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Queensland Maternity and Neonatal **Clinical Guideline**

Early pregnancy loss

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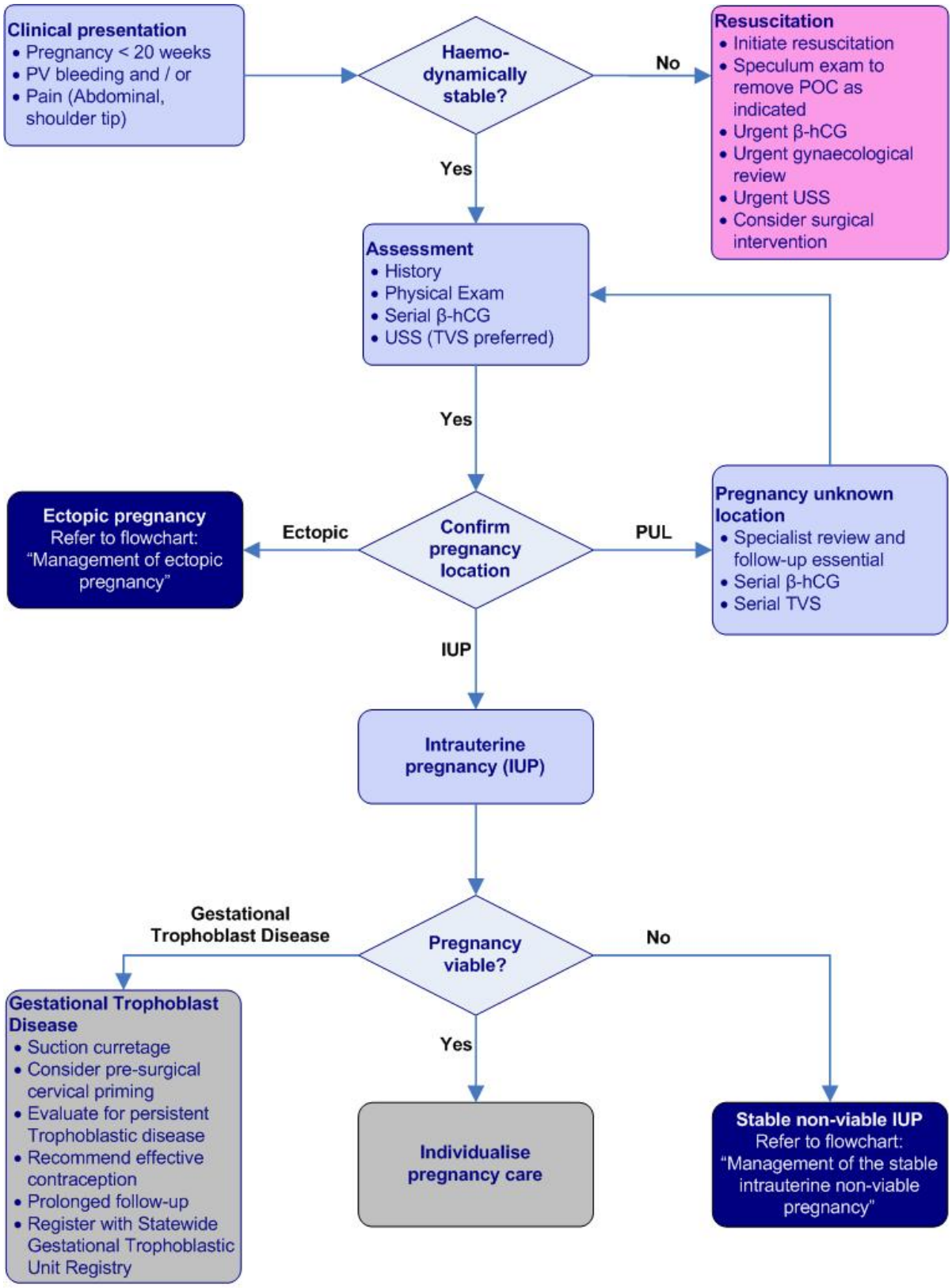
This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible to:

- Discuss care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- Advise consumers of their choice and ensure informed consent is obtained
- Provide care within scope of practice, meet all legislative requirements and maintain standards of professional conduct
- Apply standard precautions and additional precautions as necessary, when delivering care
- Document all care in accordance with mandatory and local requirements

Flow Chart: Assessment of suspected early pregnancy loss



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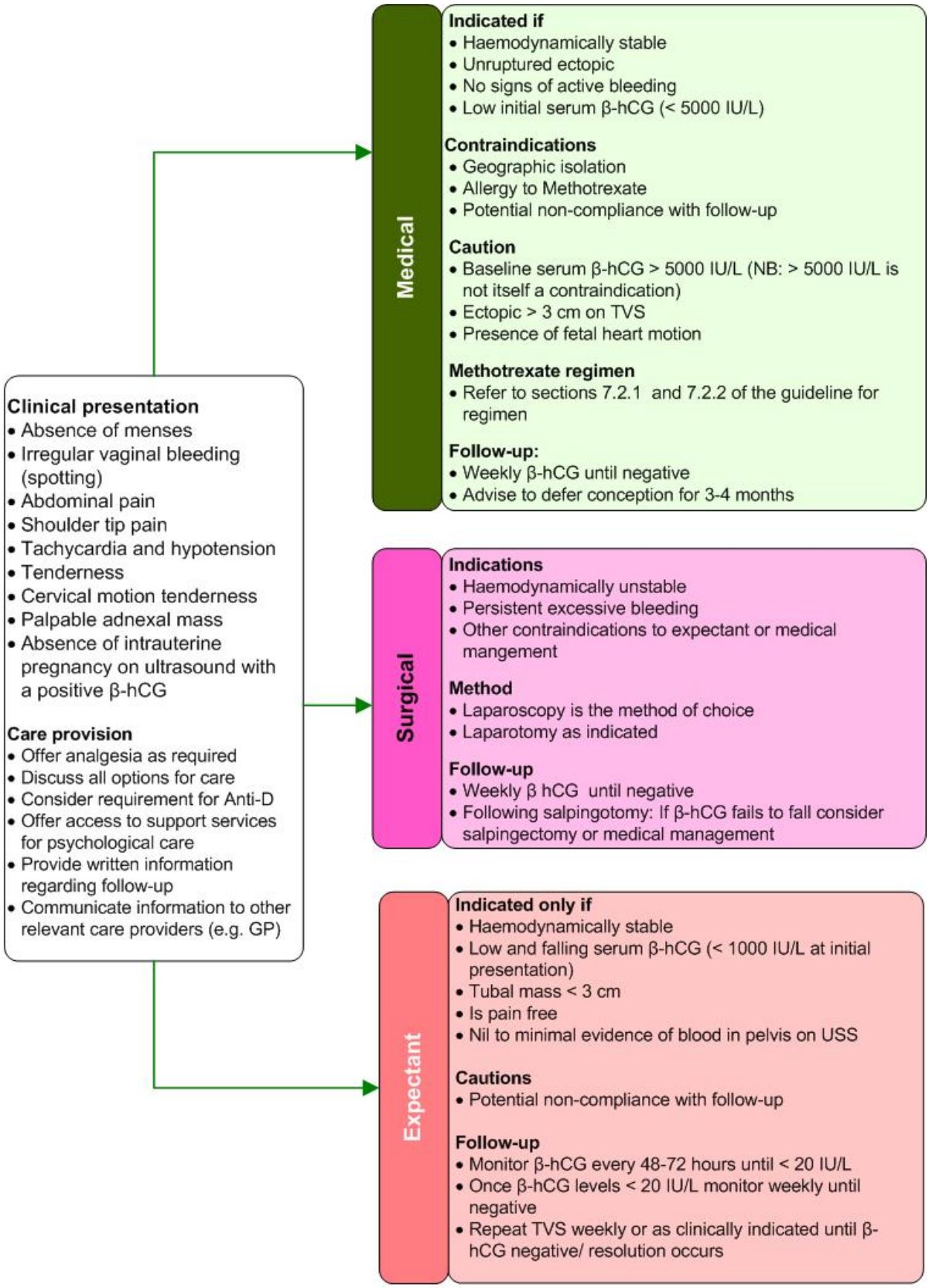
Flow Chart: Management of ectopic pregnancy



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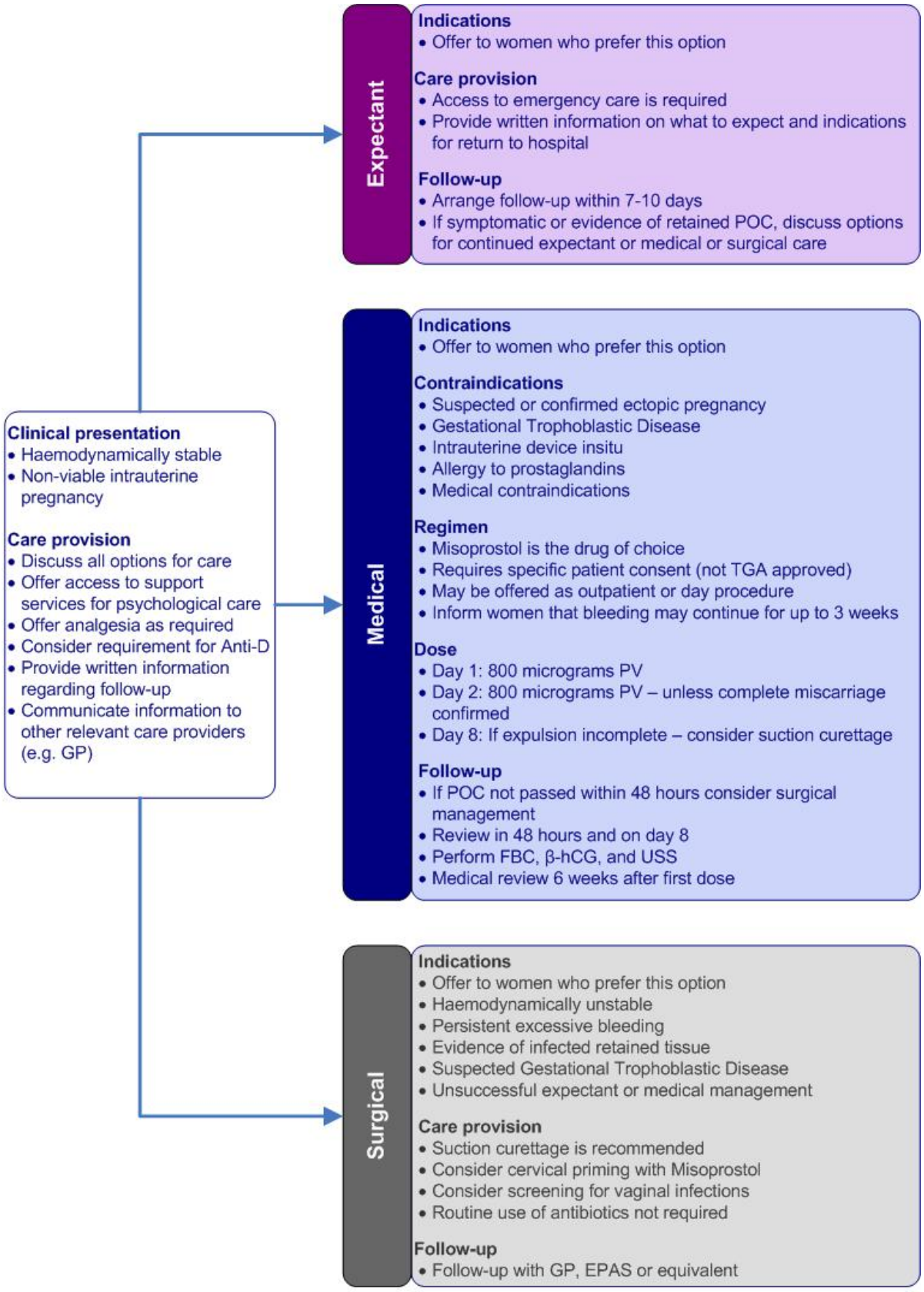
Flow Chart: Management of the stable intrauterine non-viable pregnancy



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Abbreviations

ATS	Australasian Triage Scale
bpm	Beats per minute
BSA	Body surface area
EDD	Expected delivery date
ELFT	Electrolytes, Liver Function Tests
EPAS	Early pregnancy assessment service
FMH	Fetomaternal haemorrhage
FBC	Full blood count
GP	General Practitioner
β-hCG	Beta human chorionic gonadotrophin
IUP	Intrauterine pregnancy
LMP	Last menstrual period
NSAID	Non-steroidal anti-inflammatory drugs
PDC	Perinatal Data Collection
POC	Products of conception
PUL	Pregnancy of unknown location
PUV	Pregnancy of unknown viability
PV	Per vaginam
RBDM	Registrar of Births, Deaths and Marriages
Rh D Ig	Rhesus D immunoglobulin
RCOG	Royal College of Obstetricians and Gynaecologists
RPL	Recurrent pregnancy loss
TAS	Trans abdominal ultrasound
TGA	Therapeutic goods administration
TVS	Transvaginal ultrasound
USS	Ultrasound scan

Definitions

Early pregnancy loss	Loss within the first 20 completed weeks of pregnancy
Live birth	Refers to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life - e.g. beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles - whether or not the umbilical cord has been cut or the placenta is attached. Each product of such a birth is considered live born[1]
Ectopic pregnancy	A pregnancy located outside the uterus, usually in the fallopian tubes but may be ovarian[2] or in other sites
Expectant management	No specific intervention. Allows spontaneous passage of products of conception[3]
Medical management	Use of drugs to aid the expulsion of the retained fetal products of conception[3]
Surgical management	Surgical evacuation (with or without curettage) of the retained products of conception[3]

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1 Introduction

- Miscarriage occurs in 10–20% of clinical pregnancies[4] and accounts for 55,000 couples experiencing early pregnancy loss each year in Australia
- Improved diagnostic techniques and therapeutic interventions have enabled treatment provision in General Practitioner (GP), obstetrician and hospital outpatient settings
- Significant psychological effects can occur in women (and their partners and families) who suffer a miscarriage,[4] however appropriate support during and after the event can have positive lasting effects[4]

1.1 Legal identity

In Queensland it is compulsory to register the birth of a baby that is born alive.

- The Public Health Act 2005[5] defines a baby born alive as a "baby whose heart has beaten after delivery of the baby is completed". There is no gestational age requirement specified
- It remains a clinical decision as to whether there are signs of life or not
- Refer to Guideline: Stillbirth care[6] for reporting requirements where there are signs of life

1.2 Purpose and scope

This guideline:

- Provides information related to the diagnosis and clinical management of women with early pregnancy loss
- Primarily addresses management of threatened and spontaneous miscarriage
- Is also relevant for women affected by ectopic pregnancy and Gestational Trophoblastic Disease
- Is intended primarily for use by multidisciplinary clinicians working in women's health settings, but is also applicable to anyone providing care to women experiencing early pregnancy loss
- Recommends the preferred terminology

2 Service provision

Women presenting with symptoms of early pregnancy loss (e.g. bleeding, pain) should be triaged according to the Australasian Triage Score (ATS) and assessed by an experienced clinician within the recommended waiting times.[7]

- Each woman's emotional state should be considered and counselling / psychological support offered / provided as required
- Women suitable for discharge should be referred to the most appropriate service provider (e.g. obstetrician, GP, Early Pregnancy Assessment Service (EPAS))

2.1 Early pregnancy assessment service

All maternity services should provide or be networked to a dedicated outpatient EPAS[4]:

- It is acknowledged that obstetricians and gynaecologists and GP obstetricians have been and will continue to provide such services
- In community / rural settings GPs usually provide these services. Networking with a dedicated EPAS for consultation is recommended with referral as required
- Local facilities should consider the requirements for EPAS provision as outlined in Appendix A

3 Preferred terminology

The inadvertent use of inappropriate terms such as 'pregnancy failure' can contribute to women's negative self perceptions and worsen any sense of failure, guilt and insecurity related to the miscarriage.[4] Table 1 outlines both revised terms and terms recommended for use.

Table 1. Preferred terminology

Recommended term[4]	Previous term[4]	Definition[2]
Miscarriage	Spontaneous abortion	Pregnancy loss occurring before 20 completed weeks of gestation or less than 400 g weight
Threatened miscarriage	Threatened abortion	Any vaginal bleeding other than spotting before 20 weeks completed gestation
Inevitable miscarriage	Inevitable abortion	Miscarriage is imminent or in the process of happening
Incomplete miscarriage	Incomplete abortion	Miscarriage where some of the fetus or placenta are unable to be naturally expelled by the mother
Complete miscarriage	Complete abortion	Miscarriage needing no medical or surgical intervention
Missed miscarriage	Missed abortion	USS confirmed non-viable pregnancy with no bleeding
Miscarriage with infection (sepsis)	Septic abortion	A miscarriage complicated by pelvic infection
Recurrent miscarriage	Recurrent abortion	3 or more consecutive miscarriages by the same woman
Pregnancy of unknown location		No signs of either intra or extrauterine pregnancy or retained products of conception (POC) in a woman with a positive pregnancy test[4]
Pregnancy of uncertain viability		Intrauterine sac (less than 20 mm mean diameter) with no obvious yolk sac or fetus *Or* Fetal echo less than 6 mm crown-rump length with no obvious fetal heart activity[4]
Heterotopic pregnancy		Intrauterine plus ectopic pregnancy (e.g. tubal, cervical, ovarian, abdominal)[8]
Anembryonic pregnancy	Blighted ovum	A fertilised egg implants into the uterine wall, but fetal development never begins. Often there is a gestational sac with or without yolk sac but there is an absence of fetal growth[2]
Gestational Trophoblastic Disease		Comprises a spectrum of interrelated conditions originating from the placenta. Also known as Molar pregnancy (complete or partial)

4 Assessment

Assessment and diagnosis is made through a combination of patient history, physical examination and clinical investigation. Ultrasound scan (USS) should be performed as soon as possible and urgently if clinically indicated. [Refer to Appendix B: Sonographic landmarks and anatomy] Initial assessment of haemodynamic stability is essential. If haemodynamically unstable refer to Section 5.

4.1 History

History should include:

- Menstrual history and last menstrual period (LMP)
- Previous pregnancies and outcomes, particularly miscarriages
- Other significant gynaecological history (e.g. past history of pelvic infection)
- If assisted conception, identify method of conception
- Relevant USS
- Symptoms of early pregnancy
- Presence of associated symptoms:
  - Vaginal bleeding (timing, extent and severity)
  - Pain (lower abdominal / cramping / backache)
  - Postural syncope
  - Vomiting
  - Shoulder tip pain
- Passage of products of conception (POC)

4.2 Confirmation of pregnancy

All women of reproductive age presenting with a history of recent / current abdominal pain, pelvic pain, shoulder tip pain and / or per vaginam (PV) bleeding, syncope or signs of shock should have an urgent serum pregnancy test performed (irrespective of LMP, contraception, history of sterilisation or reported sexual inactivity). Urine β-hCG may be used as clinically indicated.

- Serum β-hCG first becomes positive at 9 days post conception[4]
  - β-hCG greater than 5 IU/L confirms pregnancy (level reached 9 days)
- A negative serum β-hCG essentially excludes ectopic (except in the unusual circumstance of a chronic ectopic where β-hCG has been positive in the recent past)

4.3 Physical examination

- Baseline observations (temperature, heart rate, respiratory rate, blood pressure)
- Abdominal examination to check for:
  - Tenderness (rigidity and guarding)
  - Distension
- Vaginal examination (individualised as clinically indicated):
  - Speculum examination:
    - Source and amount of bleeding
    - Evidence of POC in the cervical os (if present, remove and submit for histopathology)
  - Bi manual examination:
    - Cervical motion tenderness
    - State of internal cervical os
    - Assess for adnexal masses (ectopic pregnancy or other masses)
    - Size of uterus related to menstrual dates
- If haemodynamically unstable refer to Section 5

4.4 Correlation of ultrasound with serial β-hCG measurements

- USS assessment and serial β-hCG enable the clinician to ascertain the location and potential viability of an early pregnancy
- Transvaginal scanning (TVS) by an experienced sonographer is the gold standard and should be utilised wherever possible
  - If TVS unavailable, transabdominal ultrasound (TAS) may be used, recognising that it is not as accurate as TVS for diagnosis of early pregnancy complications
- Individualise treatment according to the woman's clinical state, preferences, and results from TVS or other scanning and β-hCG investigations
- In 8-31% of women, it may not be possible to confirm if a pregnancy is intrauterine or extra-uterine at first visit[4]
- When a diagnosis of complete miscarriage is made, ensure adequate follow-up in case of undiagnosed ectopic

4.4.1 Intrauterine pregnancies

For a potentially viable intrauterine pregnancy (IUP) up to 6-7 weeks gestation the following applies:

- Mean doubling time for β-hCG is 1.4-2.1 days
  - 85% show serial β-hCG rise of at least 66% every 48 hours[9]
  - 15% show serial β-hCG rise between 53-66% every 48 hours[9]
  - The slowest recorded rise over 48 hours is 53%[10]
- 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[10]
- IUP is usually visible on TVS when gestational sac greater than or equal to 3 mm. This corresponds to a discriminatory zone for β-hCG of:
  - 1500-2000 IU/L on TVS (may occasionally be seen at greater than or equal to 1000 IU/L)
  - Approximately 6500 IU/L on Transabdominal scan (TAS)
- Cautions:
  - Multiple gestations: There is no proven discriminatory zone for β-hCG
  - Presence of fibroids: USS may be less reliable

Table 2. Good practice points for β-hCG and TVS correlations

β-hCG / TVS in clinically stable women	Recommendation
• β-hCG: Less than 2000 IU/L	• Repeat TVS / β-hCG from 48-72 hours
• β-hCG: Greater than 2000 IU/L AND • TVS: No IUP, complex adnexal mass and / or free fluid	• High probability of ectopic pregnancy • Refer to section 7
• β-hCG: Greater than 2000 IU/L AND • TVS: No IUP, no abnormal findings	• Repeat TVS / β-hCG from 48-72 hours
• Declining or sub-optimally rising β-hCG levels (as per above thresholds)	• Indicates a non-viable pregnancy (intrauterine or ectopic) • Ensure appropriate follow-up to ensure adequate resolution of either diagnosis

4.4.2 Ultrasound documentation

Ideally standardised documentation should be used for USS reports.[4] Table 3 outlines essential information that should be included.[11]

Table 3.Essential information to be included in USS report

Source	Information required
Patient history	• LMP if known • Expected delivery date (EDD) by LMP • Whether any USS were performed in the current pregnancy and their results • Whether β-hCG (urine / serum) was performed and when
Ultrasound (TAS / TVS)	**Intrauterine:** • Presence of intrauterine sac and if visualised whether single or multiple • Mean sac diameter in mm and estimated gestation • Presence of yolk sac (should be visualised on TVS in gestational sac greater than 8 mm with β-hCG of 5000 IU/L[12]) • Presence of any fetal pole and the length • Presence of fetal heart movement • Fetal heart rate if present in beats per minute (bpm) • Presence and size of any peri gestational bleed • Gestational age by this USS in weeks and days • EDD by this USS • Presence and size of retained POC • If multiple pregnancy, comment on 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

5 Haemodynamically unstable women

Haemodynamically unstable women require urgent intervention; presume ruptured ectopic pregnancy or incomplete miscarriage with cervical shock or massive haemorrhage.

- Resuscitate as required considering airway, breathing and circulation
- Ensure sufficient IV access (e.g. 2 x 16 gauge IV cannulae)
- Perform urgent speculum examination and remove POC as clinically indicated. This may stop bleeding and restore blood pressure
- Obtain urgent gynaecological review and USS concurrently with resuscitation
    - If ectopic pregnancy confirmed or unable to be excluded, continue resuscitation en-route to theatre
- If bleeding persists and ectopic has been excluded consider:
    - Ergometrine (250 micrograms IV as slow IV injection or 500 micrograms IM) OR
    - Oxytocin (5-10 units IV or IM) if history of heart disease, thyrotoxicosis or severe vascular disease OR
    - Misoprostol 800-1000 micrograms per rectum

Unstable haemodynamics is a clinical indication for:

- Surgical evacuation of the uterus for incomplete miscarriage
    - Suction curettage is preferable to sharp curettage as the latter is associated with increased morbidity[13]
- Laparoscopy and / or laparotomy for removal of ectopic pregnancy

6 Care considerations for early pregnancy loss

Women experiencing all types of early pregnancy loss require consideration of the following as outlined in Table 4.

Table 4. Care considerations for early pregnancy loss

Aspect	Consideration
Breaking bad news	• Inform parents of diagnosis in a timely manner and in a private area • Consider special circumstances (e.g. previous miscarriage, stillbirth or multiple pregnancy) • Ensure a support person is present for the woman. Offer contact with support services (e.g. Social Work) • When appropriate, reassure the woman that the loss was not due to anything she did or did not do • Avoid speculation regarding the cause and explain that the cause of miscarriage often remains unexplained • Use empathetic but unambiguous language (e.g. “your baby has died”) • The most experienced practitioners should be available for these difficult conversations • Allow time for parents to ask questions • Allow as much time as needed for parents to consider treatment options and make decisions • Be aware that men and women may respond and grieve differently • Encourage staff to express their sorrow for what has happened. Offering sympathy is not an admission of guilt or error
Care provision	• Promote continuity of carer for women experiencing a miscarriage • Offer / provide privacy where feasible • Provide analgesia as required • Provide information regarding care options, what to expect during treatment and arrangements / expectations for follow-up • Encourage attendance of a support person at the USS examination for confirmation of a suspected pregnancy loss • Offer access to support services (e.g. Social Work Services or Pregnancy Loss Coordinator) • Offer autopsy for late spontaneous miscarriage (17-19 weeks gestation)
Tissue sample collection	• Send tissue obtained at the time of miscarriage or via surgical intervention to pathology for histology to confirm pregnancy and exclude ectopic pregnancy or unsuspected Gestational Trophoblastic Disease[4] • Discuss with women who chose expectant care, the option of tissue collection so histology can be arranged[4] if required • Discuss the possibility of karyotyping the POC in the event of recurrent miscarriage
Discharge Information	• Communicate information to the GP and other care providers • Consider specialist review if recurrent miscarriage [refer to Section 10.2]

6.1 Rh D immunoglobulin

Blood group and antibody screen is required for women with early pregnancy complications. Rh D immunoglobulin is indicated for the prevention of Rh D sensitisation in Rh D negative women.[14] Refer to Table 5 for considerations and recommendations.

Table 5. Administration of Rh D immunoglobulin

Consideration	Recommendation[14]
Requirement for Rh D immunoglobulin	• Rh D negative women not already sensitised (the large majority of women)
Administration for successful immunoprophylaxis	• As soon as possible after (always within 72 hours of) each sensitising event • If not offered within 72 hours, a dose offered within 9-10 days may provide protection
First trimester sensitising events (up to and including week 12 of gestation)	• Miscarriage • Termination of pregnancy • Ectopic pregnancy • Chorionic villous sampling
Second trimester sensitising events (after week 12 of gestation)	• Genetic studies (chorionic villous sampling, amniocentesis and cordocentesis) • Abdominal trauma considered sufficient to cause fetomaternal haemorrhage (even if Kleihauer negative, as 0.001 mL fetal blood sensitises an Rh negative mother)[15] • Each occasion of revealed or concealed ante-partum haemorrhage • External cephalic version (performed or attempted) • Miscarriage (including threatened miscarriage) or termination of pregnancy

Dose	• 625 IU of Rh D immunoglobulin protects against 6 mL fetal red cells (12 mL whole blood), which is equivalent to 0.25% fetal cells in the maternal circulation[16]
	• Rh D Ig 250 IU for each first trimester sensitising events (minimum interval between doses not established, therefore repeat for each sensitising event)
	• Rh D Ig 625 IU for second trimester sensitising events
	  o If gestation unknown / possibly greater than 13 weeks
	  o Multiple gestation (regardless of gestation)

Assessment of fetomaternal haemorrhage	• For potentially sensitising events occurring after the first trimester, maternal blood should be collected prior to administration of Anti-D to assess volume of fetomaternal haemorrhage (FMH) • The Kleihauer Test is commonly used to identify women with a large FMH (greater than 6 mL) • A negative Kleihauer Test indicates that one dose of Rh D immunoglobulin is sufficient • If FMH is greater than covered by dose administered, an additional dose(s) of Anti-D sufficient to provide immunoprophylaxis should be given within 72 hours • In cases of continual bleeding from antepartum haemorrhage, perform weekly testing and antibody screening while either the test for FMH is positive and / or the antibody screen is negative. At this stage a further dose of Rh D immunoglobulin should be given and the testing cycle restarted • Flow cytometry is the most accurate quantitative test for fetomaternal haemorrhage and may be performed by the laboratory at their discretion
Contraindications	• Rh D positive women • Rh D Negative women with preformed Anti-D antibodies • Previous sensitivity or allergy to Anti-D

7 Ectopic pregnancy

Failure to promptly diagnose and manage an ectopic pregnancy can be catastrophic.[17]

- Accounts for 10% of all pregnancy related maternal deaths
- Is an important cause of maternal morbidity and mortality worldwide[18]
- Commonly (95%) occurs in the fallopian tube[17,18]
- Other less common situations include interstitial (corneal) pregnancy, ovarian ectopic, cervical, heterotopic pregnancy and abdominal pregnancy[18]
- Falling or stationary β-hCG does not exclude the risk of rupture following surgical, medical or expectant management
- Management options include surgical, medical and expectant care.[19] Choice of option will depend on the clinical situation and patient preference.[17]

Table 6. Ectopic pregnancy

Aspect	Consideration
Risk factors	Not all women diagnosed with an ectopic pregnancy will have risk factors, which may include[18]: • Previous ectopic pregnancy • Tubal surgery • Infertility (risk increases with duration of infertility) • Assisted reproductive technology • Intrauterine contraceptive device in situ • Use of emergency contraception • History of pelvic inflammatory / sexually transmitted disease • Documented tubal pathology • Current smoker (risk increases with amount smoked per day) • Age 40 years or older • Sterilisation (risk increased nine-fold)
Clinical presentation	• Absence of menses[17] • Irregular vaginal bleeding (spotting)[17] – but not in all cases • Shoulder tip pain in 10-20% of women with ruptured ectopic[17] • Tachycardia and hypotension as a result of profound intraperitoneal haemorrhage • Abdominal pain, tenderness and palpable adnexal mass in 50% of women[17] • Cervical motion tenderness • Absence of an intrauterine pregnancy on USS with a positive serum β-hCG level should raise suspicion of an ectopic pregnancy[17]

7.1 Surgical management of ectopic pregnancy

Table 7. Surgical management of ectopic pregnancy (excluding cervical ectopic)

Aspect	Consideration
Indications	• Offer to women who prefer this option • Haemodynamically unstable • Persistent excessive bleeding
Risk / Benefit	• Laparoscopy is the method of choice for stable women[18] • Laparotomy is preferred in cases of haemorrhagic shock o Laparoscopy may be suitable in cases of haemorrhagic shock for selected women where the surgeon is experienced • Following salpingostomy, persistent ectopic pregnancy occurs in 4-15% of cases[18]

Follow-up	**Following salpingectomy**
	• Confirm ectopic pregnancy on histology
	• β-hCG follow-up if clinically indicated
	  o Unusually may see abdominal implantation especially after ruptured ectopic with haemoperitoneum
	  o Rarely may see ongoing intrauterine gestation if undiagnosed heterotopic pregnancy
	
	Following salpingostomy
	• Weekly β-hCG until negative[18]
	• If β-hCG fails to fall appropriately, salpingectomy may be required or medical management considered
	
	Conception interval
	• There is no data on the optimal interval
	• Clinical practice varies from next menstrual period to 3 months
	• Risk of recurrent ectopic pregnancy is approximately[20]:
	  o 15% after one ectopic pregnancy
	  o 30% after two ectopic pregnancies
	• Subsequent intrauterine pregnancy rate is 38-89%[18]

7.2 Medical management of ectopic pregnancy

Methotrexate is the drug of choice. Refer to Table 9 for intramuscular regimen and Table 10 for intravenous regimen.

Table 8. Medical management of ectopic pregnancy

Aspect	Consideration
Indications	• Unruptured ectopic pregnancy; haemodynamically stable and no signs of active bleeding[19,21] • Unusual sites (e.g. cervical ectopic, interstitial) • Low initial serum β-hCG[19] • Best results achieved if β-hCG less than 5000 IU/L[18] • Full blood count (FBC), Electrolytes and Liver Function Tests (ELFT) should be within normal range
Contraindication[21]	• Haemodynamically unstable • Evidence of significant haemoperitoneum on TVS • Renal disease / insufficiency as Methotrexate is cleared via the renal system • Abnormal FBC, ELFT • Acute liver disease, aplastic anaemia, thrombocytopenia • Immunodeficiency • Active pulmonary disease • Peptic ulcer • Coexistent viable intrauterine pregnancy (heterotopic pregnancy) • Breastfeeding • Potential for non-compliance with prolonged follow-up (35-109 days) • Geographic isolation • Allergy to Methotrexate
Caution	• Baseline serum β-hCG greater than 5000 IU/L • Ectopic pregnancy greater than 3 cm diameter on TVS • Presence of fetal heart motion • Avoid sun exposure and folic acid during Methotrexate treatment
Risk / Benefit	• 4-15% of women may subsequently require surgical intervention[18] • Limited high level evidence on medical v surgical options with regard to long term fertility[19] • No significant differences between fixed multiple dose intramuscular regimen and laparoscopic salpingostomy found in long term follow-up of intrauterine pregnancy and repeat ectopic pregnancy[19]
Follow-up	• Weekly β-hCG until negative (some regimens initially twice weekly) **Interval to conception and future fertility** • There is limited high level evidence addressing this issue • Rationale for caution is due to potential teratogenicity of Methotrexate[22] • A retrospective study[23] showed no apparent deleterious effect of previous Methotrexate treatment on future offspring (no increased teratogenicity or increased adverse obstetric outcomes) when comparing conception less than 6 months with conception after 6 months • The manufacturer of Methotrexate recommends a delay of a minimum of 3 months[22] • Toxicology literature recommends a 4-6 month washout period[24] • Based on this available evidence: Recommend deferring conception for 4 months after any Methotrexate treatment • Advise to delay conception until USS resolution of ectopic mass which typically takes longer than biochemical resolution[25] • Recommend Folate as per routine preconceptual advice

7.2.1 Intramuscular Methotrexate regimens for ectopic pregnancy

Methotrexate regimens vary.[21,26,27] Two common protocols are outlined in Table 9. IMI Methotrexate regimens for ectopic pregnancy. Choice of protocol depends on provider preference.

Table 9. IMI Methotrexate regimens for ectopic pregnancy

Aspect	Recommendation
Factors associated with protocol success	• If β-hCG is[28]: o less than 5000 IU/L success rate is 95% o less than 10 000 IU/L success rate is 86% o 10 000–15 000 IU/L success rate is 82%
Factors associated with protocol failure	• Initial β-hCG as above[28] • Fetal cardiac activity [increase failure with OR 9.1][28] • Large ectopic size (greater than 3.5 cm)
Dose	• Dose is calculated per square meter of Body Surface Area (BSA) o BSA = the square root of [Height (cm) x Weight (kg) / 3600] o Pharmacy can assist with dose calculations
Methotrexate Protocol 1	Day 1 (Treatment day) • β-hCG • Methotrexate 50 mg/m^2 BSA IMI Day 7 • Repeat β-hCG • If Day 7 β-hCG decline is less than 25% of Day 1 β-hCG, then give 2nd dose of Methotrexate 50 mg/m^2 BSA IMI After Day 7 weekly quantitative β-hCG
Methotrexate Protocol 2	Day 1 (Treatment day) • β-hCG • Methotrexate 50 mg/m^2 BSA IMI Day 4 • β-hCG Day 7 • Repeat β-hCG • If Day 7 β-hCG decline is less than 15% of Day 4 β-hCG, then give 2nd dose of Methotrexate 50 mg/m^2 BSA IMI After Day 7 weekly quantitative β-hCG

7.2.2 Intravenous Methotrexate regimen for ectopic pregnancy

The following IV regimen[25] may be used for any medical treatment of ectopic and particularly where:

- There is an interstitial or cervical ectopic pregnancy
- β-hCG is greater than 5000 – 10 000 IU/L
- Fetal heart movement is present on USS
- Gestational sac is greater than 3.5 cm

Table 10. IV Methotrexate / Folinic Acid regimen for ectopic pregnancy

Treatment	
Prior to commencement	• Ensure urinary pH is greater than 7. Methotrexate is excreted renally and alkaline urine prevents crystallisation of Methotrexate in the renal tract • Advise loading with Sodium Citrotartrate (as sachets) or IV 8.4%Sodium Bicarbonate in 100mls over 1 hour • Educate the woman: o On timing of oral doses o To return immediately if vomiting • If vomiting, 15 mg Folinic Acid IMI / IV
Commence (Inpatient)	• Ondansetron 8 mg IV • Methotrexate 100 mg IV stat, slowly over 5 minutes (loading dose) • Methotrexate 200 mg IV infusion in 500mL 0.9% Sodium Choride over 12 hrs
Hours post loading dose of Methotrexate	
30 hours (Inpatient/Outpatient)	• Folinic Acid 15 mg oral (Leucovorin)
42 hours (Inpatient/Outpatient)	• Folinic Acid 15 mg oral
54 hours (Inpatient/Outpatient)	• Folinic Acid 15 mg oral
66 hours (Outpatient)	• Folinic Acid 15 mg oral

7.3 Expectant management of ectopic pregnancy

Expectant management may be considered as an option for selected women. Clear criteria for selection have not been well defined.[19] Considerations are outline in Table 11.

Table 11. Expectant management of ectopic pregnancy

Aspect	**Consideration**
Indications	Only consider if: • Haemodynamically stable • Low and falling β-hCG (less than 1000 IU/L at initial presentation) • Tubal mass less than 3 cm • No pain • Nil to minimal evidence of blood in the pelvis on USS • No geographical isolation
Cautions	• Consider individual circumstances • Not suitable for women who are potentially non compliant or not motivated to long term recovery
Risk Benefit	• There is little high level evidence to evaluate expectant management of tubal ectopic pregnancy[19]
Follow-up	• Monitor serum β-hCG every 48-72 hours until less than 20 IU/L • Once β-hCG levels are less than 20 IU/L, monitor weekly until negative • Repeat TVS as clinically indicated until β-hCG is negative. Once β-hCG negative TVS advisable to ensure resolution of ectopic occurs • Consider medical or surgical management if[21]: o Pain increases significantly o β-hCG fails to fall o Tubal rupture with haemoperitoneum occurs

8 Stable women with non-viable intrauterine pregnancy

Expectant, medical and surgical management options are outlined below where:

- The woman is haemodynamically stable
- Ectopic pregnancy has been excluded [refer to Section 7 for management of ectopic pregnancy]
- The pregnancy is not viable

8.1 Expectant management of the stable non-viable intrauterine pregnancy

Table 12. Expectant management for stable non-viable IUP

Aspect	Consideration
Indications	• Effective for incomplete miscarriage[4,29] • Offer to women who prefer this option[4]
Risk / Benefit	• Reduced risk of pelvic infection[29] • More days of bleeding and a greater amount of bleeding when compared to surgical treatment[30] • Approximately 10% of women will subsequently require surgical management[29] • Women breastfeeding an older baby may prefer to wait rather than have drug treatment[31] • For women with an intact sac, resolution may take several weeks and overall efficacy rates are lower[4]
Care provision	• Access to a telephone and emergency hospital admission is required or a plan for access to medical assistance developed where there is geographical/social isolation • Provide written information on what to expect and indications for return to hospital (e.g. pain unrelieved by Paracetamol, syncope, soaking of one pad within 60 minutes) • Advise that surgical or medical management can be chosen at a later date if desired • Advise that waiting can be emotionally difficult • If infection suspected recommend early surgical management with antibiotic cover
Follow-up	• Provide written information to the woman's GP • Arrange review within 7-10 days at EPAS or equivalent o Serial USS o If bleeding, pain or evidence of retained POC, discuss options for continued expectant, or medical or surgical management o Review histology if POC were provided

8.2 Medical management of the stable non-viable intrauterine pregnancy

Table 13. Medical management for the stable non-viable IUP in the first trimester

Aspect	Consideration
Indications	• Offer to women who prefer this option[4]
Risk / Benefit	• Misoprostol is the drug of choice[31] • Vaginal Misoprostol is more effective than oral Misoprostol[32] • Is an effective alternative to surgical evacuation for the management of confirmed first trimester miscarriage[4,33] • No significant difference between medical and expectant management for rates of[34]: o Complete miscarriage o Need for surgical evacuation • Bleeding is heavier and more prolonged after medical treatment with Misoprostol than with curettage[35]
Care provision	• Inform women that: o Bleeding may continue for up to 3 weeks[4] o Increased pain and bleeding may be experienced[4] • Provide written information on what to expect and indications for return to hospital[33] (e.g. pain unrelieved by Paracetamol, soaking of more than one pad within 60 minutes) • Treatment may be offered as an outpatient or day procedure[33] • Provide oral analgesia[33] • Provide antiemetic as nausea and vomiting may be associated with Misoprostol • Consider the requirement for Anti-D[33]
Follow-up	• Provide written information to the GP • If POC are not passed within 48 hours consider surgical management • Review on day 1, day 2 and day 8 of treatment o Initial evaluation of success is by history and examination o Perform Full Blood Count, β-hCG and USS o If ongoing heavy bleeding and / or evidence of retained POC, recommend surgical management[33] • Medical review 6 weeks following first dose of Misoprostol

8.2.1 Misoprostol for non-viable intrauterine pregnancy

There is little high level evidence for one specific Misoprostol regimen over another.[31] Where local protocols are not well established the following regimen is suggested in Table 14.

Table 14. Misoprostol regimen for non-viable IUP

Aspect	Consideration
Contraindications	• Suspected or confirmed ectopic pregnancy[36] • Gestational Trophoblastic Disease[36] • Intrauterine device (IUD must be removed)[36] • Allergy to Prostaglandins[36] • Contraindications to medical or surgical uterine evacuations (e.g. haemodynamically unstable, coagulopathy)[36] • Medical contraindications (e.g. hypertension)
Approval for use	• Misoprostol is not approved by the Therapeutic Goods Administration (TGA) for obstetric use in Australia • Queensland Health approves the use of Misoprostol for[37]: o Specialist Staff and Country Medical Superintendents for: (a) complications in patients who have a history of peptic ulcer disease and in whom non steroidal anti-inflammatory drug (NSAID) therapy is essential; and (b) second line management of primary post partum haemorrhage o Specialist Staff for the therapeutic termination of pregnancy and the management of missed miscarriage • Where medicines are used outside their TGA approved indications[37]: o Patients should be made fully aware of the status of the medicine o Appropriate consent should be obtained
Dose	There is no consensus on the optimal regimen. The following is suggested[33]: • Day 1: 800 micrograms PV • Day 2: 800 micrograms PV unless complete miscarriage confirmed • Day 8: Consider suction curettage if expulsion still incomplete[33]

8.3 Surgical management of the stable non-viable intrauterine pregnancy

Table 15. Surgical management of the stable non-viable IUP

Aspect	Consideration
Indications	• Offer to women who prefer this option[4] • Clinical indications for surgical management include[4]: o Haemodynamically unstable o Persistent excessive bleeding o Evidence of infected retained tissue o Suspected Gestational Trophoblastic Disease o Unsuccessful medical or expectant management
Risk / Benefit	• Suction curettage is safe, quick and less painful than sharp curettage and is recommended for use in the management of incomplete miscarriage[13]
Care Provision	• Suction curettage is usually performed under general anaesthetic • Provide appropriate analgesia and sedation[13] • Consider Misoprostol for pre-surgical cervical priming based on individual patient circumstance[4] (200-400 mcg PV / Oral) • Consider screening for infection including Chlamydia Trachomatis[4] • Consider vaginal swabs to exclude bacterial vaginosis if clinically indicated[4] • There is insufficient evidence to support routine antibiotic prophylaxis prior to surgery and should be given based on individual clinical indications[4] • Consider USS at time of suction curettage if clinically indicated
Follow-up	• Follow-up with GP, EPAS or equivalent as clinically indicated

9 Gestational Trophoblastic Disease

Complete molar pregnancies are more likely than partial molar pregnancies to be identified by their characteristic USS features or associated theca lutein cysts.

Table 16. Gestational Trophoblastic Disease

Aspect	Considerations[38,39]
Interventions	• Suction curettage with concomitant administration of IV uterotonic agents (e.g. Oxytocin) is required • There is limited evidence, however Misoprostol for pre-surgical cervical priming may be considered [refer to section 8.3] • Register with the Statewide Gestational Trophoblastic Unit Registry
Persistent Trophoblastic Disease	Consider where there is: • Increased, stationary or inadequately falling β-hCG trend on 3 consecutive weeks at any time following surgical evacuation • Greater than 20 IU/L β-hCG more than 12 weeks after evacuation • Continuation of abnormal uterine bleeding and detectable β-hCG • Evidence of metastases in the presence of detectable β-hCG • PV bleeding in the presence of detectable β-hCG
Follow- up	• Aim is to exclude persistent Trophoblastic Disease • Effective contraception to avoid pregnancy during follow-up is required • Perform β-hCG levels 6 weeks after any future pregnancy **Partial mole** • Serum β-hCG levels should be followed weekly until negative for 3 consecutive results • Then monthly until 6 months post evacuation **Complete mole** • Serum β-hCG levels should be followed weekly until negative for 3 consecutive results • Then monthly until 6 months after the 3rd negative result
Patient Registration	Statewide Trophoblastic Disease Service Gynaecology Outpatients & Centre for Breast Health Level 5, Ned Hanlon Building, Royal Brisbane and Women's Hospital Herston QLD 4029 Gynaecology Case Manager: Tel: 07 3636 3292 Fax: 07 3636 0888
Contact the Director of the Statewide Trophoblastic Disease Service on 3636 8111 (Royal Brisbane and Women's Hospital switch): • For any clinical concerns • In cases of persistent Gestational Trophoblastic Disease	

10 Parental support

All health professionals should be aware of the psychological sequelae associated with pregnancy loss and offer support, follow-up and access to formal counselling.[4] Appropriate support can result in significant positive psychological gain.[4] General considerations for parental support following early pregnancy loss are outlined in Table 17.

Table 17. Parental support considerations

Consideration	Recommendation
Respect	• Respect cultural and religious beliefs / practices / rituals • Support parents to feel in control of their care • Respect the wishes / preferences of parents when offering care
Information provision	• Ensure both parents are present at discussions if feasible • Allow time for discussion and listen reflectively to the parents • Communicate empathetically, clearly and honestly • Repeat important information as stress and grief may interfere with comprehension and recall of information • Provide written information for frequent reference as relevant to the circumstances (e.g. grief journey, expectant care process) • Use appropriate terminology [refer to Table 1] • Ensure privacy and confidentiality
After care	• Advise on future pregnancy / preconception care • Advise on contraception • Advise on maintaining a healthy lifestyle (e.g. avoiding smoking, alcohol) • Advise on maintaining a healthy diet and weight by exercising regularly • Offer access to support services (e.g. social work services, case worker) for information and practical assistance
Memory creation	• Discuss options for memory creation with the parents as appropriate to the circumstances • Offer time with baby – inform parents they may hold, undress, bath baby if desired - complete all swabs and tests on baby before bathing • Offer options to include extended family (e.g. photographs of family groups, relatives / siblings to hold baby, video conferencing if available) • Facilitate memento creation / gathering following parental consent (e.g. identification tags, hand and footprints, digital photographs, cot cards, hair collection) • Where immediate memento creation is declined – offer storage of mementos for future access. Mementos can be stored in a sealed envelope in the woman's health record until / if parents request them
Referral and follow-up	• The grieving process following pregnancy loss is complicated and the psychological consequences may include[40]: o Anxiety and depression which may persist for up to six months o Increased risk of developing an anxiety disorder in the six months after a pregnancy loss o Precipitation of any pre-existing psychotic disorders. Consider the requirement to involve usual Mental Health service provider • Individualise follow-up as appropriate to the circumstances • Offer referral to relevant health care professionals and support groups prior to discharge – particularly for counselling / psychological support services (e.g. Genetic Counsellor, Social Worker, Child Health Services, Pastoral Care Worker) [refer to Appendix C: Support group contacts] • Plans for follow-up (including consent) should be clearly recorded in the referral or discharge letter from the EPAS or ward[4] • Regular follow-up is recommended for the first 6 months[40] • Follow-up can involve any member of the multidisciplinary team based in the hospital or community[4] • Ensure early pregnancy loss are communicated to all the woman's relevant primary care professionals (e.g. GP, Midwife)[4] • Cancel future antenatal appointments to avoid generation of reminder notices

10.1 Sensitive disposal of fetal tissue / remains

After an early miscarriage it may not be possible to find recognisable tissue, however if there is tissue, parents should be given the same choice for the disposal of fetal remains as for a stillborn child.[41] The decisions parents make at this time can have a significant impact on the grieving process. Table 18 outlines recommendations.

Table 18. Sensitive disposal of fetal remains

Consideration	Recommendation
Information provision	• Inform parents clearly and sensitively of options available to them[41] and possible associated costs • Provide information regarding options (e.g. local funeral directors, hospital chaplain, local hospital procedures)[41]
Signs of life (however brief)	• Medical certification of cause of death (Form 9) is required • Birth must be registered with Registrar of Births, Deaths and Marriages (RBDM) and birth data sent to Perinatal Data Collection Unit (PDC) - regardless of gestational age or birth weight • Death must be registered with RBDM and death data sent to PDC o RBDM – notification by parent(s) and requires certification by a funeral director that a cause of death certificate has been issued o PDC – notification by maternity unit staff using PDC Form MR63D • Burial or cremation must be arranged • Refer to guideline Stillbirth care[6]
No signs of life	• Where there are no signs of life, a pregnancy loss less than 20 weeks gestation does not need to be registered as a birth or death and there is no legal requirement for a funeral, burial or cremation. However, many parents choose this option o Some parents don't recognise their loss at the time but may return months or even years later to enquire about the disposal arrangements[41] o Respect the wishes of parents who may not want to be involved
Options	**Hospital burial or cremation** • Usually arranged by the hospital o Provide information on opportunities to mourn the loss (e.g. hospital memorial services, remembrance services) • Cremation of fetal tissue does not often produce any ashes to scatter[42] **Private burial or cremation** • Parents may wish to make their own arrangements • Facilities should develop local protocols to facilitate this option

10.2 Recurrent miscarriage

- Recurrent pregnancy loss (RPL) is classically defined as the occurrence of three or more consecutive miscarriages prior to 20 weeks of gestation[43]
- There is no specific term for non-consecutive pregnancy losses[43]
- Specialist gynaecological consultation is recommended and referral to other specialist physicians may be arranged if underlying medical conditions are suspected
- The prevalence of miscarriage is higher with increasing maternal age, especially greater than 40 years, and at earlier gestational ages (less than 6 weeks)[43]
- The investigation of couples with RPL is often disappointing with many unanswered questions regarding aetiology, evaluation and management[43]
- The prognosis is better, where a live birth has occurred[43]
- Further discussions of this topic is beyond the scope of this guideline

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Appendix A: Early pregnancy assessment service

Aspect	Recommendation

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 Rhesus antibody testing
	  o Selective serum ß-hCG
	  o Ideally progesterone estimation
	• Be available on a daily basis Monday - Friday
	  o If possible available on weekends and after hours

Governance	• Clinical inclusion/exclusion criteria should be determined by the facility based on the Clinical Service Capability Framework[44] • Written pathways for clinical management should be established • Clearly defined lines of communication identified • Governance and accountability for clinical practice established • Guidance for appointment booking (i.e. referral only or self referral)
Documentation	• Standardised written patient information • Referral and transfer of care (discharge) letters available

Appendix B: Sonographic anatomy and landmarks

Aspect	Findings[45]
Identifying the gestational sac	• Earliest appearance (TVS) is usually between 4 weeks + 1 day and 4 weeks + 3 days when sac is approximately 3 mm • Mid to upper uterus placement, adjacent to linear central cavity complex and surrounded by hyperechogenic rim is an early decidual sign • As sac enlarges, it gradually impresses / deforms central cavity echo complex – double decidual sign, seen when mean sac diameter (MSD) is 10 mm
Identifying the yolk sac	• Yolk sac usually first structure visible within the gestational sac and should be apparent by 5.5 weeks gestation or by MSD 8 mm • Number of yolk sacs usually indicates the number of amniotic sacs in the case of twin pregnancies (i.e. 2 yolk sacs indicated a diamniotic pregnancy)
Identifying the embryo and cardiac activity	• The fetal pole (embryonic disc) is usually visible by the time the gestation is between 5 and 6 weeks and MSD is 6-12 mm • Cardiac activity should be detected routinely by the time the fetal pole is 5 mm - which correlates with 6 to 6.5 weeks gestation • Before 6 weeks gestation, the cardiac rate will be slow i.e. between 100 and 115 bpm, and increases rapidly after 6 weeks • During the embryonic period (weeks 6-10) the Crown Rump Length (CRL) increases about 1 mm/day
Dating the pregnancy during early first trimester:	• Gestational sac (no yolk sac, embryo or heartbeat) = 5 weeks • Gestational sac and yolk sac (no embryo, no heartbeat) = 5.5weeks • Gestational sac and yolk sac (living embryo, CRL less than 5 mm too small to measure) = 6 weeks • Embryo / fetus greater than or equal to 5 mm length = age based on CRL
β-hCG	• An intrauterine gestational sac should be visible (TVS) when quantitative β-hCG level is between 1000 IU/L and 2000 IU/L • β-hCG levels approximately double every 2 days in a viable ongoing pregnancy • Quantitative β-hCG levels used in conjunction with serial TV USS are often the only way to distinguish between early failed pregnancy and ectopic pregnancy in gestation less than 6-7 weeks

Appendix C: Support contacts

The following not for profit organisations offer support for families who have experienced an early pregnancy loss.

Organisation	Contact Details
Small Miracles Foundation	Offers free grief counselling service for families that have experienced the loss of a baby through miscarriage, stillbirth, neonatal loss or prematurity and related issues such as infertility. Web: www.smallmiraclesfoundation.org.au Bereavement support phone: 1300 266 643
SANDS (QLD) Inc. (Stillbirth and Neonatal Death Support)	Provide support to parents and families who experience reproductive loss. Web: http://www.sandsqld.com/ Bereavement support phone: 07 3254 3422 (Office hours) Free Call 1800 228 655 (24 hour)
SIDS and KIDS	Advocate for and fund research into stillbirth and other areas of sudden and unexpected child death. Extend bereavement support and counselling to families who have experienced stillbirth or the sudden and unexpected death of a child, regardless of the cause. Web: http://www.sidsandkids.org/ Bereavement support phone: 1300 308 307 (24 hour)
Teddy Love Club	A support program for bereaved families who have experienced loss through miscarriage, stillbirth, termination for fetal abnormalities or neonatal death. Web: http://www.teddyloveclub.org.au/ Bereavement support phone 1800 824 240
Lifeline	Provide telephone crisis support to anyone needing emotional support. Web: http://www.lifeline.org.au/ Phone: 13 11 14
Queensland Health 13 Health	Provides health information, referral and tele-triage services to the public. Web: http://www.health.qld.gov.au/13health/ Phone: 13Health (13 43 25 84)
Allied Psychological Services (ATAPS) through Divisions of General Practice	Access to the ATAPS program is via a referral from a GP, Midwife or Obstetrician, but will require the completion of a Mental Health Assessment and Plan by a GP. Advise women to check with their general practice as an extended appointment may be required. The GP, working with the local Division of General Practice / Medicare Local will link the woman with a psychologist for five-six sessions, with a possibility of an extension of up to a total of 12 sessions. All Queensland Divisions / Medicare Locals are currently funded to assist patients with perinatal mental health issues to access ATAPS services. Contact your local Division of General Practice or Medicare Local for more information

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