Queensland Clinical Guidelines

Translating evidence into best clinical practice

Maternity and Neonatal **Clinical Guideline**

Early pregnancy loss

Queensland Government

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Acknowledgement

We acknowledge the Traditional Custodians of the land on which we work and pay our respect to the Aboriginal and Torres Strait Islander Elders past, present and emerging.

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The guideline is not a substitute for clinical judgement, knowledge and expertise, or medical advice. Variation from the guideline, taking into account individual circumstances, may be appropriate.

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

- Providing care within the context of locally available resources, expertise, and scope of practice
- Supporting consumer rights and informed decision making, including the right to decline intervention or ongoing management
- Advising consumers of their choices in an environment that is culturally appropriate and which enables comfortable and confidential discussion. This includes the use of interpreter services where necessary
- Ensuring informed consent is obtained prior to delivering care
- Meeting all legislative requirements and professional standards
- Applying standard precautions, and additional precautions as necessary, when delivering care
- Documenting all care in accordance with mandatory and local requirements

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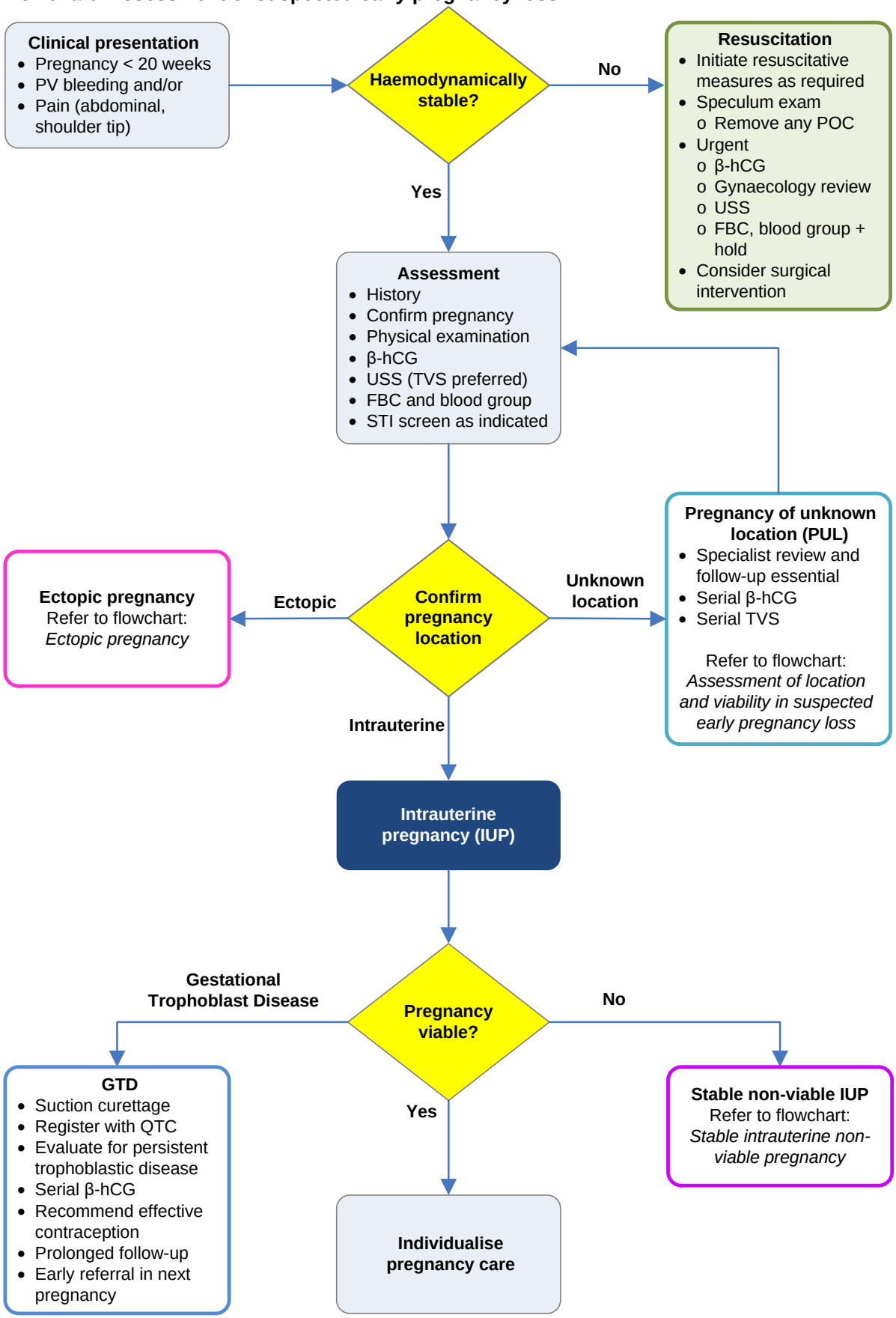
Flowchart: Assessment of suspected early pregnancy loss

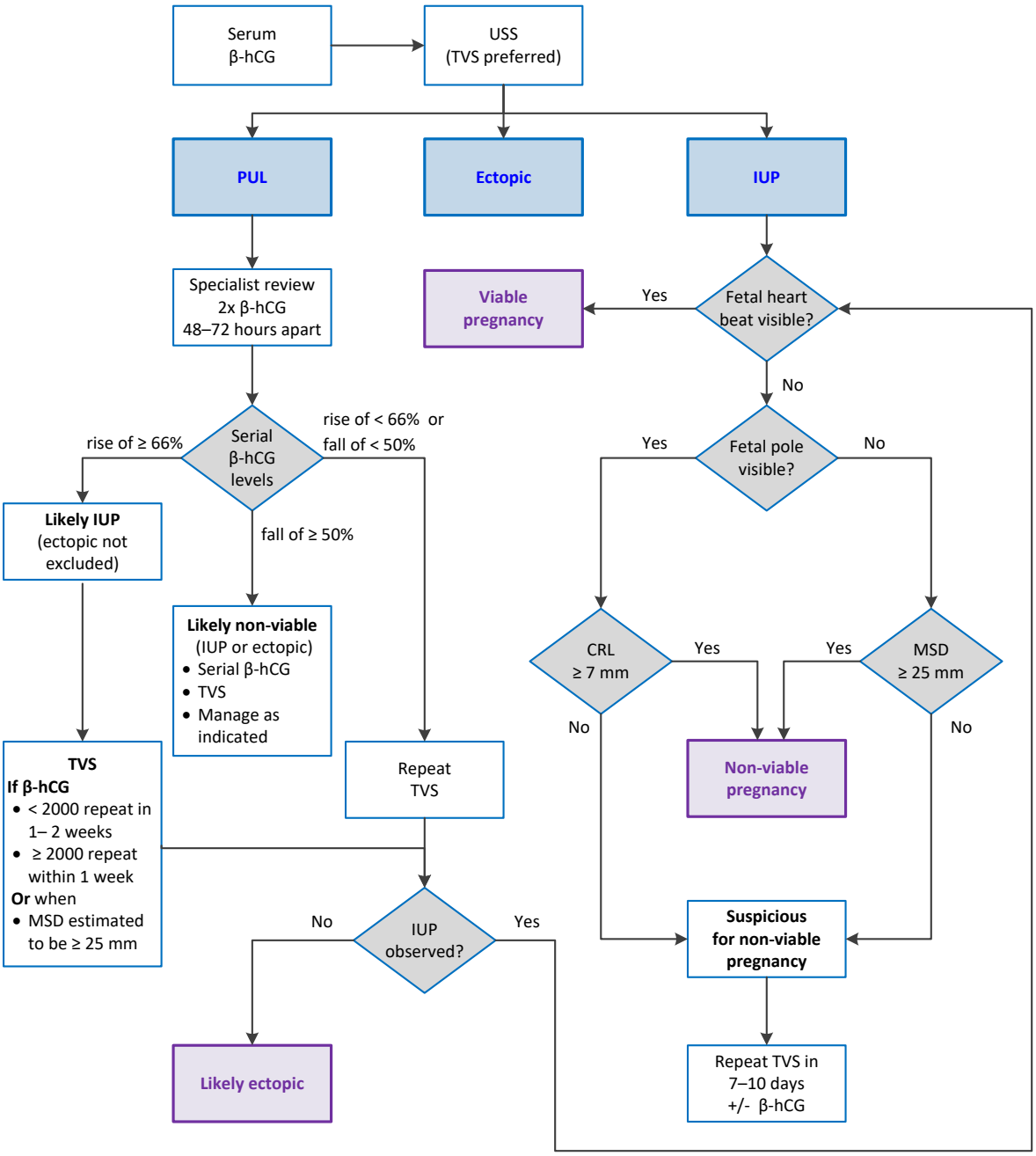


β-hCG: human chorionic gonadotropin, **FBC:** full blood count, **GP:** General practitioner, **GTD:** gestational trophoblast disease, **IUP:** intrauterine pregnancy, **POC:** products of conception, **PUL:** pregnancy of unknown location, **PV:** per vaginam, **QTC:** Queensland Trophoblast Centre, **STI:** sexually transmitted infection, **TVS:** transvaginal scan, **USS:** ultrasound scan, **>:** greater than

Flowchart: F22.29-2-V5-R27

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

Use clinical judgement and consider the woman's individual circumstances when recommending management and the need for specialist referral



Non viable diagnostic criteria (TVS)

- MSD ≥ 25 mm and no fetus present
- Fetus with CRL ≥ 7 mm is visible, but no fetal heart movements demonstrated after observation of ≥ 30 seconds
- Absence of embryo with heartbeat ≥ 2 weeks after a scan that showed a gestational sac without a yolk sac
- Absence of embryo with heartbeat ≥ 11 days after a scan that showed a gestational sac with a yolk sac
- Absence of embryo with heartbeat 7 days or more after USS that showed a fetal pole less than 7 mm with no cardiac activity

TVS interval

- Estimate repeat TVS interval based on expected normal gestational sac growth rate of 1 mm/day

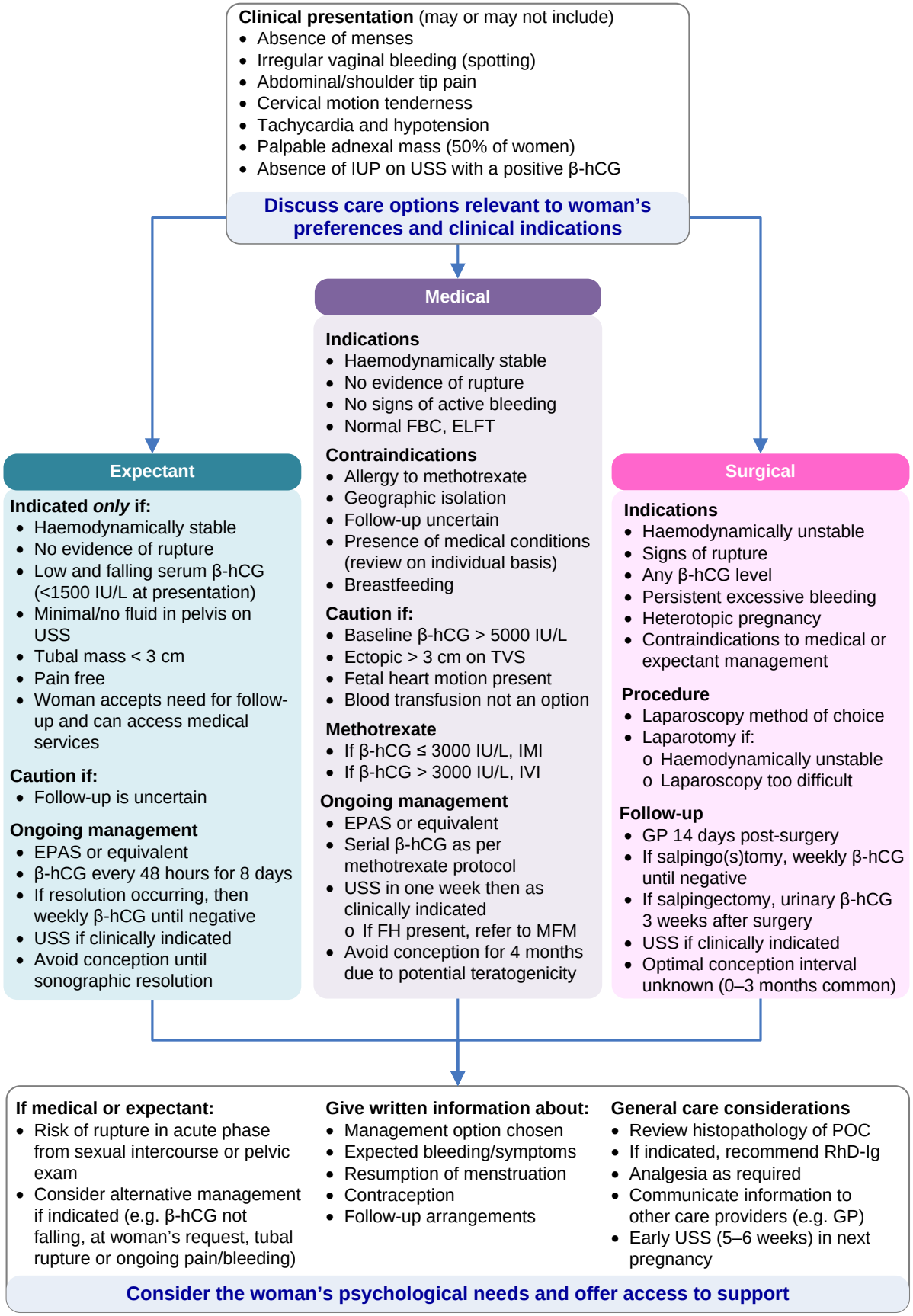
Worked example

- If MSD =12 mm, repeat TVS in 13 days or more (12 mm MSD + 13 mm growth over 13 days equals expected MSD of 25 mm)

β-hCG: human chorionic gonadotropin (all β-hCG measurements in international units/L (IU/L)), **CRL:** crown rump length, **IUP:** intrauterine pregnancy, **MSD:** mean sac diameter, **PUL:** pregnancy of unknown location, **TVS:** transvaginal scan, **USS:** ultrasound scan, **>:** greater than, **<:** less than, **≥:** greater than or equal to, **≤:** less than or equal to

Flowchart: F22.29-4-V3-R27

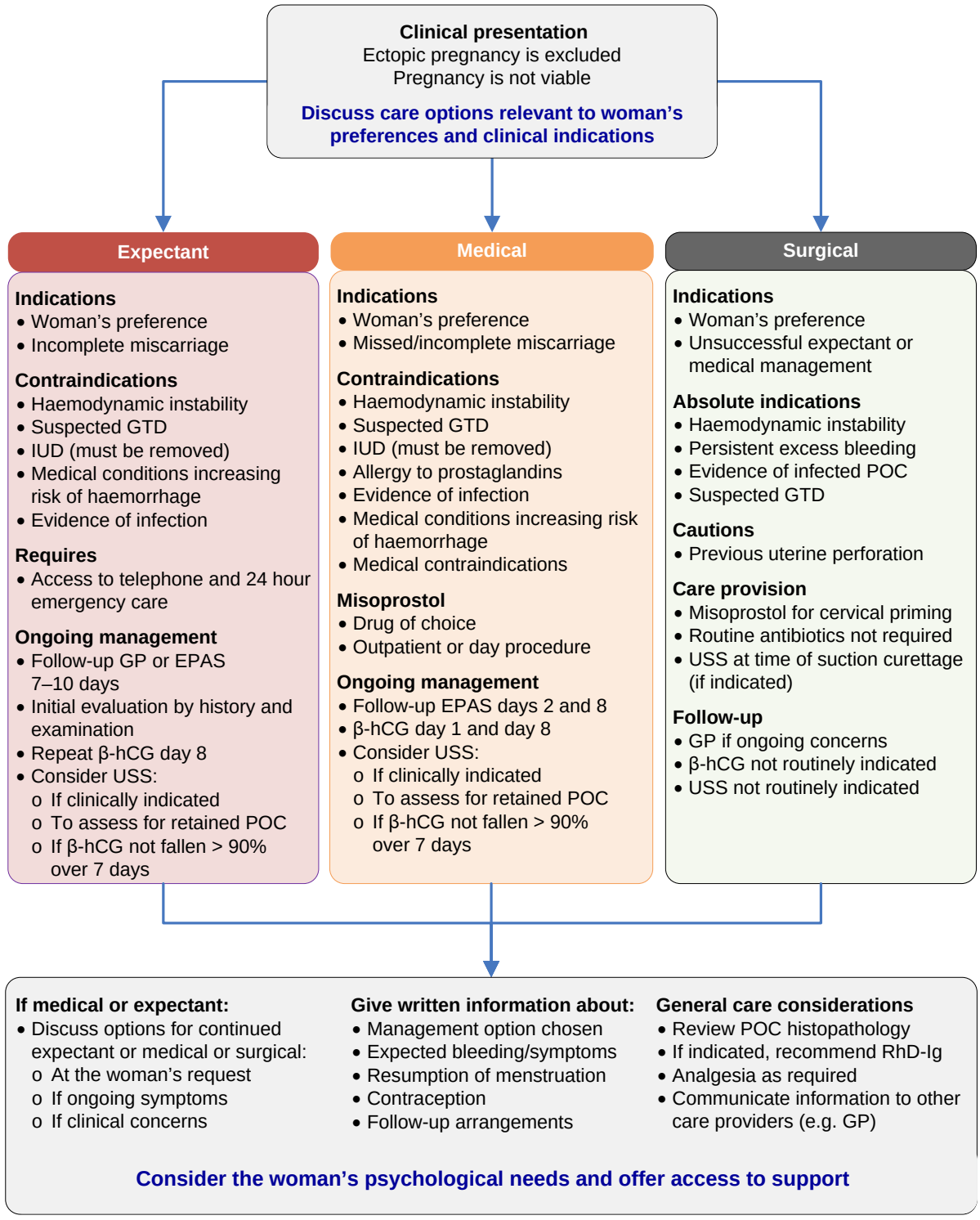
Flowchart: Ectopic pregnancy



β-hCG: human chorionic gonadotropin, **ELFT:** electrolyte & liver function test, **EPAS:** Early Pregnancy Assessment Service, **FBC:** full blood count, **GP:** General Practitioner, **GTD:** gestational trophoblast disease, **IMI:** intramuscular injection, IU/L: international units per litre, **IUP:** intrauterine pregnancy, **IVI:** intravenous injection, **MFM:** maternal fetal medicine, **POC:** products of conception, **PUL:** pregnancy of unknown location, **PV:** per vaginam, **QTC:** Queensland Trophoblast Centre, **RhD-Ig:** RhD immunoglobulin, **TVS:** transvaginal scan, **USS:** ultrasound scan, **>:** greater than

Flowchart: F22.29-3-V6-R27

Flowchart: Stable intrauterine non-viable pregnancy



β-hCG: human chorionic gonadotropin (all β-hCG measurements in International units/L (IU/L)), **EPAS:** early pregnancy assessment service, **FBC:** full blood count, **GP:** General Practitioner, **GTD:** gestational trophoblast disease, **IUD:** intrauterine device, **IUP:** Intrauterine pregnancy, **POC:** products of conception, **PUL:** pregnancy of unknown location, **PV:** per vaginam, **QTC:** Queensland Trophoblast Centre, **RhD-Ig:** RhD immunoglobulin, **TVS:** transvaginal scan, **USS:** ultrasound scan, **>:** greater than

Flowchart: F22.29-1-V5-R27

Table of Contents

List of Tables

Abbreviations

β-hCG	Beta human chorionic gonadotropin
BMI	Body mass index
CRL	Crown rump length
ELFT	Electrolytes, liver function test
EPAS	Early pregnancy assessment service
EPL	Early pregnancy loss
FBC	Full blood count
FMH	Fetomaternal haemorrhage
GP	General practitioner
GTD	Gestational trophoblast disease
HM	Hydatidiform mole
IUP	Intrauterine pregnancy
LNMP	Last normal menstrual period
MSD	Mean sac diameter
POC	Products of conception
PUL	Pregnancy of unknown location
PV	Per vaginam
QTC	Queensland Trophoblast Centre
Rh D	Rh D blood type
RhD-Ig	RhD immunoglobulin
TAS	Transabdominal ultrasound
TVS	Transvaginal ultrasound
USS	Ultrasound scan

Definitions

Anembryonic pregnancy	Gestational sac develops, but the embryo does not form.
Complete miscarriage	Complete expulsion of products of conception (POC). Further management of miscarriage by medical or surgical intervention is not required.
Early Pregnancy Assessment Service	A hospital based service which is able to assess and manage early pregnancy loss. Equivalent services may have different names or structures across Queensland.
Early pregnancy loss	For the purposes of this document, early pregnancy loss refers to a loss within the first 20 completed weeks of pregnancy.
Ectopic pregnancy	Pregnancy located outside of the uterus, usually in the fallopian tubes but may be in the cornu, cervix, caesarean section scar, ovary or other sites.
Expectant management	No specific intervention; awaiting spontaneous passage of POC.
Gestational Trophoblastic Disease	A spectrum of disease characterised by an autonomous overgrowth of fetal chorionic tissue or trophoblast. Includes molar pregnancy (complete or partial).
Heterotopic pregnancy	Multiple pregnancy with an intrauterine plus ectopic pregnancy (e.g. tubal, cervical, ovarian, abdominal).
Incomplete miscarriage	Incomplete expulsion of POC.
Inevitable miscarriage	Miscarriage or expulsion of products is imminent or happening.
Medical management	Use of drugs to aid the expulsion of POC.
Miscarriage	Pregnancy loss occurring before 20 completed weeks of gestation or at less than 400 g birth weight.
Missed miscarriage	Ultrasound confirmed non-viable pregnancy with no bleeding.
Pregnancy of unknown location	Pregnancy test is positive but the pregnancy cannot be visualised by ultrasound.
Recurrent miscarriage	Three or more consecutive miscarriages. There is no specific term for non-consecutive pregnancy losses.
Threatened miscarriage	Any vaginal bleeding other than spotting before 20 weeks completed gestation with evidence of a progressive, viable pregnancy at ultrasound.
Woman/women	QCG recognise that individuals have diverse gender identities. In QCG documents, although the terms *woman* and *women* are used, these guidelines are inclusive of people who are pregnant or give birth and who do not identify as female.[1,2]

1 Introduction

Early pregnancy loss (EPL) is estimated to occur in approximately 15% of recognised pregnancies.[3] It can have negative consequences both physically and psychologically. Physical complications can include infection, haemorrhage, embolism, damage to uterus and associated structures, and anaesthetic complications. Psychological complications such as grief, depression and anxiety are common.[3]

Little can be done to prevent a threatened pregnancy loss from progressing. However, high quality care can increase levels of satisfaction with care, minimise negative outcomes, and support women and their families to navigate their way through an emotional and highly stressful time.[4]

1.1 Clinical standards

Table 1. Clinical standards

Aspect	Consideration
Standard care	• Refer to Queensland Clinical Guideline *Standard care*[5] for care considered 'usual' or 'standard' • Includes for example: privacy, consent, decision making and discussion about the risks and benefits of treatment options, sensitive communication, medication administration, staff education and support and culturally appropriate care, documentation

1.2 Emergency presentation

Table 2. Presentation at emergency department

Aspect	Consideration
Context	• Presentation at emergency departments (ED) for threatened or actual early pregnancy loss is common[6] • As ED are structured primarily to address urgent and trauma care (i.e. triage is based on medical emergency), the importance of psychosocial care during EPL and follow-up afterwards can be underappreciated[7,8]
EPAS	• A dedicated outpatient early pregnancy assessment service (EPAS) can reduce length of stay in ED, reduce hospital admissions, improve service delivery and the woman's experience of care[8-10] o Refer to Definition of terms and Appendix A: Early pregnancy assessment service
Care provision	• Individualise care and acknowledge the woman's experience of the loss • Involve expert and specialised multidisciplinary health care professionals (including social workers) in care planning[7] • Minimise waiting times, particularly in public areas such as waiting rooms[11] • Offer and facilitate the presence of a support person • Establish and communicate clear pathways for referral and follow-up after discharge (e.g. to general practitioner (GP)) • Offer connections and referral to local community resources specialising in pregnancy loss • Incorporate psychological care in service delivery models[8] o Refer to Section 2.1 Psychological support

1.3 Haemodynamic instability

Women who are believed to be pregnant, with haemodynamic instability and vaginal bleeding and/or pain (abdominal, diaphragmatic or shoulder tip pain) require urgent intervention. Presume ruptured ectopic pregnancy or incomplete miscarriage with cervical shock or massive haemorrhage.

Table 3. Haemodynamic instability

Aspect	Consideration
Context	• Between 2010–2019, four of the 97 direct maternal deaths in Australia were attributed to ruptured ectopic pregnancies[12]
Resuscitate[13]	• Resuscitate following standard medical emergency procedures • Establish intravenous (IV) access (e.g. two x 16 gauge IV cannulas) • Perform urgent speculum examination, and remove POC from cervix and or vagina o May stop vaginal bleeding and restore blood pressure • Insert indwelling catheter to empty bladder • Obtain urgent gynaecological review concurrently with resuscitation • Consider point of care USS to assess for hemoperitoneum • If medically unsafe, do not delay treatment to achieve formal USS • If ectopic pregnancy confirmed or unable to be excluded, continue resuscitation en-route to theatre • Urgent full blood count (FBC), and group and hold
Control bleeding	• If vaginal bleeding persists and ectopic has been excluded, consider pharmacological therapy • Refer to Queensland Clinical Guideline: *Postpartum haemorrhage*[14] for first and second line drug regimens and considerations including: o Ergometrine maleate 250 micrograms IV or intramuscular (IM) injection o Misoprostol 800–1000 micrograms per rectum o Critical bleeding massive transfusion protocol
Surgical intervention	• Haemodynamic instability is a clinical indication for: o Surgical evacuation of the uterus for incomplete EPL[13] o Laparoscopy and/or laparotomy for removal of ectopic pregnancy o In the second trimester, consideration of hysterotomy or laparotomy as indicated

2 Principles of EPL care

The following care is common to women experiencing EPL irrespective of pregnancy location or management option. Consider in conjunction with other care recommendations.

Table 4. General care principles for EPL

Aspect	Consideration
Rh D immunoglobulin	• Collect blood group and antibody screen for women with early pregnancy complications[15] • If Rh D negative with no preformed anti-D antibodies, recommend a dose of Rh D immunoglobulin to prevent Rh D alloimmunisation[15] • If Rh D immunoglobulin is indicated o Administer as soon as possible and within 72 hours of pregnancy loss o Can be administered up to 10 days after pregnancy loss but efficacy may be lower o If gestation is 12 weeks or less the recommended dose is 250 international units (IU) o If gestation more than 12 weeks the recommended dose is 625 IU
Histopathology	• Send POC for histopathology to confirm pregnancy, and exclude ectopic pregnancy or unsuspected gestational trophoblastic disease (GTD) o Transvaginal ultrasound (TVS) is not reliable in the detection of GTD • Discuss implications/requirements for histopathology with women who may miscarry at home according to their individual circumstances o May be practically difficult and some may find it distressing o If POC collection chosen, provide a labelled specimen container, pathology request form and instructions for delivery to pathology • If POC not collected, reassure that there are other options for follow-up
Return to normal menstrual cycle	• Resumption of normal menstrual cycle indicates resolution of EPL complications and completion of management[16] • Ongoing, irregular bleeding requires follow-up—consider[16]: o Beta human chorionic gonadotropin (β-hCG) to exclude GTD o Retained products o Infection
Ongoing and follow-up care	• There is limited evidence or consensus about optimal follow-up protocols • Establish local procedures and protocols: o For follow-up care arrangements o To ensure histopathology results are reviewed and actioned as required • Vary the recommendations for follow-up in this guideline as clinically appropriate and indicated for individual women • If GTD, register with Queensland Trophoblast Centre (QTC) o Refer to Section 7 Gestational trophoblastic disease
Advice after EPL	• Provide information (written and verbal) about EPL o When to seek emergency assistance: ▪ If experiencing strong pain unrelieved by paracetamol ▪ Shoulder tip or diaphragmatic pain ▪ Soaking of more than one pad within 60 minutes ▪ Fainting ▪ Elevated temperature o Timing and nature of follow-up investigations and appointments, including contact details of relevant care providers o Resumption of sexual activity o Contraception o Recommendations for conception interval (if any) o Future pregnancy planning o Resumption of menstruation/expected bleeding o Accessing psychological support • Refer to Queensland Clinical Guidelines patient information: o *Ectopic pregnancy*[17] o *Bleeding and pain in early pregnancy*[17] o *After a miscarriage*[17]

2.1 Psychological support

Early pregnancy loss is an experience common to many women, and yet it is simultaneously an intensely personal, private, intimate and individual experience. It is important for longer term health and wellbeing, that a woman's psychological needs are not overlooked, and that any symptoms of grief, depression and anxiety are recognised and acknowledged by health professionals.[18]

Table 5. Context and experience of early pregnancy loss

Aspect	Consideration
Unique challenges of EPL	• The loss is often sudden and unexpected, limiting the opportunity for anticipatory grieving and practical preparation • May be largely unacknowledged by society, contributing to a feeling of isolation[19,20] • Society can trivialise the impact of EPL and downplay the need for women to mourn their loss • Frequently no formal or public commemoration, funeral or ritual to mark the loss • Often no known cause, contributing to a sense of self-blame or failure • The meaning women attach to their pregnancies varies, and in turn affects the way they interpret an EPL o Feelings range from relief through to devastation • Partners may experience and respond differently to the loss[21,22] o Assumed role as the woman's 'protector and supporter' may result in neglect of the partner's psychological needs[22]
Communication	• Emotional care is central to women's perception about the quality of care received[7] • Use sensitive and empathetic communication and listening that mirrors the language used by the woman[7] (e.g. use 'baby' rather than 'fetus' if this language the woman uses/prefers) • Recognise and acknowledge the loss no matter how early the loss occurs[7] • Involve experienced practitioners in difficult discussions • Offer practical support (including written resources) about: o What their baby remains may look like (where appropriate) o Options for the management of baby remains [refer to Section 9 Sensitive management of fetal tissue/remains] o Observing the absence of a heartbeat during ultrasound scan (USS) if desired o USS results in writing and/or a photo as a memento
Psychoeducation	• Psychoeducation can increase knowledge and understanding, facilitate control and coping, and decrease fear and anxiety as well as help prevent longer term complications[7] o Counsel women regarding the potential to experience symptoms of grief, depression and anxiety following an EPL[23] o Offer information about the prevalence and causes of EPL, which may help to reduce feelings of guilt, shame and personal failure[23] o When appropriate, reassure the woman that the loss was not due to anything they did or did not do
Memory creation	• Parents may or may not wish to create memories of their pregnancy/baby • Discuss options for memory creation with the parents as appropriate to the gestational age, circumstances and cultural preferences[24] o Refer to Queensland Clinical Guideline *Stillbirth care*[25]
Follow-up support	• Refer to counselling, peer or community groups or organisations for follow-up support, recognising and incorporating: o The unique circumstances and individual history of the woman o The need to create referral pathways appropriate to the individual woman

2.2 Psychological morbidity

Table 6. Psychological morbidity

Aspect	Consideration
Psychological morbidity	• Suicide is a significant cause of direct and indirect maternal deaths in Queensland and Australia[12,18] • In the first month following EPL, studies consistently demonstrate an association between EPL and the proportion of women who experience[26]: o Anxiety (18–32%) o Moderate depression (8–20%) o Post-traumatic stress disorder (PTSD) (25–39%) • Pathological grief (characterised by despair, deep feelings of worthlessness and hopelessness, and difficulty resuming normal interactions and activities of daily life) can develop
Risk factors for psychological morbidity	• Risk factors for longer term morbidity are not clearly understood[3,26,27] • May include: o History of mental illness[26,27] o Previous pregnancy loss[27] o Being without a supportive partner [26] o Having no living children[26] o Longer interval (more than one year) to achieve pregnancy[27]
Prevention and support	• Evidence is limited about effective psychological and support interventions[28] • Be proactive in assessing psychological wellbeing following EPL • Assess each woman's response to EPL and individualise care • Consider risk factors for longer term morbidity to aid identification of women at risk of perinatal mental health issues • Offer information about community and peer support organisations • Consider if formal perinatal mental health screening and referral indicated • Promote non-directive pregnancy support counselling services which are available via Medicare to a person who is currently pregnant or has been pregnant in the preceding 12 months[18,29]

3 Assessment

Assessment and diagnosis are made through a combination of a physical examination, history and clinical investigations.

Table 7. Confirmation of pregnancy and assessment

Aspect	Consideration
Haemodynamic instability	• Initial assessment of haemodynamic stability is essential • Refer to Section 1.3 Haemodynamic instability
History	• Menstrual history and last normal menstrual period (LNMP) • Date of positive pregnancy test • Previous pregnancies and outcomes, particularly miscarriages • Other significant gynaecological history • If assisted conception, identify method of conception • Relevant ultrasound scan (USS) and quantitative β-hCG • Symptoms of early pregnancy
Clinical signs and symptoms	• Vaginal bleeding (review timing, extent and severity) • Pain (lower abdominal cramping or backache) • Postural syncope • Vomiting • Shoulder tip/diaphragmatic pain • Signs of shock • Passage of POC
Confirm pregnancy	• Perform an urgent serum quantitative β-hCG (pregnancy test) on women of reproductive age presenting with suspected EPL, irrespective of LNMP, contraception, history of sterilisation or reported sexual inactivity o If delay in reporting a serum test is expected, use urine β-hCG as clinically indicated • A negative serum β-hCG essentially excludes ectopic pregnancy (except in the unusual circumstance of a chronic ectopic where β-hCG has been positive in the recent past)
Physical examination	• Baseline observations (temperature, heart rate, respiratory rate, blood pressure) • Abdominal examination o Tenderness (rigidity and guarding) o Distension • Vaginal blood loss (check loss on pad) • Vaginal examination (individualised as clinically indicated): o Speculum examination: ▪ Source and amount of bleeding ▪ Evidence of POC in the cervical os (if present, remove and submit for histology) o Bi-manual examination: ▪ Cervical motion tenderness ▪ State of internal cervical os ▪ Assess for adnexal masses (ectopic pregnancy or other masses) • Size of uterus relative to menstrual dates
Ultrasound scan	• Perform an USS as soon as possible and urgently if clinically indicated • Document whether TVS or transabdominal (TAS) on the USS report to aid interpretation • Refer to Appendix B: Sonographic anatomy, landmarks and documentation
Other investigations	• FBC, blood group, antibody screen • Screen for sexually transmitted infections as clinically indicated (e.g. for women in high risk groups)

3.1 Determining viability and location of pregnancy

Table 8. Determining viability and location of pregnancy

Aspect	Consideration
Normal β-hCG	• Serum β-hCG first becomes positive at 9 days post conception o β-hCG greater than 5 IU/L confirms pregnancy[30] • For a potentially viable intrauterine pregnancy (IUP) up to 6–7 weeks gestation o Mean doubling time for β-hCG is 1.4–2.1 days[31] o 85% show serial β-hCG rise of at least 66% every 48 hours[32] o 15% show serial β-hCG rise between 53–66% every 48 hours[32] o The slowest recorded rise over 48 hours is 53%[31]
Ultrasound scan	• TVS by an experienced sonographer is the gold standard in first trimester o If TVS unavailable, recognise that TAS may be less accurate • An IUP is usually visible on TVS when mean sac diameter (MSD) is greater than or equal to 3 mm[30] • USS may be less reliable if fibroids, diffuse adenomyosis, early multiple pregnancy present
Serial β-hCG	• Serial β-hCG is recommended in stable circumstances[33] • Repeat β-hCG 48 hours (up to 72 hours) after initial level • A single β-hCG value: o Does not differentiate between a viable and nonviable pregnancy[34] o Cannot be used to exclude IUP
Discriminatory zone	• The discriminatory zone is the serum β-hCG level above which a gestational sac should be visible on TVS or TAS if an IUP is present[31] o A single β-hCG value is not considered discriminatory • No consensus on β-hCG level that defines the discriminatory zone with TVS[35] o 1000 IU/L to 3500 IU/L in international guidelines (TVS) o Much higher β-hCG levels if TAS only is used
Normal progesterone	• Normal serum progesterone levels increase over pregnancy • A decline between 6 and 8 weeks of gestation (with a nadir at week 7) corresponds to the luteal-placental shift[36] o Levels may be influenced by maternal age, body mass index (BMI) and parity[36] • May be a marker of pregnancy viability, but not able to predict location of a pregnancy of unknown location (PUL)[37] • Pathology Queensland does not have formal reference ranges for progesterone levels in early pregnancy • May be a useful adjunct in some cirucumstances
Combined assessment variables	• Quantitative serial serum β-hCG levels used in conjunction with serial TVS are often the only way to distinguish between an early non-viable pregnancy and an ectopic pregnancy in gestations less than 6–7 weeks • If β-hCG levels and TVS are not performed simultaneously, interpret results cautiously • Combined variables in prediction models outperform any variable in isolation[34,38-40] • All management protocols are designed to be predictive and risk stratify women, and not used as diagnostic tools[38] • Test performance is influenced by the population in which it is used, the available resources and the rate of PUL within an assessment unit

3.2 Diagnosis of non-viable intrauterine pregnancy

Table 9. Diagnosis of non-viable IUP

Aspect	Consideration
Context	• Diagnosis of non-viable IUP requires: o Experienced clinicians o High quality TVS equipment and experienced operator[33] • Criteria for excluding a viable pregnancy must be stringent enough to avoid interventions that inadvertently damage a viable pregnancy[30]
Findings suspicious but not diagnostic[41]	• MSD 16–24 mm and no embryo visible • Crown rump length (CRL) less than 7 mm and no heartbeat • Absence of embryo with heartbeat 7–13 days after USS that showed a gestational sac without a yolk sac • Absence of embryo with heartbeat, 7–10 days after USS that showed a gestational sac with a yolk sac • Absence of embryo 6 weeks or more after LNMP • Empty amnion (amnion seen adjacent to yolk sac with no visible embryo) • Enlarged yolk sac (greater than 7 mm) • Small gestational sac in relation to the size of the embryo (less than 5 mm difference between MSD and CRL)
TVS diagnostic criteria[33]	• MSD is greater than or equal to 25 mm and no fetus present • Fetus with CRL greater than or equal to 7 mm is visible, but no fetal heart movements demonstrated after observation of at least 30 seconds • Absence of embryo with heartbeat, 2 weeks or more after USS that showed a gestational sac without a yolk sac • Absence of embryo with heartbeat, 11 days or more after USS that showed a gestational sac with a yolk sac • Absence of embryo with heartbeat 7 days or more after USS that showed a fetal pole less than 7 mm with no cardiac activity
Repeat TVS interval	• When no fetal pole is visible diagnosis cannot be made until the MSD is (or has failed to reach) 25 mm therefore the interval between initial and subsequent USS is dependent on the MSD at initial presentation • Estimate TVS interval based on expected normal gestational sac growth rate of 1 mm/day o Example: If MSD = 12 mm, repeat TVS in 13 days or more (12 mm MSD+13 mm growth over 13 days = expected MSD of 25 mm) • Avoids repeated inconclusive TVS

3.3 Pregnancy of unknown location

PUL is a classification not a final diagnosis. Following a classification of PUL, a final diagnosis of ectopic pregnancy places women at the most risk of clinical complications and harm.[38] Therefore, it is the most important outcome to predict or exclude.[38]

Table 10. Pregnancy of unknown location

Aspect	Consideration
Ongoing vigilance	• A single cut-off level for β-hCG, β-hCG ratio or progesterone cannot be clinically interpreted in isolation[34] • Specialist review and close follow-up is essential until resolution • Perform serial β-hCG (48–72 hours apart) • Perform TVS as clinically indicated • Serum progesterone may be useful adjunct • Triage of PUL using a mathematical risk prediction model (e.g. M6P, 2 step triage strategy) demonstrated to be a useful decision support tool[38,40,42] • Individualise care according to clinical circumstances
Serial β-hCG	• If serial β-hCG rises more than 66% o An IUP is more likely o An ectopic pregnancy cannot be excluded • If serial β-hCG falls 50% or more o A non-viable pregnancy is more likely (IUP or ectopic) • If serial β-hCG rises less than 66 % or falls less than 50% o If no IUP on repeat TVS, suspect ectopic pregnancy
Progesterone	• If the initial measurement is less than or equal to 2 nmol/L o A non-viable pregnancy is likely (IUP or failed PUL) o An ectopic pregnancy cannot be excluded

3.3.1 Frequency of outcome after classification of PUL

Outcomes reported from an evaluation of various cut off levels following a TVS and an initial classification of PUL, among women who were clinically stable.[34]

Table 11. Frequency of outcome following PUL

Cut offs[34]	*N*	Ectopic/PPUL % (95% CI)	Non-viable IUP/FPUL % (95% CI)	Viable IUP % (95% CI)
Initial β-hCG				
> 1000 IU/L	832	10.5 (7.5 to13.6)	70.6 (67.6 to 73.8)	18.9 (15.9 to 22.1)
> 2000 IU/L	513	8.4 (5.1 to12.0)	77.8 (74.5 to 81.4)	13.8 (10.5 to 17.5)
> 2500 IU/L	428	7.9 (4.4 to 11.6)	80.6 (77.1 to 84.2)	11.4 (7.9 to 15.1)
> 3000 IU/L	358	7.5 (3.9 to 11.5)	81.6 (77.9 to 85.5)	10.9 (7.3 to 14.9)
Initial progesterone				
≤ 2 nmol/L	327	1.8 (0.6 to 3.1)	98.2 (96.9 to 99.4)	0 (0.0 to 1.2)
≤ 10 nmol/L	1112	7.8 (6.4 to 9.4)	92.0 (90.6 to 93.6)	0.18 (<0.01 to 1.8)
β-hCG ratio				
< 0.87	883	6.2 (4.8 to 7.8)	93.8 (92.3 to 95.3)	0 (0.0 to 1.5)
< 1.5	1205	16.9 (14.9 to 19.1)	81.7 (79.7 to 84.0)	1.3 (<0.01 to 3.5)

Viable IUP: an embryo with visible cardiac activity was seen at initial follow up and was still present at the time of the dating scan at 11–14 weeks of gestation. Non-viable IUP where an IUP seen on TVS had miscarried by the time of the dating scan FPUL: where βhCG levels reduced and resolved spontaneously without the visualization of a pregnancy on TVS. Ectopic: an extrauterine mass seen on TVS. PPUL where TVS did not reveal the pregnancy location when more than three βhCG levels taken over 48-hour intervals remained static with a difference of 15% or less each time.[34]

3.4 Other pregnancy outcomes

Table 12. Other pregnancy outcomes

Aspect	Consideration
Complete miscarriage	• IUP can only be confirmed conclusively after identification of a yolk sac[43] • If no prior report or evidence of an IUP, a diagnosis of complete miscarriage cannot be made based on TVS findings of an 'empty uterus' • A diagnosis of complete miscarriage requires follow-up with serum quantitative β-hCG until negative and TVS if clinically indicated, to exclude undiagnosed ectopic pregnancy
Caesarean section (CS) scar pregnancy	• Incidence increasing with rising CS rate and advanced imaging modalities[44] o With one or more previous CS, rate estimated as 1 per 531 women[45] • Limited evidence to inform optimal management[44,46] o Expectant management can result in live birth, but also severe morbidity (e.g. uterine rupture, placenta accreta, haemorrhage)[44,47] o Multidisciplinary approach required[47]
Threatened miscarriage	• Follow-up with GP may be appropriate • Progesterone may improve live birth outcome in women with one or more previous miscarriages and early pregnancy bleeding (*ARR: 5.72%; 95% CI 1.65 to 9.8) • No improvement in live birth outcome in women with no previous miscarriage and early pregnancy bleeding (*ARR 0.43%; 95% CI -3.17 to 4.02%)

ARR: absolute risk reduction

4 Ectopic pregnancy

Table 13. Ectopic pregnancy

Aspect	Consideration
Context	• Occurs in 1–2% of pregnancies[48] • 92–95% occurring in the fallopian tube[46] o Increasing trend of non-tubal ectopic pregnancy (i.e. interstitial (cornual), caesarean scar, cervical, heterotopic, ovarian and abdominal), especially caesarean scar pregnancy[46] • Failure to promptly diagnose and manage an ectopic pregnancy can be life threatening[46] o Responsible for 80% of maternal deaths in the first trimester[46]
Clinical presentation[13,48]	• Absence of menses • Irregular vaginal bleeding (spotting)—but not in all cases • Abdominal pain, tenderness and palpable adnexal mass in 50% of women • Cervical motion tenderness • Absence of IUP on TVS with positive serum β-hCG • Suspect a ruptured ectopic if: o Shoulder tip or diaphragmatic pain (10–20% of ruptured ectopic) o Tachycardia/hypotension from profound intraperitoneal haemorrhage
Options for treatment	• There is limited quality evidence comparing expectant, medical and surgical options[49-51] o Incidence of recurrent ectopic comparable between options[52] o One study reported success rates of 70% (49/70), 82.6% (38/46), and 100% (86/86) for expectant, medical and surgical management respectively[52] • Choice depends on the clinical situation and woman's preference • Falling or stationary β-hCG does not exclude the risk of rupture following medical or expectant management
Non fallopian tube ectopic[46]	• Optimal management not established • Surgical or medical may be appropriate depending on individual circumstances (e.g. location, gestation and urgency of treatment) o Expectant management not a suitable choice for most women • Individualise management and seek expert advice as required

4.1 Risk factors for ectopic pregnancy

One half of women diagnosed with an ectopic pregnancy will have no known risk factors[53]

Table 14. Risk factors associated with ectopic pregnancy

Risk factor[54]	(Adjusted*) OR	95% CI
Sterilisation^	9.3	4.9 to 18.0
Previous ectopic pregnancy (increased risk if > 1)	8.3	6.0 to 11.5
Previous tubal surgery	4.0*	2.6 to 6.1
Documented tubal pathology	3.7*	1.2 to 4.8
Previous genital infection confirmed	3.4*	2.4 to 5.0
Previous miscarriage	3.0*	> 2
Intrauterine device use more than 2 years	2.9*	1.4 to 2.3
Age 40 or older (compared to 25–29 years)	2.9*	1.4 to 6.1
Infertility (risk increases with length of)	2.1–2.7*	–
Current smoker (risk increases with amount/day)	1.7–3.9*	–
Smoking (past or ever)	1.5*	1.1 to 2.2

*adjusted for: previous pelvic infection, smoking, recruitment area, level of education and age
^ compared with pregnant controls only

4.2 Expectant management of ectopic pregnancy

Expectant management is an option for selected women. Clear criteria for selection are not well defined.[50]

Table 15. Expectant management of ectopic pregnancy

(Aspect	Consideration
Context	• Advances in imaging technology has enabled earlier and accurate diagnosis of ectopic pregnancy[50,55] • Among selected women (early gestation, with β-hCG values below 1000 IU/L and decreasing) up to 70% reported to resolve spontaneously without therapy[52,56] • More likely to have successful resolution if no previous history of ectopic[49]
Suggested criteria[50,57]	• Haemodynamically stable • Low and falling β-hCG (less than 1500 IU/L at initial presentation) o Physical resolution is positively correlated with initial and maximum β-hCG[55] • Tubal mass less than 3 cm • No pain • Nil to minimal evidence of blood in the pelvis on USS • No geographical isolation • Not recommended where follow-up uncertain
Ongoing management	• Follow up via EPAS • β-hCG: o Every 48 hours for 8 days (to confirm levels falling) o If satisfactory resolution occurring, commence weekly levels until negative • USS not routinely recommended—consider if: o β-hCG not consistently falling o Clinically indicated • Offer surgical or medical management: o At the woman's request o If there is ongoing or increasing pain or bleeding o If β-hCG is not consistently falling o If tubal rupture with haemoperitoneum occurs
Advice for women	• Advise: o Of the possibility of tubal rupture despite decreasing β-hCG o Pelvic examination and sexual intercourse carry risk of rupture in acute phase of resolution o Avoid future pregnancy until sonographic resolution of mass, noting that sonographic resolution of mass takes longer than biochemical resolution of β-hCG[55] • Recommend early USS in next pregnancy (5–6 weeks gestation) as increased risk of future ectopic • Refer to Table 14. Risk factors associated with ectopic pregnancy

4.3 Medical management of ectopic pregnancy

Methotrexate is the drug of choice for medical management, although regimens vary.[58,59] If no local protocols exist, refer to Appendix C: Methotrexate regimens for ectopic pregnancy.

Table 16. Medical management of ectopic pregnancy

Aspect	Consideration
Context	• Methotrexate is a folic acid antagonist which prevents the growth of rapidly dividing cells by interfering with DNA synthesis[60]
Indications	• Unruptured ectopic pregnancy; haemodynamically stable and no signs of active bleeding[53,58,61] • Unusual sites (e.g. cervical ectopic, interstitial, caesarean scar)[44] • Low initial serum β-hCG o Best results achieved if β-hCG less than 5000 IU/L but may be used at any β-hCG level in the unruptured ectopic[59] • FBC, electrolytes and liver function tests (ELFT) are within normal range
Contra-indication[53]	• Haemodynamically unstable • Hypersensitivity to methotrexate • Evidence of haemoperitoneum on TVS • Renal disease/insufficiency (methotrexate cleared via the renal system) • Abnormal FBC and/or ELFT • Acute liver disease, aplastic anaemia, thrombocytopenia • Immunodeficiency • Active pulmonary disease • Active peptic ulcer disease • Coexistent viable IUP (heterotopic pregnancy) • Breastfeeding • Unable to participate in prolonged follow-up (35–109 days) • Geographic isolation
Cautions[53]	• Baseline serum β-hCG greater than 5000 IU/L • Ectopic pregnancy greater than 3–4 cm diameter on TVS • Presence of fetal heart motion on TVS • When blood transfusion is not acceptable to the woman • If BMI greater than or equal to 40 kg/m^2, and IM injection dosage is capped at 2 m^2 body surface area (BSA), an additional dose is more likely to be required to achieve complete resolution[62]
Ongoing management	• Follow up with EPAS • β-hCG as per methotrexate protocol o Refer to Appendix C: Methotrexate regimens for ectopic pregnancy • Repeat USS in one week and thereafter as clinically indicated (e.g. β-hCG not consistently falling, ectopic site other than fallopian tube) o If fetal heart present on USS, refer urgently to maternal fetal medicine for follow-up—direct injection of potassium chloride may be indicated

4.3.1 Advice for women treated with methotrexate

Table 17. Advice for women post methotrexate

Aspect	Consideration
Side effects	• Common side effects include: nausea, tiredness, altered bowel habits and mouth ulcers which usually settle without treatment within a few days[60] o Anti-emetics are routinely prescribed
Cytotoxic precautions	• Methotrexate can remain in the body (vomit, urine, faeces) for up to seven days after treatment completed o Provide information about cytotoxic precautions post treatment (e.g. close the lid of toilet after use, use full flush, use gloves if handling or washing linen/clothes contaminated with body fluids) • Refer to Queensland Clinical Guideline patient information *Methotrexate for ectopic pregnancy*
Advise to avoid during treatment[63]	• Excessive or prolonged sun exposure, and to wear protective clothing and use sunscreen (to limit skin inflammation) • Foods and vitamins containing folate/folic acid during treatment as can decrease effectiveness of therapy • Sexual intercourse as risk of rupture in acute phase of resolution • Alcohol for seven days after injection as can increase side effects • Anti-inflammatory medicines (e.g. ibuprofen and aspirin) during and for one week after treatment, as can increase risk of side effects
Conception/ contraception[60]	• Advise to delay next pregnancy for three months post administration of methotrexate due to potential teratogenicity • Recommend contraception and pregnancy avoidance until medical follow-up completed • Recommend early USS in next pregnancy (5–6 weeks gestation) as increased risk of future ectopic
Return to hospital	• Advise methotrexate can cause myelosuppression and increase risk of infection (although uncommon) o Seek medical attention if unwell with fever 38°C or more • Advise to seek urgent medical attention at hospital (as may be suggestive of ruptured ectopic) if clinically symptomatic with: o Abdominal or shoulder tip pain, dizzy spells or fainting, o Heavy vaginal bleeding

4.4 Surgical management of ectopic pregnancy

Table 18. Surgical management of ectopic pregnancy

Aspect	Consideration
Indications[53]	• Woman's preference • Haemodynamic instability • Persistent excessive bleeding • Expectant or medical management contraindicated or fails
Approach	• Laparoscopy is the method of choice for stable women[51,53] • Laparotomy may be required in cases of haemorrhagic shock[53]
Follow-up	• GP follow-up around 2 weeks post-surgery o USS not routinely required—consider if β-hCG does not fall or there are other clinical indications • If salpingo(s)tomy, weekly β-hCG until negative o If β-hCG does not fall, consider medical treatment or salpingectomy • If salpingectomy o Unusually may see abdominal implantation especially after ruptured ectopic with haemoperitoneum o Rarely may see ongoing intrauterine gestation if undiagnosed heterotopic pregnancy o Urinary β-hCG three weeks after surgery
Advice for women	• The optimal interval to next conception is unknown—clinical practice varies from next menstrual period to 3 months • Recommend early USS in next pregnancy (5–6 weeks gestation) as increased risk of future ectopic

5 Non-viable intrauterine pregnancy

There are no significant differences between expectant, medical and surgical management for a non-viable IUP. Surgical management has the timeliest resolution (defined in most studies as complete emptying of the uterus and lack of need for unplanned surgery). The individual preferences and values of the woman as well as the clinical situation determine the choice of management.[64]

5.1 Risk factors

Table 19. Risk factors associated with non-viable intrauterine pregnancy loss

Risk factor group	Relationship to miscarriage
Maternal age[3]	• Lowest risk of miscarriage is between 20–29 years o Less 20 years (15.9%) o 20–29 years (12%) o 35–39 years (18%) o 40–44 years (37%) o 45 years or more (65%)
Previous miscarriage[3]	• Risk of miscarriage increases with number of previous miscarriages o 0 previous (11%) o 1 previous (20%) o 2 previous (28.3%) o 3 or more previous (42%)
Body mass index(BMI)[3]	• Lowest risk of miscarriage is for BMI between 18.5–24.9 kg/m^2
Maternal conditions[3]	• Anatomic factors (e.g. uterine septum) • Endocrinopathy (e.g. thyroid disease) • Immunologic factors (e.g. systemic lupus erythematosus) • Infections o Bacterial (e.g. bacterial vaginosis, brucellosis, chlamydia trachomatis, syphilis) o Viral (e.g. herpes viruses, cytomegalovirus, HIV, rubella, dengue) o Protozoa infections (e.g. malaria and toxoplasmosis) • Severe acute illness • Thrombophilia (e.g. factor V Leiden) • Uncontrolled chronic illness (e.g. diabetes, hypertension)
Fetal[3]	• Chromosomal abnormalities o Among miscarriages, autosomal trisomy most frequent abnormality followed by monosomy X and triploidy • Congenital abnormalities[65]
Lifestyle[3]	• Cigarette smoking o Risk of miscarriage increases with amount • Alcohol use o Risk of miscarriage increases with high intake during first trimester • Environmental pollution (e.g. air pollution, pesticides)

5.2 Expectant management of non-viable intrauterine pregnancy

Table 20. Expectant management for stable non-viable IUP

Aspect	Consideration
Indications	• Woman's preference • Most suited to the management of incomplete miscarriage[66,67] • The lower the β-hCG and progesterone values, the higher the likelihood of success[67]
Contraindications	• Suspected GTD • Haemodynamically unstable • Intrauterine device (requires removal) • Women at increased risk of haemorrhage (e.g. late in first trimester) or the effects of (e.g. unable to have blood transfusion or coagulopathies) • Evidence of infection
Risk/benefit	• Less effective (defined as need for further treatment) than either medical or surgical manangement[66,68,69] • More days of bleeding and a greater amount of bleeding compared to surgical treatment[66] • Fertility is similar after both medical and expectant management[68] • Timeframe to complete miscarriage is unpredictable[67] • No differences between medical and expectant management for[70]: o Short and long-term emotional distress o Satisfaction with management option
Ongoing management	• Follow-up within 7–10 days at GP or EPAS • Initial evaluation by history and examination o Remain vigilant for GTD and/or ectopic • Repeat β-hCG day 8 • Consider USS: o If clinically indicated (symptomatic) o To assess for retained POC o If β-hCG level has not fallen more than 90% over 7 days[71] • Discuss options for continued expectant management or surgical or medical management: o At the woman's request o If there is ongoing heavy bleeding, pain or persistent intrauterine gestational sac identified on USS o If other clinical concerns identified (e.g. heavy bleeding, pain) • If infection suspected, recommend early surgical management with antibiotic cover • Recommend urinary pregnancy test at 3–6 weeks if[16]: o No POC histopathology o Failure to return to normal menstruation by 4–6 weeks o Ongoing abnormal bleeding
Advice for women	• Recommend access to a telephone and 24 hour emergency hospital admission or a plan for access where there is geographical/social isolation • Expect bleeding for up to two weeks (or longer in individual cases) • Advise surgical or medical management can be chosen at a later date • Refer to QCG Patient information *After a miscarriage*

5.3 Medical management of first trimester non-viable intrauterine pregnancy

Table 21. Indications for medical management for the stable non-viable IUP

Aspect	Consideration
Indications	• Woman's preference • Missed or incomplete miscarriage
Contraindications	• Suspected GTD • Haemodynamically unstable • Increased risk of haemorrhage (e.g. late first trimester) or effects of haemorrhage (e.g. coagulopathy, unable to have blood transfusion) • Evidence of infection • Intrauterine device (requires removal) • Medical contraindications (e.g. hypertension, allergy to prostaglandins)
Risk/benefit	• An effective alternative to surgical evacuation for first trimester miscarriage[69] • If missed miscarriage, medical management is more effective than expectant management[67] • If incomplete miscarriage, no significant difference in effectiveness between medical and expectant management[72] • Bleeding is heavier and more prolonged after medical treatment with misoprostol than with curettage[72]
Mifepristone and misoprostol	• If missed miscarriage, mifepristone and misoprostol combined regimen may be more effective (less need for surgical intervention) than misoprostol alone[73,74]
Misoprostol	• For incomplete miscarriage before 13 weeks, multiple regimens are reported with the optimal uncertain[64,72] • If no local protocol, recommended regimen is: o Day 1: misoprostol 400–800 micrograms PV, oral or sublingual o Day 2 or Day 3: repeat misoprostol 400–800 micrograms PV, oral or sublingual ▪ If good history of POC passed, second dose may be omitted
Administration	• Treatment may be offered as an outpatient or day procedure[16] • Provide oral analgesia and anti-emetics as required
Ongoing management	• β-hCG day 1 (day of first misoprostol), and day 8 (to confirm levels falling) • Follow up with EPAS on day 2 and day 8 • Initial evaluation of success is by history and examination o Remain vigilant for GTD and/or ectopic[16] • Consider USS: o If clinically indicated (symptomatic) o To assess for retained POC o If β-hCG level has not fallen more than 90% over 7 days[71] • Surgical management not indicated within one week of medical management unless: o The woman requests it o There are other clinical concerns (e.g. ongoing heavy bleeding, pain) • Recommend urinary pregnancy test at 3–6 weeks if[16]: o No POC histology o Failure to return to normal menstruation by 4–6 weeks o Ongoing abnormal bleeding
Advice for women	• Inform women: o Bleeding heavier than menses is likely o Cramping may accompany bleeding o If bleeding has not commenced by 24 hours following treatment, to contact healthcare provider to determine ongoing care o Potential side-effects include pain, diarrhoea and vomiting

*Refer to an Australian pharmacopeia for complete drug information

5.4 Surgical management of first trimester non-viable IUP

Table 22. Surgical management of the stable non-viable IUP

Aspect	Consideration
Indications	• Woman's preference • Unsuccessful medical or expectant management • Recommend if: o Haemodynamic instability o Persistent excessive vaginal bleeding o Evidence of infected retained tissue o Suspected GTD • Suction curettage is the recommended method[75]
Cautions	• Caution if: o Increased risk of haemorrhage (e.g. suspected arteriovenous malformation or coagulopathy) o Previous uterine perforation
Risk/benefit	• As a primary approach, surgical management results in a more immediate outcome with less follow-up[66] • Standard risks associated with procedure and anaesthesia
Cervical priming*	• Clinical experience supports the use of cervical ripening agents prior to surgical evacuation, although evidence is limited[76] • If no local protocol, recommended dose is[77]: o Misoprostol 400 micrograms PV 3–4 hours prior to surgery OR o Misoprostol 400 micrograms oral, sublingual, buccal 2–3 hours prior to surgery o Use water as lubricant
Care provision	• Suction curettage is usually performed under general anaesthetic • Provide analgesia as indicated • There is insufficient evidence to support *routine* antibiotic prophylaxis prior to surgery[78] o Consider based on individual clinical indications (e.g. endometritis) • If clinically indicated, consider USS at time of suction curettage
Follow-up	• Advise GP follow-up if ongoing clinical concerns • β-hCG not routinely indicated • USS not routinely recommended • Check histology results • If Rh D negative blood group, refer to Section 2 Principles of EPL care • Refer to Section 9 Recurrent early pregnancy loss for other investigations
Repeat curettage	• If repeat curettage is required (experienced operator required): o Consider initial hysteroscopy or USS guided curettage to facilitate uterine evacuation and minimise risk of Asherman's syndrome o Administer antibiotics

*Refer to the Australian pharmacopeia for complete drug information

6 Second trimester pregnancy loss

Second trimester pregnancy loss represents 1–2% of recognised pregnancies.[79] A cause and effect relationship is difficult to establish and there may be multiple contributing pathologies.[80] There is limited evidence on the best management.[72] Where there is evidence of maternal compromise (e.g. sepsis, large placental abruption, severe or rapidly worsening pre-eclampsia), expedite birth.

Table 23. Second trimester loss

Aspect	Consideration
Potential aetiologies	• Fetal o Chromosomal abnormalities o Congenital abnormalities[81] • Maternal o Previous second trimester loss[79] o Uterine malformations[82] o Maternal medical illness (e.g. cardiac disease, autoimmune disease, thrombophilia)[79] o Preterm rupture of membranes[79] o Placental complications(e.g. abruption)[79] o Chorioamnionitis[79]
Presentation	• Majority present as intrauterine fetal death (IUFD) • May present with preterm labour or premature rupture of membranes
Assessment	• Perform low-vaginal and peri-anal swabs • Refer to Queensland Clinical Guidelines: *Stillbirth care*[25] protocol for maternal investigations
Care setting	• Where feasible, provide care in a setting away from women with uncomplicated pregnancies or healthy babies • Provide adequate analgesia consistent with the woman's choices
Medical management*	• Appropriate for all gestations • If previous uterine surgery, risk of rupture with misoprostol is low with lower complication rate than oxytocin[83] • If cervix is closed and membranes intact, mifepristone and misoprostol are first-line agents for induction of labour o Misoprostol alone may also be used o If no local protocol, refer to Queensland Clinical Guideline: *Therapeutic termination of pregnancy*[78] • If membranes are ruptured and/or the cervix is dilated, consider misoprostol or intravenous oxytocin
Third stage	• Recommend active management • If not complete within: o 30 minutes–empty bladder and consider oxytocin infusion o 60 minutes–consider manual removal of placenta • Anticipate and prepare for postpartum haemorrhage (PPH) • Retain cord, membranes and placenta for histopathology
Surgical management	• Generally suitable for gestations up to 14 completed weeks[84] o May be suitable beyond 16 weeks where baby has died at an earlier gestation and surgery is deemed to be safe • May be indicated in cases of persistent excessive bleeding, haemodynamic instability, evidence of retained POC, suspected GTD
Lactation suppression	• Recommend conservative and comfort measures (e.g. minimal breast stimulation, cold compresses and analgesia)[85] • If pharmacological agents considered, consult with relevant health professionals (e.g. pharmacists, lactation consultants)
Follow-up	• Arrange follow-up appointment with obstetrician • Consider postnatal USS to assess for uterine malformations • Inform GP and provide a clinical summary • Refer to the Queensland Clinical Guideline: *Stillbirth care*[25] for follow-up maternal and fetal investigations (e.g. autopsy, pathology)

*Refer to the Australian pharmacopeia for complete drug information

7 Gestational trophoblastic disease (GTD)

Table 24. Classification of GTD

Classification	Includes[86]
Non-neoplastic lesions	• Exaggerated placental site reaction • Benign placental site nodule
Molar pregnancies	• Partial hydatiform mole (HM) • Complete hydatiform mole (HM)
Gestational Trophoblastic Neoplasms (GTN)	• Persistent GTD (invasive mole) • Gestational choriocarcinoma • Placental site trophoblastic tumour (PSTT) • Atypical placental site nodule (APSN) • Epithelioid trophoblastic tumour (ETT)

7.1 Management of GTD

Table 25. Gestational Trophoblastic Disease

Aspect	Considerations
Queensland Trophoblast Centre (QTC)	• Mortality with GTD treated at a trophoblast centre was 2.1% compared to 8% among women referred after failure of primary treatment[87] • Refer women to the QTC at the Royal Brisbane and Women's Hospital, Queensland 4029 • Contact QTC: o In all cases of GTD or possible GTD diagnosis o For any clinical concerns o Email: QTC@health.qld.gov.au o http://www.health.qld.gov.au/rbwh/services/gtd-unit.asp
Clinical presentation	• Most common: abnormal vaginal bleeding[88] • Incidental finding on pelvic ultrasound in first trimester • Less common (due to earlier USS diagnosis): excessive hyperemesis, hyperthyroidism, early onset pre-eclampsia, excessive uterine enlargement[88] • More common in Asia (as high as 2 per 1000 pregnancies) compared with Europe and North America (less than 1 per 1000 pregnancies)[89] • Consider GTD as differential diagnosis if abnormally high β-hCG
Diagnosis	• Complete HM are more likely than partial HM to be identified by their characteristic USS features[89] o Normal USS does not exclude the diagnosis of a HM • Quantitative β-hCG (T)–tumour marker • Definitive diagnosis is made by histological examination of the POC and ancillary testing (p57 staining, DNA index, QF-PCR studies)
Interventions	• Recommend suction curettage[89] and consider: o Misoprostol for pre-surgical cervical priming o Performance may be assisted by USS guidance • If retained POC a possibility, repeat uterine evacuations may be recommended by QTC (with or without hysteroscopy/USS guidance) o Taking care to avoid Ashermann's syndrome • If future fertility not desired, hysterectomy may be an alternative[90], however usually reserved for selected cases of persistent GTD • Medically induced evacuations of known molar pregnancies not usually recommended[89,91] • If Rh D negative, recommend Rh D immunoglobulin[89] • Provide counselling about the importance and implications of follow-up

7.2 Follow-up

Post-evacuation weekly surveillance of β-hCG (T) is essential.

Table 26. Follow-up after GTD

Aspect	Considerations
Follow-up	**Partial HM** • Weekly serum β-hCG (T) levels until negative for three consecutive weeks[89] • Advise can try to conceive following 3rd weekly negative test • Annual follow-up for five years with QTC **Complete HM** • Weekly serum β-hCG (T) until negative for three consecutive weeks[89] • Then monthly for 6 months after the third negative result[89] • Advise can try to conceive following 6 months of negative testing • Annual follow-up for five years with QTC
Future fertility	• Recommend effective contraception to avoid pregnancy until β-hCG follow-up is complete[88] • Hormonal contraception during follow-up does not increase risk or severity of GTN nor postpone normalisation of hCG[89] • Intrauterine device insertion after normalisation of β-hCG levels[91] is acceptable • Perform β-hCG levels 6 weeks after any future pregnancy • Risk of recurrent GTD approximately 1 per 100 future pregnancies[91]
Post molar GTN	• Overall incidence of post-molar GTN is approximately 20% for complete mole and 4% for partial mole[92] • Risks for development include: β-hCG at diagnosis greater than 100,000 IU/L, excessive uterine size, theca lutein cysts and age more than 40 years[89] • Consider persistent disease after surgical evacuation where there is[89]: o Plateauing of β-hCG (+/-10%) for 4 consecutive values over 3 weeks (i.e. day 1, 7, 14, 21) o A rise in β-hCG levels (10% or more) for 3 values over 2 weeks (i.e. day 1,7,14) o Histologic diagnosis of choriocarcinoma or clinical and/or radiologic evidence of metastases

8 Recurrent early pregnancy loss

Recurrent early pregnancy loss is variously defined as either two or more, or three or more miscarriages. The definition is further complicated by whether previous pregnancy losses need to be consecutive or not.[3,93] Consider the individual circumstances of each woman when determining if further investigation is warranted after recurrent EPL

Table 27. Recurrent early pregnancy loss

Aspect	Consideration
Care provision	• Recommend specialist gynaecological consultation after three consecutive miscarriages o After two consecutive miscarriages, consider the woman's age in relation to opportunity to achieve a live birth • If underlying medical conditions are suspected, refer to specialist physicians as indicated • Individualise the investigation of recurrent EPL based on a comprehensive history of both partners and the clinical circumstances • Investigation is often disappointing with unanswered questions regarding aetiology, evaluation and future management
Risk factors[3]	• Risk of subsequent miscarriage increases after each miscarriage • Similar to risk factors for non-viable intrauterine pregnancy • Refer to Section 5.1 Risk factors
Lifestyle[94]	• Advise to: o Cease smoking, alcohol and illicit substance use o Limit caffeine consumption to three or fewer cups per day o Normalise BMI
Standard investigations[94]	• Routine bloods (e.g. FBC, ELFT, fasting blood glucose level (BGL)) • Acquired thrombophilia o Testing for congenital thrombophilia not recommended • Thyroid stimulating hormone (TSH) o FT3/4 and antibodies if TSH abnormal • Karyotyping of POC • Dedicated pelvic ultrasound scan to exclude structural abnormalities
Possible investigations to consider[94]	• Karyotyping of parents • Low/high vaginal swab • Chlamydia • Antinuclear antibody (anticardiolipin and antiphospholipid antibodies • Semen analysis for abnormality
Potential treatments	• For women with unexplained recurrent miscarriages, supplementation with progestogen therapy may reduce the rate of miscarriage in subsequent pregnancies[95] o Refer to Section 3.4 Other pregnancy outcomes • There is limited evidence to support an increase in live birth rate (when compared to placebo) of low dose aspirin, enoxaparin or intravenous immunoglobulin[96] o Recommend aspirin and unfractionated heparin in the context of antiphospholipid syndrome (APS)[94] and refer to an obstetric physician

9 Sensitive management of fetal tissue/remains

The decisions parents make after EPL can have a significant impact on the grieving process. Even where there is no legal requirement for a funeral, burial or cremation, parents may still desire this option or return months, or even years, later to enquire about the manner in which their baby's remains were managedf.[97]

Table 28. Sensitive management of fetal remains

Consideration	Recommendation
Birth registration	• It is compulsory to register the birth of a baby born in Queensland if any of the following conditions are met; the baby is: o Born alive (a baby whose heart has beaten after delivery of the baby is completed[98]) o 20 weeks or more gestation o 400 g or more • If birth registration is compulsory (i.e. one or more of the above conditions are met), a death certificate and burial or cremation are also compulsory and perinatal data collection is required • If birth registration is not compulsory (i.e. none of the above conditions are met), then a death certificate, burial or cremation, and perinatal data collection are not required • Inform parents that an 'Early pregnancy loss recognition certificate' can be obtained free of charge from the Registry of Births, Deaths Marriages and Divorces
Management options	• Queensland Health facilities may release a deceased fetus which does not require burial or cremation to the parents, provided that: o The facility is satisfied there is no risk of transmission of notifiable conditions o Parents have been informed as to the manner in which the fetal tissue/remains may be lawfully managed • Options for management include: o Hospital arranged cremation o Transfer to a funeral director for private arrangements o If there are no prohibiting local council requirements, burial on private property
Facility responsibilities	• Develop local options and protocols to facilitate sensitive management of fetal remains including (but not limited to): o Identification of local council requirements (if any) regarding burial on private property o Release of fetal remains to parents and subsequent return for hospital cremation o Documentation in case of community queries regarding the transport and/or management of fetal remains • Document in the health record, the arrangements that are made for fetal tissue management
Information provision	• Inform parents clearly and sensitively of the options available • Allow time for decision making and provide written information where possible • If parents choose to take fetal remains home, provide information about temperature and timeframes for optimal preservation (e.g. intermittent refrigeration) and expected look and feel • Advise that cremation of fetal tissue often does not produce any ashes to scatter[99] • Respect the wishes of parents who may not want to be involved • Refer to Section 2.1 Psychological support

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Appendix A: Early pregnancy assessment service

Aspect	Consideration
Benefits of dedicated EPAS	• Streamlining of care and improved efficiency and higher quality of care • Reduction in admissions and shorter inpatient hospital stay for those requiring admission • Greater satisfaction from women regarding their perceived quality of care*
Service provision	• May be provided by o Obstetricians and gynaecologists o GP obstetricians o GPs in community/rural settings o Nurse practitioners with relevant skill set • Network with a dedicated EPAS for consultation and referral as required
Service requirements	• An appointment system • A discrete waiting area and appropriate consultation room • USS equipment (including transvaginal probe) or access to USS evaluation • Easy access to laboratory facilities for: o Rh D antibody testing o Selective serum ß-hCG o Ideally progesterone estimation • Be available on a daily basis Monday to Friday o If possible available on weekends and after hours
Governance	• Establish governance and accountability for clinical practice • Identify defined lines of communication • Determine clinical inclusion/exclusion criteria based on the Clinical Service Capability Framework • Establish written pathways for clinical management • Provide guidance for appointment booking (i.e. referral only or self-referral) • Establish referral and transfer of care pathways within and external to the service
Documentation	• Access to standardised written patient information • Referral and transfer of care (discharge) letters available

*Tsartsara E, Johnson MP. Women's experience of care at a specialised miscarriage unit: an interpretative phenomenological study. Clinical Effectiveness in Nursing 2002;6:55-65

Appendix B: Sonographic anatomy, landmarks and documentation

Sonographic landmarks: TVS is recommended for the accurate assessment of early pregnancy

Aspect	Findings
Gestational sac	• Earliest sonographic finding in pregnancy • Use mean sac diameter (MSD) to determine gestational age before crown rump length (CRL) can be clearly measured • Usually visible (with TVS) from 4 weeks and 3 days after LNMP • True gestational sac is eccentrically placed within the endometrial cavity and surrounded by 'echogenic ring' on TVS o Intra-cavity fluid (previously called 'pseudo gestational sac') is in the midline of the endometrial cavity, displacing the anterior and posterior surfaces of the endometrial cavity • With a positive pregnancy test and no signs of intra or extra uterine pregnancy on TVS, pregnancy is identified as PUL
Yolk sac	• Yolk sac is usually first structure visible within the gestational sac and usually visible by 5.5 weeks gestation or MSD of 8–10 mm • Presence of yolk sac is definitive evidence to differentiate a sac into a gestational sac • Number of yolk sacs usually indicates the number of amniotic sacs in the case of twin pregnancies (i.e. two yolk sacs indicated a diamniotic twin pregnancy, MCMA twins have one yolk sac)
Embryo and cardiac activity	• The fetal pole (embryonic disc) is usually visible by 5–6 weeks gestation • CRL at 6 weeks and 0 days is 4 mm • During the embryonic period (weeks 6–10) the CRL increases about 1 mm per day • Cardiac activity is routinely detected by 6 to 6.5 weeks gestation • Before 6 weeks gestation, the cardiac rate will be slow (i.e. between 100 and 115 beats per minute and increases rapidly after 6 weeks
Corpus luteum	• Can vary greatly in appearance from solid to cystic forms, up to 3cm in size • Peripheral vascularity often detected
Early first trimester dating	• Gestational sac (no yolk sac, embryo or heartbeat) = 5 weeks • Gestational sac and yolk sac (no embryo, no heartbeat) = 5.5 weeks • Gestational sac and yolk sac (living embryo, CRL less than 5 mm (too small to measure) = 6 weeks • When CRL available, use Australasian Society of Ultrasound Medicine measurements to date the pregnancy

Sourced primarily from Australasian Society of Ultrasound Medicine guidelines. Available from http://www.asum.com.au/

Standard ultrasound documentation

Aspect	Information required
Approach	• Specify if TVS or TAS to aid interpretation
Patient history	• LNMP if known and estimated date of delivery by LNMP • Any USS performed in the current pregnancy and the results • Whether β-hCG (urine or serum) performed and when
Intrauterine	• Presence of intrauterine sac and if visualised whether single or multiple • Mean sac diameter in mm and estimated gestation • Presence of yolk sac • Presence of fetal pole and the length • Presence of fetal heart movement and/or rate in beats per minute (bpm) • Presence and size of any peri-gestational bleed • Gestational age in weeks and days and estimated date of delivery by this USS • Presence and size of retained POC • If multiple pregnancy, number of yolk sacs and chorions, and thickness of dividing membrane • Possible ectopic intrauterine implantation (cornual, intramural, cervical, scar, ectopic)
Extrauterine	• Ovary—left and right • Adnexa—left and right • Presence of free fluid and volume (minimal, moderate, extensive) if any

Appendix C: Methotrexate regimens for ectopic pregnancy

Follow local protocols for the safe administration/disposal of cytotoxic medications and equipment. Refer to an Australian pharmacopeia for complete drug information.

Intramuscular injection (IM) methotrexate	
Indications	• Unruptured tubal ectopic pregnancy with **all** of the following: o β-hCG less than 3000 IU/L (may also be administered IV) o Fetal sac less than 3.5 cm o **NO** fetal cardiac activity
Dose calculation	• Dose is calculated per square meter of body surface area (BSA) o BSA = the square root of [Height (cm) x Weight (kg) divided by 3600] • No consensus on methotrexate dose capping, but commonly capped at 2 m^2 BSA (equivalent to methotrexate 100 mg IM injection) o If capped, morbidly obese women may require an additional dose o If BSA greater than 2 m^2 seek expert advice
Prior to commencement	• FBC, ELFT, β-hCG prior to each dose of methotrexate • Antiemetic 30 minutes prior to methotrexate (e.g. ondansetron 8 mg IV/PO OR granisetron 3 mg IV)
Post-dose	• Monitor woman for 30 minutes post methotrexate administration for hypersensitivity reactions (rare), consider antihistamine or steroid cream • Give ondansetron 4 mg BD PRN for 2 days
Day 1 (Treatment day)	• β-hCG • Methotrexate 50 mg/m^2 BSA IM injection (rounded to the nearest 5 mg) • Given IM into the buttock or lateral thigh by chemotherapy competent clinician
Day 4	• β-hCG
Day 7	• β-hCG • If day 7 β-hCG reduction is less than 15% of day 4 β-hCG, (or if no day 4 level, then less than 25% of day 1 β-hCG) give a second dose of methotrexate 50 mg/m^2 BSA IM injection
Day 14	• β-hCG • If day 14 β-hCG reduction is less than 15% of day 7 β-hCG, give a third dose of methotrexate 50 mg/m^2 BSA IM injection
β-hCG	• Monitor the β-hCG weekly until less than 5 IU/L
Intravenous injection (IVI) methotrexate	
Indication	• Any stable ectopic pregnancy (including unusual sites) at the discretion of the medical officer, particularly if **any** of the following: o β-hCG greater than 3000 IU/L o Fetal sac greater than 3.5 cm o Presence of cardiac activity
Prior to commencement	• β-hCG, FBC, ELFT • Ensure adequate hydration • 24 hours prior (or as soon as practical) ensure urinary pH greater than 7.0 o Give two sachets of sodium citrotartrate 6 hourly and continue until final dose of leucovorin o Test (each urinary void during treatment and prior to discharge)
Commence as inpatient	• Antiemetic 30 minutes prior to methotrexate (e.g. ondansetron 8 mg IV/PO OR granisetron 3 mg IV) • Loading dose of methotrexate 100 mg IV stat, over 5–10 minutes • Then methotrexate 200 mg IV infusion in 500 mL 0.9% sodium chloride over 12 hours
Post loading dose folinic acid ***(inpatient or outpatient)***	• Give ondansetron 4 mg BD PRN for 2 days • Give folinic acid 15 mg oral (leucovorin) at each of the following times (**timing is critical**): o 30 hours post-loading dose of methotrexate o 42 hours post loading dose of methotrexate o 54 hours post loading dose of methotrexate o 66 hours post loading dose of methotrexate • Confirm timings with follow-up telephone call the day after discharge
β-hCG	• Monitor the β-hCG weekly until less than 5 IU/L

NB: In some circumstances, alternative treatment may involve USS guided direct injection of methotrexate into ectopic pregnancy (plus or minus feticide). Seek expert advice**.**

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