite the need of frequent monitoring and blood tests, medical or expectant management is feasible for women living in urban areas and willing to be closely monitored over a few weeks. Salpingectomy remains common and we do not foresee any feasibility issues.

Clinical Question 14 – Salpingectomy vs. salpingostomy/salpingotomy

What are the benefits and harms of salpingectomy compared with salpingostomy/salpingotomy for surgical management of ectopic pregnancy?

PICO (14.1)

Population: Pregnant women with suspected ectopic pregnancy who do not meet the criteria for non-surgical management

Intervention: Salpingostomy/salpingotomy

Comparator: Salpingectomy

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Salpingectomy	Salpingostomy salpingotomy		
Resolution of the ectopic pregnancy - Salpingotomy versus salpingectomy (NMA Al Wattar 2023)	Relative risk: 0.94 (95% CI 0.84 - 1.04) Based on data from 2938 participants in 31 studies Follow up network			**Moderate** Due to serious risk of bias[1]	Salpingotomy probably has little or no difference on the likelihood of resolution of the ectopic pregnancy compared to salpingectomy
Treatment failure - Salpingotomy versus salpingectomy (NMA Al Wattar 2023)	Relative risk: 12.46 (95% CI 5.1 - 30.48) Based on data from 2938 participants in 31 studies			**Moderate** Downgraded for serious imprecision and serious risk of bias, Upgraded for large magnitude of effect[2]	Salpingotomy probably increases the likelihood of treatment failure compared to salpingectomy
Postoperative (within 18 months) **intrauterine pregnancy** rate - salpingotomy versus salpingectomy (SR Wenjing 2022)	Odds ratio: 2.49 (95% CI 1.61 - 3.86) Based on data from 1718 participants in 15 studies	**400** per 1000	**624** per 1000 Difference: **224 more per 1000** (95% CI 118 more - 320 more)	**Low** Downgraded for serious risk of bias, serious inconsistency and serious imprecision, Upgraded for large magnitude of effect[3]	Salpingotomy may increase postoperative intrauterine pregnancy rate compared to salpingectomy
Postoperative (within 18 months) **ectopic pregnancy** rate - salpingotomy versus	Odds ratio: 1.15 (95% CI 0.64 - 2.07) Based on data from 1627 participants in 14 studies	**97** per 1000	**110** per 1000 Difference: **13 more per 1000** (95% CI 33 fewer - 85 more)	**Low** Due to serious risk of bias and serious inconsistency[4]	Salpingotomy may have little or no difference on postoperative ectopic pregnancy rate compared to salpingectomy

salpingectomy (SR Wenjing 2022)				
IUP via natural conception after salpingotomy versus salpingectomy (SR Cheng, 2016)	Relative risk: 1.04 (95% CI 0.98 - 1.21) Based on data from 575 participants in 2 studies	**525** per 1000 **546** per 1000 Difference: **21 more per 1000** (95% CI 10 fewer - 110 more)	**Moderate** Due to serious imprecision[5]	Salpingotomy probably has little or no difference on subsequent likelihood of an intrauterine pregnancy compared to salpingectomy
Repeat tubal ectopic pregnancy after salpingotomy versus salpingectomy (SR Cheng 2016)	Relative risk: 1.3 (95% CI 0.72 - 2.38) Based on data from 575 participants in 2 studies	**61** per 1000 **79** per 1000 Difference: **18 more per 1000** (95% CI 17 fewer - 84 more)	**Moderate** Due to serious imprecision[6]	Salpingotomy probably has little or no difference on subsequent likelihood of a repeat ectopic pregnancy compared to salpingectomy
Intraoperative blood loss - salpingotomy compared to salpingectomy (SR Wenjing 2022)	Lower better Based on data from 946 participants in 11 studies	Difference: **MD 164.86 lower** (95% CI 195.37 lower - 134.34 lower)	**Low** Due to serious inconsistency and serious risk of bias[7]	Salpingotomy may decrease intraoperative blood loss compared to salpingectomy
Operating duration - salpingotomy compared to salpingectomy (SR Wenjing 2022)	Lower better Based on data from 750 participants in 9 studies	Difference: **MD 1.73 lower** (95% CI 6.10 lower - 2.65 higher)	**Very low** Due to serious risk of bias, serious inconsistency and serious imprecision[8]	We are uncertain whether salpingotomy increases or decreases operating duration compared to salpingectomy
FSH levels - salpingotomy compared to salpingectomy (SR Wenjing 2022)	Lower better Based on data from 579 participants in 9 studies	Difference: **MD 2.22 lower** (95% CI 2.83 lower - 1.61 lower)	**Low** Downgraded for serious inconsistency, serious risk of bias and serious imprecision, Upgraded for large magnitude of effect[9]	Salpingotomy may decrease level of FSH compared to salpingectomy
Number of follicles on ultrasound examination of the affected ovary - salpingotomy	High better Based on data from 190 participants in 3 studies	Difference: **MD 3.84 more** (95% CI 3.49 more - 4.20 more)	**Low** Due to serious risk of bias and serious imprecision[10]	Salpingotomy may increase the number of follicles on ultrasound examination of the affected ovary compared to salpingectomy

compared to salpingectomy (SR Wenjing 2022)				

1. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation.
2. **Risk of Bias: serious.** due to high risk of performance bias in 2/3 of the included studies + 47% of included studies had high risk of bias for randomisation; **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
3. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 75%.; **Imprecision: serious.** Wide confidence intervals; **Upgrade: large magnitude of effect.**
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals.
5. **Imprecision: serious.** Low number of patients; **Publication bias: no serious.** included studies 10 years old (2013 and 2014).
6. **Imprecision: serious.** Low number of patients; **Publication bias: no serious.** included studies 10 years old (2013 and 2014).
7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 99%.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 98%.; **Imprecision: serious.** Wide confidence intervals, Low number of patients.
9. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 79%.; **Imprecision: serious.** Wide confidence intervals, Low number of patients; **Upgrade: large magnitude of effect.**
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Imprecision: serious.** Wide confidence intervals, Low number of patients.

Evidence to decision – Clinical Question 14, Salpingectomy vs. salpingostomy/salpingotomy

Domain	Summary of judgement	Comments
Certainty of evidence	Moderate	In Al Wattar's systematic review, outcomes were downgraded for high risk of performance and for high risk of bias for randomisation. The risk of treatment failure outcome was further downgraded for wide confidence intervals and upgraded for large magnitude of effect. The certainty of the evidence was therefore moderate for both outcomes. In Cheng's systematic review, outcomes were downgraded for high risk of imprecision, due to a small sample size leading to insufficient statistical power. The certainty of the evidence was therefore moderate for both outcomes.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	There are few studies on patients' preferences when it comes to surgical treatment of an ectopic pregnancy. However, a 2010 study indicates that women may prioritise resolution of the EP and low likelihood of treatment failure over preservation of future fertility. Salpingectomy may therefore be favoured by some women. However, other considerations may also influence a woman's decision. This may include patency of the other fallopian tube and the ability to access and afford assisted reproductive treatment (ART) if needed. Of note, ART is funded in New Zealand for women with no fallopian tubes; however, the waitlist to access treatment is around two years. Some clinical considerations may also come into play (e.g., the size of the EP, previous history of ectopic pregnancy, severity of the damage to the tube).
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Resources are out of scope however salpingectomy may be more cost-efficient than salpingotomy.
Domain	**Summary of judgement**	**Comments**
Equity	Important issues, or potential issues not investigated	Equity issues related to access to care for First Nations women remain. There may be decreased access to surgery. Living remotely may also be an issue, especially if urgent surgery is needed.
Domain	**Summary of judgement**	**Comments**

Acceptability	Probably acceptable	Salpingectomy is more often practiced than salpingotomy; we do not foresee any acceptability issues from recommending salpingectomy. Offering salpingotomy may not be acceptable for some, as it is a specialist technique that few practitioners are trained to do (see feasibility below).

Domain	Summary of judgement	Comments
Feasibility	Probably feasible	The salpingotomy technique may not be known by many practitioners as it has somewhat fallen out of practice and training schedules in recent years; it may not be feasible to offer it to participants, especially in areas with low access to expert surgery. The outcomes may also vary and depend on the skill and experience of the surgeon. It may therefore be more feasible to offer salpingectomy, which is more often practiced.

Part 4: Non-tubal ectopic pregnancy

Clinical Question 15 - Management of interstitial ectopic pregnancy

What are the benefits and harms of surgical management compared to medical management for interstitial ectopic pregnancy?

PICO (15.1)

Population: Pregnant women with cornual/interstitial suspected ectopic pregnancy
Intervention: Surgical management by laparoscopy or open surgery
Comparator: Medical management with methotrexate or other medications, ultrasound-guided injections

Clinical Question 16 - Management of cervical ectopic pregnancy

What are the benefits and harms of surgical management compared to medical management for cervical ectopic pregnancy?

PICO (15.1)

Population: Pregnant women with cervical ectopic pregnancy
Intervention: Surgical management: dilation and curettage, dilation and curettage combined with uterine artery embolisation, uterine artery embolisation, hysterectomy, balloon tamponade, other surgical techniques, ultrasound-guided injections of methotrexate and other medications (e.g., KCl)
Comparator: Medical management with methotrexate

Evidence to decision – Clinical Questions 15 & 16, Management of interstitial ectopic pregnancy & cervical ectopic pregnancy

Domain	Summary of judgement	Comments
Certainty of evidence	Low	Cervical and interstitial pregnancies are rare with most evidence based on case reports or case series. There are no known RCTs.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	In women with a stable ectopic pregnancy, expectant, medical and surgical management and their associated risks should be discussed emphasising that expectant management is not recommended for cervical pregnancies due to the risk of severe haemorrhage. A study conducted in New Zealand in 2001 did not find a significant difference in psychological scores between women treated with MTX and women treated by surgery. However, other considerations should also be taken into account. This includes family planning, patency of the other fallopian tube, ability to access and afford assisted reproductive treatment if needed. Management also depends on the woman's availability and willingness for long follow up including blood tests (in the case of expectant and medical management) and her ability to reach the emergency department in adequate time if needed. This may be an issue for patients living in remote

		areas. The lack of surgical options for cervical pregnancy should also be discussed.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Resources are out of scope. However, a 2003 economic evaluation done in New Zealand compared the cost of MTX treatment with that of laparoscopic surgery for unruptured ectopic pregnancy. It found a significant reduction in direct costs when using MTX. Indirect costs were also decreased in women with a hCG < 1500 IU/L treated with MTX.
Domain	**Summary of judgement**	**Comments**
Equity	Likely increases inequity	No equity issues specifically related to the impact and treatment of ectopic pregnancy were identified. However, equity issues related to access to care for First Nations women remain. In the context of an ectopic pregnancy, this may present as a decreased likelihood of the ectopic pregnancy being identified early. This risk may be amplified for cervical and interstitial pregnancies which may be harder to identify than tubal pregnancies. This may mean an increased risk of an emergency procedure. There may also be challenges to accessing medical or expectant management for women living remotely, as frequent monitoring and blood tests are needed. Living remotely may also be an issue if medical or expectant management fails and urgent surgical care is needed, leading to an increased risk of maternal death for those living in remote or very remote areas. In New Zealand, data on ectopic pregnancy is sparce. However, Māori women are more at risk of maternal death than non-Māori women.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	Some practitioners may be wary of expectant management despite evidence of some effectiveness in stable EP particularly for cervical pregnancy given the severe risk of haemorrhage. Medical management may seem more acceptable. The rates of medical management of EP have risen in the last decades - we do not foresee any acceptability issue with our recommendation. Salpingectomy remains common as does dilatation and curettage for cervical pregnancy and we do not foresee any acceptability issue with a surgical management.

Domain	Summary of judgement	Comments
Feasibility	Probably feasible	The rates of medical management of EP have risen in the last decades - despite the need of frequent monitoring and blood test, medical or expectant management is feasible for women living in urban areas and willing to be closely monitored over a few weeks. Salpingectomy remains common, as does dilatation and curettage for cervical pregnancy and we do not foresee any feasibility issues. For cervical and interstitial pregnancies, specialist medical staff who may noy be readily available may be required to diagnose and perform certain procedures.

Clinical Question 17 - Management of caesarean scar pregnancy

What are the benefits and harms of different treatment options (surgical/medical/expectant management) compared to expectant management for caesarean scar pregnancy?

PICO (17.1)

Population: Pregnant women with caesarean scar pregnancy

Intervention: UAE or UACE + MTX

Comparator: MTX

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		MTX	UAE or UACE + MTX		
Treatment success after initial treatment - UAE* vs systemic MTX (Cochrane SR Long 2020)[1] 6 months	Relative risk: 1.0 (95% CI 0.9 - 1.12) Based on data from 72 participants in 1 study	**943** per 1000	**943** per 1000 Difference: **0 fewer per 1000** (95% CI 94 fewer - 113 more)	**Low** Due to serious inconsistency and serious imprecision[2]	Uterine arterial embolisation may have little or no difference on treatment success compared to systemic methotrexate
Treatment success after initial treatment - UACE* + MTX vs systemic MTX (Cochrane SR Long 2020)[3] 6 months	Relative risk: 0.87 (95% CI 0.54 - 1.38) Based on data from 28 participants in 1 study	**769** per 1000	**669** per 1000 Difference: **100 fewer per 1000** (95% CI 354 fewer - 292 more)	**Low** Due to very serious imprecision[4]	Uterine arterial chemoembolisation + methotrexate may have little or no difference on treatment success compared to systemic methotrexate
Complications* - UAE vs systemic MTX (Cochrane SR Long 2020)[5] 6 months	Relative risk: 0.47 (95% CI 0.13 - 1.75) Based on data from 72 participants in 1 study	**171** per 1000	**80** per 1000 Difference: **91 fewer per 1000** (95% CI 149 fewer - 128 more)	**Low** Due to very serious imprecision[6]	Uterine arterial embolisation may have little or no difference on the risk of complications compared to systemic methotrexate

Complications - UACE + MTX vs systemic MTX (Cochrane SR Long 2020) 6 months	Relative risk: 0.62 (95% CI 0.26 - 1.48) Based on data from 28 participants in 1 study	**538** per 1000 **334** per 1000 Difference: **204 fewer per 1000** (95% CI 398 fewer - 258 more)	**Low** Due to very serious imprecision[7]	Uterine arterial chemoembolisation + methotrexate may have little or no difference on the risk of complications compared to systemic methotrexate
Adverse events* - UAE vs systemic MTX (Cochrane SR Long 2020)[8] 6 months	Relative risk: 1.58 (95% CI 0.41 - 6.11) Based on data from 72 participants in 1 study	**86** per 1000 **136** per 1000 Difference: **50 more per 1000** (95% CI 51 fewer - 439 more)	**Low** Due to very serious imprecision[9]	Uterine arterial embolisation may have little or no difference on the risk of adverse events compared to systemic methotrexate
Adverse events* - UACE + MTX vs systemic MTX (Cochrane SR Long 2020)[10] 6 months	Relative risk: 1.16 (95% CI 0.32 - 4.24) Based on data from 28 participants in 1 study	**231** per 1000 **268** per 1000 Difference: **37 more per 1000** (95% CI 157 fewer - 748 more)	**Low** Due to serious risk of bias and serious imprecision[11]	Uterine arterial chemoembolisation + methotrexate may have little or no difference on the risk of adverse events compared to systemic methotrexate
Treatment success: UACE + MTX vs ultrasonography-guided local MTX injection (Cochrane SR Long 2020)	Relative risk: 0.95 (95% CI 0.56 - 1.6) Based on data from 45 participants in 1 study	**571** per 1000 **542** per 1000 Difference: **29 fewer per 1000** (95% CI 251 fewer - 343 more)	**Low** Due to very serious imprecision[12]	UACE + MTX may have little or no difference on treatment success compared to ultrasonography-guided local MTX injection
Treatment success - Suction curettage under hysteroscopy versus under ultrasonography after UAE (Cochrane SR Long 2022) 12 months	Relative risk: 0.91 (95% CI 0.81 - 1.03) Based on data from 66 participants in 1 study	**1000** per 1000 **910** per 1000 Difference: **90 fewer per 1000** (95% CI 190 fewer - 30 more)	**Low** Due to serious imprecision and serious risk of bias[13]	Suction curettage under hysteroscopy may have little or no difference on treatment success compared to suction curettage under ultrasonography after UAE
Treatment success - Suction curettage under hysteroscopy	Relative risk: 1.02 (95% CI 0.96 - 1.09)	**977** per 1000 **997** per 1000 Difference: **20 more per 1000**	**Low** Due to serious imprecision and serious inconsistency[14]	Suction curettage under hysteroscopy may have little or no difference on treatment success compared to suction

versus under ultrasonography after UACE (Cochrane SR Long 2022) 2 months	Based on data from 92 participants in 1 study	(95% CI 39 fewer - 88 more)		curettage under ultrasonography after UACE
Complications - Suction curettage under hysteroscopy versus under ultrasonography after UAE (Cochrane SR Long 2022) 12 months	Relative risk: 4.0 (95% CI 0.47 - 33.91) Based on data from 66 participants in 1 study	**30** per 1000 Difference: **90 more per 1000** (95% CI 16 fewer - 987 more)	**120** per 1000	**Very low** Due to serious risk of bias and very serious imprecision[15]	We are uncertain whether suction curettage under hysteroscopy increases or decreases the risk of complications compared to suction curettage under ultrasonography after UE
Complications - Suction curettage under hysteroscopy versus under ultrasonography after UACE (Cochrane SR Long 2022) 2 months	Relative risk: 0.18 (95% CI 0.01 - 3.72) Based on data from 92 participants in 1 study	**45** per 1000 Difference: **37 fewer per 1000** (95% CI 45 fewer - 122 more)	**8** per 1000	**Low** Due to very serious imprecision[16]	Suction curettage under hysteroscopy may have little or no difference on risk of complications compared to suction curettage under ultrasonography after UACE
Blood loss - UAE vs systemic MTX (Cochrane SR Long 2020)	Measured by: Scale: - Lower better Based on data from 72 participants in 1 study	mL Difference: **MD 378.70 lower** (95% CI 401.43 lower - 355.97 lower)	mL	**Low** Due to very serious imprecision[17]	Uterine arterial embolisation may decrease blood loss compared to systemic methotrexate
Blood loss - UACE + MTX vs systemic MTX (Cochrane SR Long 2020)	Measured by: Scale: - Lower better Based on data from 28 participants in 1 study	mL Difference: **MD 879 lower** (95% CI 1135.23 lower - 622.77 lower)	mL	**Low** Due to very serious imprecision[18]	Uterine arterial chemoembolisation + methotrexate may decrease blood loss compared to systemic methotrexate

1. *Uterine arterial embolisation
2. **Inconsistency: serious.** No data available to assess heterogeneity; **Imprecision: serious.** Low number of patients, only data from one study.
3. *Uterine arterial chemoembolisation
4. **Imprecision: very serious.** Low number of patients, only data from one study, Wide confidence intervals.
5. *Complications including heavy bleeding, recurrence of active bleeding, and hysterectomy.
6. **Imprecision: very serious.**

7. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, only data from one study.
8. *Adverse effects in the MTX group included abnormal liver function and severe vomiting; in the UAE group included fever and pain and 1 readmitted woman
9. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, only data from one study.
10. *Adverse effects included mild increase in liver enzymes, mild vomiting, and moderate abdominal or pelvic pain.
11. **Risk of Bias: serious.** due to all treatment were followed by suction curettage; **Imprecision: serious.** Wide confidence intervals, Low number of patients, only data from one study.
12. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, only data from one study.
13. **Risk of Bias: serious.** limitations in the design and implementation of available studies.; **Imprecision: serious.** Low number of patients, only data from one study.
14. **Inconsistency: serious.** no data available to assess heterogeneity.; **Imprecision: serious.** Low number of patients, only data from one study.
15. **Risk of Bias: serious.** limitations in the design and implementation of available studies; **Imprecision: very serious.** Wide confidence intervals, Low number of patients, only data from one study.
16. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, only data from one study.
17. **Imprecision: very serious.** Low number of patients, only data from one study.
18. **Imprecision: very serious.** Low number of patients, only data from one study.

Evidence to decision – Clinical Question 17, Management of caesarean scar pregnancy

Domain	Summary of judgement	Comments
Certainty of evidence	Low	Long's 2020 Cochrane review was downgraded due to very serious imprecision: only one RCT was included, with a low number of participants and wide confidence intervals. The systematic review by Cali et al (2018) is considered low certainty due to wide confidence intervals for the included outcomes. The systematic review by Marchand (2022) included 37 studies, of which three were RCTs. High heterogeneity was noted. The systematic review by Knapman (2023) included 60 studies: two RCTs and 58 observational studies. Knapman intended to do a meta-analysis but could not because most studies used combination therapy, which made comparison difficult, and there was high heterogeneity. The evidence was deemed of low certainty. The RCT by Peng (2015) was of low certainty due to high risk of bias: systematic approaches in the sequence generation process. The RCT by Di Spiezio Sardo (2023) was of low certainty due to risk of bias: blinding was not possible due to the nature of the intervention. The remaining studies by Kaelin Agten (2024), Shen (2021) and Kaelin Agten (2017) were observational and grading therefore started at low. The certainty of the evidence could not be upgraded.
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	Patient preferences, especially in the presence of a viable pregnancy, may vary. Some women may wish to continue with the pregnancy and accept the risks involved, including the risk of hysterectomy. The decision may depend on the woman's age and family planning expectations.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Resources are out of scope
Domain	**Summary of judgement**	**Comments**
Equity	Likely increases inequity	First Nations women in Australia have a higher rate of caesarean section than non-Indigenous women. This could therefore mean an increased risk of caesarean scar pregnancy. This inequity may be compounded by issues related to access of care. For women who choose to continue with the pregnancy,

		frequent monitoring will be necessary, and urgent intervention may be required, which may be an issue for those living remotely. In Aotearoa New Zealand, Māori women have a lower rate of caesarean section compared to European/other women. This could therefore mean a decreased risk of Caesarean scar pregnancy. However, equity issues related to access of care remain.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	Medical and surgical management of caesarean scar pregnancy, especially for non-viable pregnancies (e.g., no heartbeat) is already being done. We do not foresee any acceptability issue. Expectant management and ongoing caesarean scar pregnancy involves several risks; some physicians may be reluctant to offer this option to patients.
Domain	**Summary of judgement**	**Comments**
Feasibility	Probably feasible	The recommended interventions are already being done and we do not foresee any feasibility issues.

Part 5: Anti-D

Clinical Question 18 - Anti-D rhesus prophylaxis

What are the benefits and harms of anti-D rhesus prophylaxis for women with a positive pregnancy test and vaginal bleeding, miscarriage or ectopic pregnancy up to 12 weeks?

PICO (18.1)

Population: Pregnant women up to 12 weeks with a positive pregnancy test and vaginal bleeding, miscarriage and ectopic pregnancy

Intervention: Anti-D rhesus prophylaxis

Comparator: Placebo, no intervention

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Summary
		Placebo, no intervention	Anti-D rhesus prophylaxis		
Risk of seroconversion in threatened miscarriage					
Anti-D seroconversion during pregnancy - PV bleeding at any stage of pregnancy vs no PV bleeding [Cohort Hernandez-Andrade 2003]	Odds ratio: 11.4 (95% CI 2.9 - 44.0) Based on data from 48 participants in 2 studies	**208** per 1000	**750** per 1000	**Very low** Due to serious imprecision[1]	We are uncertain if PV bleeding at any time in the pregnancy has an impact on the risk of anti-D seroconversion during pregnancy in Rh negative women due to very low certainty evidence and very wide confidence intervals
Anti-D seroconversion during pregnancy - PV bleeding before 20 weeks of pregnancy vs no PV bleeding [Cohort Hernandez-Andrade 2003]	Odds ratio: 7.6 (95% CI 0.8 - 69.5) Based on data from 48 participants in 2 studies	**42** per 1000	**250** per 1000	**Very low** Due to serious imprecision[2]	We are uncertain if PV bleeding before 20 weeks has an impact on the risk of anti-D seroconversion during pregnancy in Rh negative women due to very low certainty evidence and very wide confidence intervals

Anti-D seroconversion during pregnancy - Threatened miscarriage vs no PV bleeding [Cohort Hernandez-Andrade 2003]	Odds ratio: 3.7 (95% CI 0.6 - 32.2) Based on data from 48 participants in 2 studies	42 per 1000 — 167 per 1000	Very low Due to serious imprecision[3]	We are uncertain if threatened miscarriage has an impact on the risk of anti-D seroconversion during pregnancy in Rh negative women due to very low certainty evidence and very wide confidence intervals
Efficacy of anti-D prophylaxis in spontaneous miscarriage				
Anti-D sensitisation within 2 yrs - anti-D vs no anti-D miscarriage [RCT Visscher 1972][4]	Based on data from 57 participants in 1 study	0 per 1000 — 0 per 1000 Difference: **0 fewer per 1000**	Low Due to serious risk of bias, Due to serious imprecision[5]	There were too few who experienced anti-D sensitisation within 2 yrs to determine whether anti-D rhesus prophylaxis made a difference
Anti-D sensitisation within 6 months - anti-D vs no anti-D miscarriage [Cohort Goldman 1972][6]	Odds ratio: 0.53 (95% CI 0.02 - 11.4) Based on data from 79 participants in 1 study	35 per 1000 — 0 per 1000 Difference: **35 fewer per 1000** (95% CI 34 fewer - 258 more)	Very low Due to serious imprecision[7]	We are uncertain if anti-D rhesus prophylaxis has an impact on the risk of anti-D seroconversion within 6 months of pregnancy in Rh negative women due to very low certainty evidence and very wide confidence intervals

1. **Imprecision: serious.** Wide confidence intervals.
2. **Imprecision: serious.** Wide confidence intervals.
3. **Imprecision: serious.** Wide confidence intervals.
4. Included women with spontaneous miscarriage and those having surgical management of incomplete miscarriage
5. **Risk of Bias: serious.** high risk of bias for attrition and reporting biases. No placebo used; **Imprecision: serious.** No events, only data from one study.
6. Included women with spontaneous miscarriage and those having abortion - spontaneous miscarriage subgroup only used
7. **Imprecision: serious.** Only data from one study, Wide confidence intervals.

Evidence to decision – Clinical Question 18, Anti-D

Domain	Summary of judgement	Comments
Certainty of evidence	Very low	Visscher 1972 and Gavin 1972 RCTs were downgraded due to being assessed as being at a high risk of bias Goldman 1972 and Hernandez-Andrade 2003 were observational studies
Domain	**Summary of judgement**	**Comments**
Values and preferences	Substantial variability is expected or uncertain	A lack of information about the prevention of Rh D sensitisation and anti-D immunoglobulin was an important theme in qualitative research of this topic. Many women were not aware the evidence is not strong for anti-D use in the first trimester, that they had a choice whether or not to receive anti-D. Some women wanted more involvement in the decision-making process. Given the limitations in the evidence to support anti-D use in the first trimester, decision making should be informed and take into account individual circumstances. For expectant or medical management of miscarriage, especially at earlier gestations and where the woman considers her family complete, women may conclude that anti-D is not warranted.
Domain	**Summary of judgement**	**Comments**
Resources	N/A	Formal economic evaluation is outside the scope of this question. Anti-D immunoglobin for vaginal bleeding in the first trimester for Rh D negative women comes at a considerable cost for health services. However, the cost of treatment is unknown for a pregnancy affected by HDFN as is the quality-of-life cost for women/couples associated with fetal loss due to this condition.
Domain	**Summary of judgement**	**Comments**
Equity	Substantial variability is expected	Anti-D immunoglobulin is widely available across Australia and Aotearoa New Zealand currently and is routinely used later in pregnancy and during the postnatal period. Although it requires cold storage in a refrigerator no equity concerns with access are identified. Some evidence suggests that anti-D is less frequently discussed in ED and GP settings than by health professionals who specialize in caring for pregnancy (midwives, GP obstetricians, O&G clinicians etc.). First Nations women, and Māori women, are more likely to book with a maternity care provider after the first trimester according to national maternity clinical indicator statistics, so may be more likely to receive care for early pregnancy bleeding from ED or a GP.
Domain	**Summary of judgement**	**Comments**
Acceptability	Probably acceptable	

Additional considerations
Indirect evidence from use of prophylactic anti-D in the 3rd trimester: Harkness 2016 - Qualitative focus groups with 11 British midwives regarding routine prophylactic anti-D in the 3rd trimester (referred to as RAADP). Among themes identified, a consideration of informed consent featured. It was noted that "the process of providing written information and receiving formal, written consent seemed well-established when offering RAADP. In particular, documentation of refusal of consent was considered important. However, the process of facilitating informed decision-making seemed less clear. The midwives described their discussion with women as conveying the need for anti-D Ig because it was policy, rather than explaining the pros and cons of accepting it." The authors made note that the midwives always referred to 'giving', rather than 'offering', anti-D.

Domain	Summary of judgement	Comments
Feasibility	Probably feasible	Anti-D immunoglobulin is a human blood product extracted from the plasma of blood donors with high-titre circulating anti-D antibodies. Since Rh D immunoglobulin must be stored at 2°C to 8°C until ready for use, it is typically dispensed through the hospital blood bank or pharmacy but also may be stocked in the obstetric office or clinic. Requires signed consent as it is a blood product.

Additional considerations
No studies were identified that specifically considered the prevalence of Rh D negative blood types in Australia and Aotearoa New Zealand populations.

Appendix H: Māori equity toolkit

The College is committed to considering equity, including for First Nations peoples, Māori and Pacific peoples as part of guideline development.

The following tool was developed by Dr Maira Patu, Dr Angela Beard and Professor Suzanne Pitama- Maori Indigenous Health Innovation, University of Otago, Christchurch. The toolkit seeks to identify any differences in how Māori patients receive and experience care within health systems, particularly as it relates to the principles of Te Whare Tapa Whā (a model/understanding of the concept of Māori health).

Questions within each domain also provide opportunity to highlight ways to address or mitigate these gaps and work towards reducing health inequities between Māori and non-Māori in Aotearoa New Zealand.

The complete equity toolkit is available in the RANZCOG Handbook for the development of statements and guidelines.

1. Marginalisation data

What is the prevalence for this condition for Māori compared to non-Māori?
What are the morbidity and mortality rates for Māori compared to non-Māori?

- See Introduction- Epidemiology section of this statement.

2. Racism (including personally mediated racism (unintentional and intentional), institutionalised racism causing inequity, internalised racism

Is there any evidence that Māori do not receive best practice for this condition?
Do rates of diagnosis for Māori match the prevalence, age of onset, and severity for the condition?
Do rates of treatment, referral, and intervention for Māori match the prevalence, age of onset, and severity for the condition?

- No data for Māori wahine identified.

3. Colonisation

What barriers to health care might a Māori patient with this condition encounter?

Access to care

- We suggest that Māori may find attending appointments and or hospital for diagnosis and management a barrier.

4. Ratonga hauora (Barriers to health)

How can these barriers be mitigated at the point of care, including: Actions by clinician

- Provision of culturally safe and competent care to foster improved clinician-patient trust and rapport in provision of antenatal care; including explanation of the reason for interventions, involvement of whanau, respectful communication, using te reo if possible.

Funding streams available for hauora Māori and non-Māori services

- Resources and funding are out of scope for this Clinical Guideline. The availability of hauora Māori and non-Māori services is likely to differ within each jurisdiction.
- The Te Whatu Ora directory provides a search tool to assist clinicians and patients with a search tool to help identify services offered by Kaupapa Māori organisations and practitioners (by Māori, for Māori). The directory enables searches to filter by health service type (including maternity services and

pregnancy ultrasound), provider (including Lead Maternity Carers), region and language spoken (including Māori). See- https://www.adhb.health.nz/your-health/find-a-midwife/

5. Te reo Māori and whakawhanaungatanga

What opportunities are there to use te reo Māori headings?
Are key Māori concepts communicated using suitable, respectful language? Is te reo included if appropriate, with correct translation where necessary?

- Limited in most maternity services in Aotearoa.

What terms in the SNOMED NZ edition Te Reo Māori language reference set are relevant to this page?

- None identified. Te reo Māori terms used throughout guideline where suitable.

Version	Date of Version	Pages revised / Brief Explanation of Revision
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