South Australian Perinatal Practice Guideline

Bleeding & Pain in Early Pregnancy

Ectopic Pregnancy, Miscarriage & PUL

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing 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,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant women. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of Perinatal Practice Guideline (PPG)

This PPG will assist primary care, emergency and specialist clinicians in metropolitan and regional South Australia to investigate, diagnose and manage complications in early pregnancy. It provides a standardised approach to the assessment and treatment of women experiencing pregnancy loss because of miscarriage or ectopic pregnancy, with appropriate referral pathways. Ectopic pregnancy remains a leading cause of maternal death in early pregnancy and whilst all South Australian women should have access to both surgical and non-surgical management options in appropriate and carefully selected cases, clinicians must remain vigilant to the risk of rupture and counsel women appropriately.

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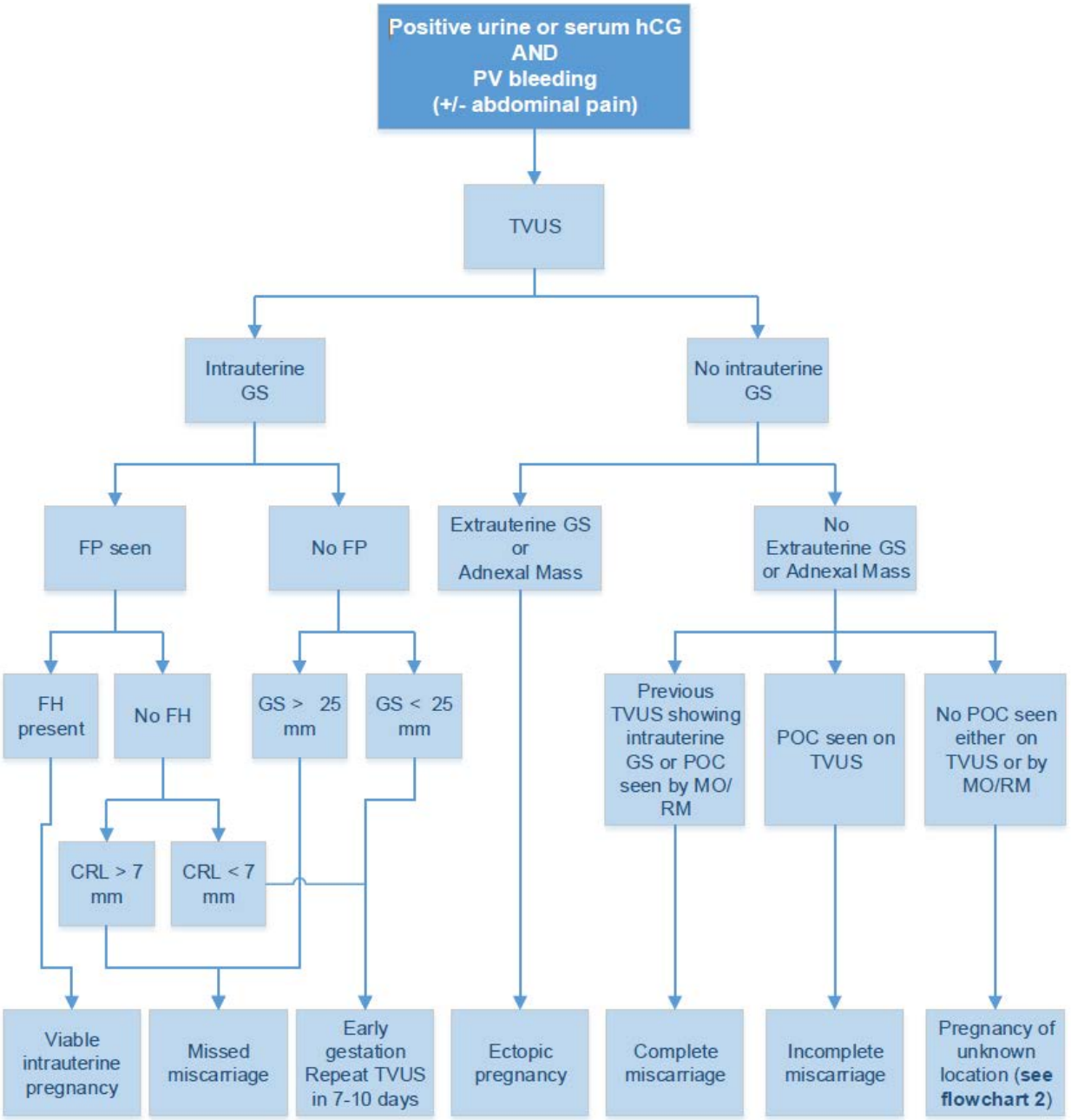
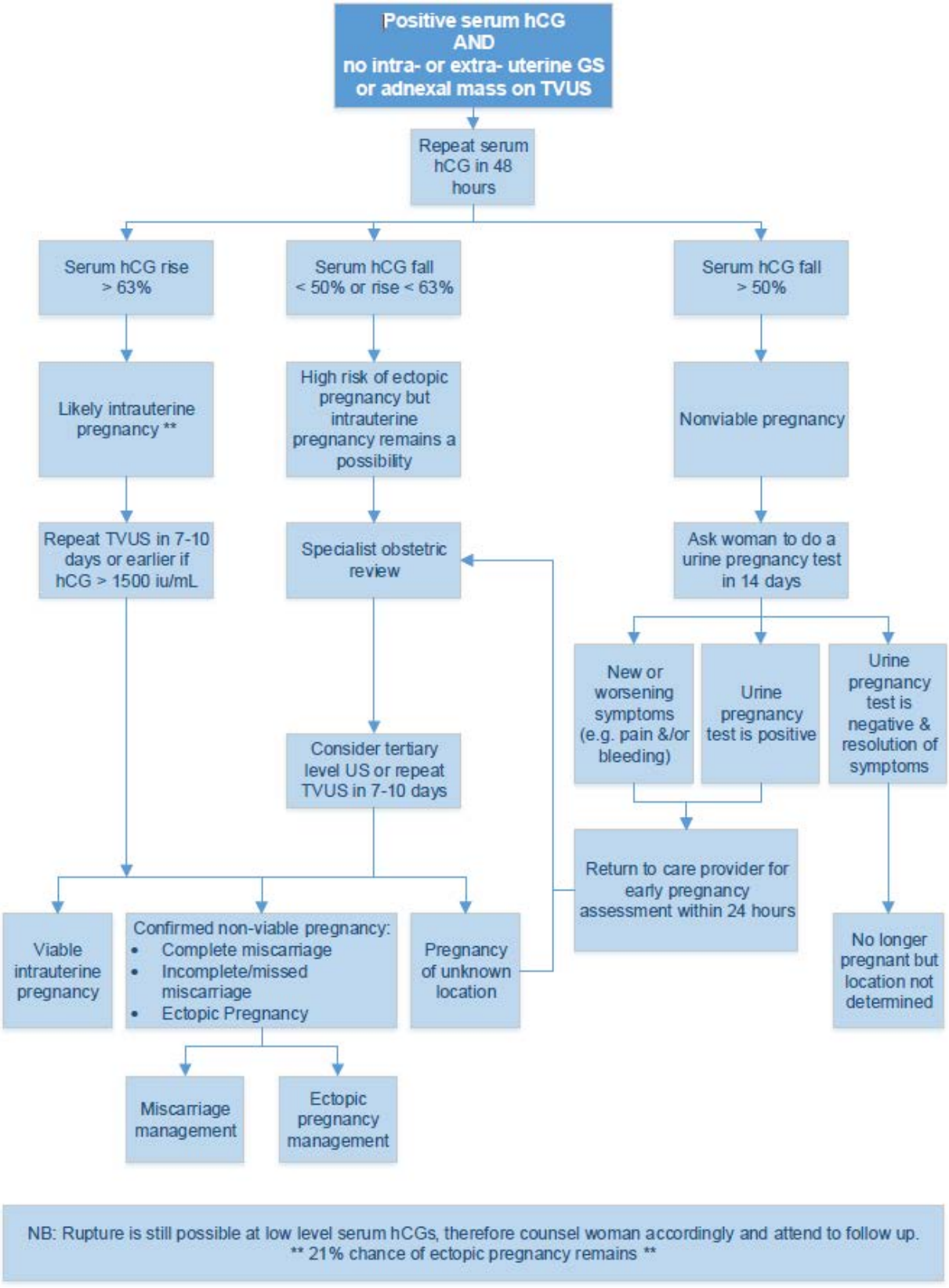
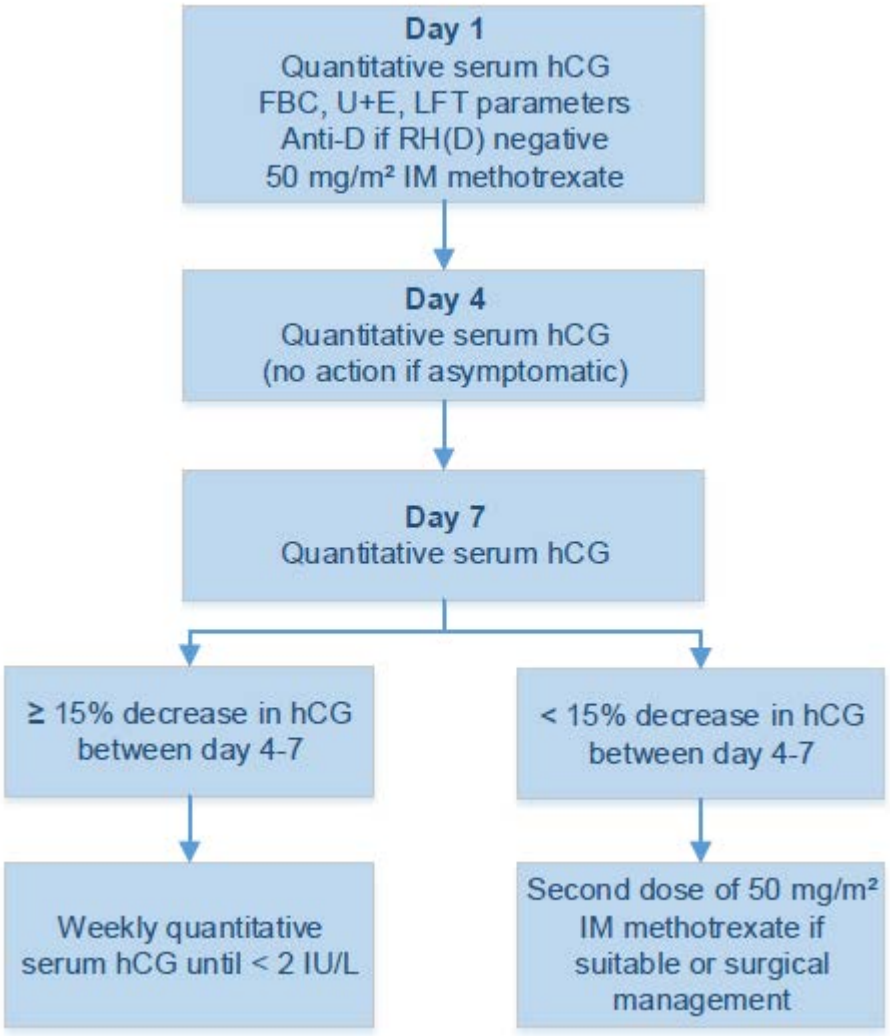
Flowchart 1: Investigation and Differential Diagnosis for Bleeding and Pain in Early Pregnancy



Flowchart 2: Investigation and Follow-Up of Pregnancy of Unknown Location (PUL)



Flowchart 3: Medical Management of Ectopic Pregnancy



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Summary of Practice Recommendations

Practice points are highlighted in boxes throughout the Perinatal Practice Guideline.

Abbreviations

ASUM	Australian Society of Ultrasound in Medicine
CRL	Crown rump length
ED	Emergency department
EPU	Early pregnancy unit
FODMAP	Fermentable oligo-, di-, mono-saccharides and polyols (short chain carbohydrates resistant to digestion)
GS	Gestational sac
hCG	human chorionic gonadotrophin
NAAT	Nucleic acid amplification test
NSAID	Non-steroidal anti-inflammatory drug
OT	Operating theatre
POC	Products of conception
PUL	Pregnancy of unknown location
SAAS	South Australian Ambulance Service
STI	Sexually transmitted infection
TAUS	Trans-abdominal ultrasound
TVUS	Trans-vaginal ultrasound

Introduction

Early pregnancy correlates to the first trimester of pregnancy, incorporating the time from first diagnosis of pregnancy (positive urinary or serum hCG) until 13 weeks completed gestation. Per vaginum bleeding is the most common presentation to a care provider in early pregnancy and will affect an estimated 20-25% of women, the commonest cause of which is miscarriage (up to 20% of recognised pregnancies).[1] Ectopic pregnancy remains a relatively rare (1-2%)[2] but potentially life-threatening cause of early pregnancy bleeding and must be considered. Other causes of bleeding in the first trimester of pregnancy include implantation, lower genital tract lesions, infections and gestational trophoblastic disease, all of which should be recognised with a standardised approach to examination and investigation as presented here.

Bleeding in the first trimester of pregnancy is often painless; however, the presence, location and nature of associated lower pelvic pain may suggest a pregnancy-related cause. Miscarriage is generally associated with lower, central or generalised abdominal pain which is crampy in nature and comes in waves. Pain associated with ectopic pregnancy is more likely to be unilateral and sharp in nature, and may be associated with shoulder tip pain, a sinister clinical finding indicating intra-abdominal bleeding. Pelvic pain without bleeding in the first trimester is a less common presentation but should nonetheless prompt timely ultrasound examination to exclude ovarian pathology or ectopic pregnancy, particularly if unilateral.

Any woman of reproductive age presenting for acute care with abdominal pain should have either a urinary or serum hCG test to exclude a pregnancy related cause.

Once pregnancy is confirmed with a positive hCG, determining the location of the pregnancy with trans-vaginal ultrasound (TVUS) as either intra-uterine or ectopic is critical to the ongoing safe and appropriate care of that woman.

Assessment

Acute

The priority in assessing early pregnancy bleeding is to determine whether the woman is haemodynamically stable and to triage her as per the Australasian Triage Scale (Appendix 1).[3] A blood pressure and heart rate should be measured upon presentation, including lying and standing measurements.

A significant postural drop in blood pressure and/or rise in heart rate between lying and standing measurements, or pre-/syncope, are signs of significant hypovolaemia and the woman should be immediately transferred to an emergency facility.

Hypotensive women with bradycardia may be experiencing profound vagal (parasympathetic) stimulation from either cervical dilatation in miscarriage or massive haemoperitoneum in ruptured ectopic pregnancy.

Women who are shocked require 2 large bore intravenous cannulae with blood sent for:

- Group and hold
- Cross-match of red blood cells
- Full blood examination,
- Urea and electrolytes and;
- Coagulation studies.

Thromboelastometry is a useful adjunct to guide blood product replacement where available and similarly, activation of a massive transfusion code may be appropriate. Fluid resuscitation should be commenced with crystalloid fluids and O negative blood if required.

A speculum examination may reveal heavy vaginal bleeding or products of conception (POC) in the cervical os, which should be removed and sent for histopathology. Alternatively, there may be modest vaginal losses and a distended, guarded abdomen suggestive of a ruptured ectopic pregnancy. Women with ongoing heavy vaginal bleeding or with a large intra-abdominal bleed who remain haemodynamically unstable require urgent transfer to the operating theatre for either a suction dilatation and curettage or a laparoscopy/laparotomy. Where available, cell salvage options should be utilised in theatre.

History

Where the woman is stable, a pertinent history should be taken including:

- Amount of bleeding, duration, course and nature
- Associated symptoms such as pain, syncope/pre-syncope
- Date of last menstrual period
- Gestation
- Gravidity and parity
- Past obstetric history
- Past gynaecological history including Cervical Screening Test status, sexually transmitted infections and contraception
- Past medical and surgical history
- Medications and allergies
- Any recent sexual intercourse or trauma, including where necessary, screening for potential domestic violence
- Access to transport and telephone advice, availability of support person(s) and ability to comply with treatment plan to assess suitability for various treatment options

Examination

After initial triage and assessment of haemodynamic stability, physical examination of the woman should be undertaken in an adequately screened and private cubicle or room, with an assistant or chaperone present, and include:

- Blood pressure and heart rate (lying and standing), respiratory rate, oxygen saturation and temperature
- Abdominal examination looking for any distension, masses, tenderness, guarding or rigidity and an assessment of whether a palpable uterus is consistent with dates
- A speculum examination is essential to assess the amount of vaginal bleeding and to ensure there are no POC at the external os; if present, POC should be removed with sponge forceps to prevent or treat cervical shock and be sent for histopathology; swabs to exclude lower genital tract infection can be taken and a visual inspection of the vagina and cervix performed to exclude other causes of bleeding such as ectropion, polyps and malignancy
- Bimanual examination will often reveal tenderness and/or cervical excitation in pregnancy and so may be of little discriminatory value for non-experienced clinicians, however, it can help ascertain uterine size and mobility, cervical dilatation and any adnexal tenderness or masses; this should only be performed if you feel it will contribute to your clinical assessment

Investigations

Routine investigations for any woman presenting with bleeding in early pregnancy include:

- Blood group and antibody status to assess need for Anti D immunoprophylaxis
- Quantitative serum hCG
- Transabdominal pelvic ultrasound (TAUS) with a full bladder and/or TVUS with an empty bladder

For women <25 years or who are otherwise high risk, opportunistic screening for Chlamydia trachomatis and to a lesser extent, Neisseria gonorrhoea, should be performed, ideally with a high vaginal swab at the time of speculum examination. Women with an ectopic pregnancy should also be screened for Chlamydia with either a high vaginal swab or first pass urine nucleic acid amplification test (NAAT). Whilst endocervical swabs provide better detection of STIs, they are not recommended where the pregnancy may be viable and ongoing.

Additional investigations for women who are experiencing significant vaginal or intra-abdominal bleeding include:

- Cross-match of red blood cells and/or activation of a massive transfusion protocol
- Full blood examination
- Electrolytes, urea and creatinine
- Coagulation studies +/- thromboelastometry

Ultrasound

A TVUS is the key investigation for assessing pregnancy location. It is reasonable to begin ultrasonographic assessment of a woman with a TAUS at higher serum hCG levels (>1500IU/L) to see whether an intrauterine gestational sac (GS) is apparent. If an intrauterine GS cannot be confirmed on TAUS or the serum hCG is below the discriminatory zone of 1500IU/L, TVUS by an experienced sonographer is required to try to locate the pregnancy as either intrauterine or ectopic.

An intrauterine GS requires the presence of a yolk sac to be confirmed as such. If a fetal heartbeat is not apparent, the fetal pole should be measured for a crown-rump length (CRL). If the CRL is greater than 7mm and there is no fetal heartbeat, the diagnosis is likely that of a missed miscarriage, however, the woman can be offered a repeat TVUS in 7-10 days to confirm the diagnosis; if the CRL is <7mm, a repeat TVUS in 7-10 days is required to determine the viability of the pregnancy (Flowchart 1).[4,5]

If there is no fetal pole visible on TVUS, the GS should be measured and if greater than 25mm, a diagnosis of missed miscarriage is again likely, however, it is again prudent to offer a repeat TVUS in 7-10 days to confirm the diagnosis. Similarly, if the GS is less than 25mm, the woman will require a repeat TVUS in 7-10 days to determine viability (Flowchart 1).[4,5]

Neither gestational age based on the last menstrual period nor serum hCG levels should be used to determine whether a fetal heartbeat should be visible or not. If recommended for a repeat TVUS, women should be counselled about the possibility of increased pain and vaginal bleeding and given information about when and how to present for care if this occurs.

A diagnosis of complete miscarriage based on ultrasound alone should not be made unless POC have been visualised by staff or confirmed on histopathology, or an intrauterine GS was clearly seen and documented on a previous TVUS. Where no intrauterine GS is seen on TVUS above the discriminatory zone (hCG >1500IU/L), careful inspection of the adnexae may reveal an ectopic pregnancy. Ectopic pregnancy is diagnosed on TVUS as a GS with a yolk sac and/or fetal pole outside the uterine cavity, or more commonly, as an inhomogeneous mass in the adnexa, with or without associated free fluid. Ectopic pregnancies can often be seen on TVUS at serum hCG levels below the discriminatory zone due to associated oedema and haematoma formation.

A woman with a positive serum hCG, an empty uterus and no adnexal masses or free fluid on TVUS has a pregnancy of unknown location (PUL) and requires close specialist follow up until a diagnosis is made or the pregnancy resolves (Flowchart 2). Where there is an unexpectedly high serum hCG and either a large placenta with vesicular anechoic lesions (“bunch of grapes” sign), with or without identifiable fetal parts, or an intra-uterine “snowstorm” appearance, a molar pregnancy should be considered and investigated accordingly.

Serum hCG

Serum hCG is one of the most useful and specific biomarkers in medicine. It is highly specific for viable trophoblastic tissue and hCG levels are directly correlated to the amount or development of trophoblastic tissue in early pregnancy. Serial serum hCG measurements should be performed at the same laboratory due to variations in the sensitivity of assays.[6]

A baseline serum hCG (0 hours) is helpful in confirming pregnancy and predicting the ability of TVUS to visualise a GS. Whilst serial hCG measurement (as close to but not less than 48 hours after baseline) cannot locate a pregnancy, it assists in stratifying PULs as either high or low risk for ectopic pregnancy (Flowchart 2):

- Where the serum hCG rises by >63% between 0-48 hours, the pregnancy is likely viable and the woman considered low risk for an ectopic pregnancy; nevertheless she still needs to complete follow up with a repeat TVUS in 7-10 days as ectopic pregnancy is not excluded [5,7];
- A rapid fall in serum hCG of >50% is suggestive of a failing pregnancy, but again does not differentiate between intra- and extra-uterine pregnancies and follow up is required with urine hCG in 2 weeks [5,8].
- For women with a plateauing or suboptimal rise in serum hCG of <63%, the PUL is considered high risk for ectopic pregnancy and should be referred for specialist management.[5]

Diagnosis

Once a woman has had an initial serum hCG and TVUS, the pregnancy can be classified as either a viable or non-viable intrauterine pregnancy (miscarriage), ectopic or the woman has a PUL.

PUL is not a diagnosis and requires further investigation and follow up until either a diagnosis is made or the pregnancy is resolved.

Pregnancy of Unknown Location

PULs occur when a woman has a positive hCG but a TVUS cannot identify or locate the gestational sac and/or pregnancy. This may be because the pregnancy is not sufficiently developed and below the discriminatory zone of ultrasound identification (serum hCG of <1500IU/L)[8], or alternatively, because it is ectopic. Women with a PUL must be counselled about the possibility of ectopic pregnancy and given clear instructions on when and where to present should they experience severe pain and/or syncope whilst awaiting follow up. South Australian Ambulance Service (SAAS) membership is strongly advised.

Follow up for PULs will entail a combination of serial serum hCG 48 hours after the first measurement and repeat TVUS 7-10 days after the first. Follow up will generally allow categorisation of the pregnancy as either intrauterine or ectopic, but in a small number of women the pregnancy will remain unidentified.

Specialist management of women whose pregnancy remains unclassified will depend on their serial hCG measurements:

- A falling serum hCG of >50% is indicative of a failing pregnancy and can be followed up with a urine pregnancy test in 14 days (self-resolving PUL).[5,8] The woman and her clinicians should remain vigilant to the risk of ectopic pregnancy, rupture and intra-abdominal bleeding until the hCG is negative.
- A rising serum hCG of >63% is suggestive of a viable pregnancy and the woman should be offered repeat TVUS in 7-10 days, or sooner if the hCG is >1500IU/L.[5,7]
- For women whose serum hCG has plateaued or is slow rising, specialist review is recommended where:
    - A third and final hCG may be requested 48 hours after the second if there was a rise of 35% or more between the first and second measures[9];
    - A tertiary level TVUS may be repeated, depending on the quality and findings of external US or if the hCG has risen above 1500IU/L;
    - Suction dilatation and curettage may be performed after three sub-optimally rising hCGs to determine the location of the pregnancy based on histopathology; if no trophoblastic villi are identified after intrauterine sampling, the woman should be offered treatment with methotrexate or surgery, as detailed elsewhere in this guideline.
    - A diagnostic laparoscopy +/- suction dilatation and curettage may be performed, particularly if free fluid is seen on US.

Two serial serum hCG measurements 48 hours apart and two TVUSs 7-10 days apart should suffice to establish a diagnosis and determine a course of management. Specialist referral and/or Consultant Gynaecological review is recommended prior to ordering any subsequent serum hCGs and/or TVUSs.

Miscarriage

When a pregnancy is confirmed as intrauterine by TVUS AND there is no fetal heartbeat with a CRL >7mm OR no fetal pole with a GS > 25mm on serial scans, 7-10 days apart, a miscarriage is diagnosed[4].

Miscarriages occur in 20-25% of clinically recognised pregnancies, with an even greater proportion of pregnancies lost before clinical detection[10]. The risk of miscarriage increases with age, obesity, substance abuse and autoimmune conditions.

Miscarriage is an emotionally challenging diagnosis for many women and staff should provide empathic, woman-centred care at all times. Measures to help achieve this include the provision of a private room for counselling and adequate time to process the diagnosis and its implications.

Aboriginal people experience very high levels of grief and loss in their communities. Miscarriage demands diverse ceremonial acknowledgement. Discuss with an aboriginal health professional.

Miscarriages can be further classified as missed, threatened, inevitable, incomplete, complete and septic depending on visualisation of products of conception (POC) clinically and/or on serial TVUS:

- A **missed miscarriage** is diagnosed by TVUS as above in patients who have had no early pregnancy bleeding or pain (asymptomatic). Management options are detailed below.
- A **threatened miscarriage** describes early pregnancy bleeding and/or abdominal pain where a TVUS demonstrates an intrauterine GS that does not yet meet ultra-sound criteria for miscarriage or alternatively, demonstrates a viable intrauterine pregnancy. These should be followed up expectantly with repeat TVUS in 7-10 days. A 2.6 times increased risk of miscarriage as well as ongoing increased risk of pregnancy complications (17%) remains[11].
- An **inevitable miscarriage** is diagnosed when POC are being passed or are about to passed through an open or bulging cervix. Any tissue sitting in the cervix should be removed with sponge forceps at the time of speculum examination.
- An **incomplete miscarriage** occurs when POC have been passed by the patient but there are still intrauterine POC seen on TVUS. After checking for POC in the cervix, management options are detailed below.
- A **complete miscarriage** is confirmed only when a previously identified intrauterine GS is no longer seen on TVUS after passage of POC; these should ideally be kept and sent for histopathology. The subsequent TVUS should demonstrate a midline sagittal view of the endometrium of no more than 10mm in anteroposterior diameter[12]. Where no previous intrauterine GS has been identified but there is a declining hCG, women should be followed up as a self-resolving PUL, with both clinician and patient remaining vigilant to the possibility of ectopic pregnancy complications.
- **Septic miscarriages** occur when any of the above are complicated by intrauterine or systemic infection. Management includes resuscitation, systemic antibiotics and surgical evacuation of the infected POC.

Expectant Management of Miscarriage

Expectant management should be implemented for all threatened miscarriages and for women who choose this treatment option once a miscarriage has been confirmed and there is no evidence of haemodynamic instability or sepsis.

Expectant management is less likely to be successful for missed miscarriage (76%) compared to incomplete miscarriages (91%) and less likely again for anembryonic pregnancy (blighted ovum) (66%). Nevertheless, 81% of expectantly managed women will complete evacuation of POC within 4 weeks of diagnosis, with the majority (70%) competed within the first two weeks of follow up[13].

Women should be given advice, preferably written, about what to expect, where and when to represent and to keep POC for histopathology. Follow up is indicated if there is excessive blood loss, pain, fever or if POC have not been expelled after 4 weeks (or earlier if the woman changes her mind), at which time surgical management should be considered. Anti D immunoprophylaxis should be administered to Rhesus negative women.

Access to 24-hour telephone advice and emergency facilities within 30 minutes of a woman's place of residence, including O negative blood and surgical management, are conditions of undertaking expectant treatment of miscarriage. SAAS membership is strongly advised.

Medical Management of Miscarriage

Medical management of miscarriage with misoprostol is a safe and effective option where vaginal bleeding is not excessive. The diagnosis of miscarriage must be confirmed as per the ASUM criteria above[4]; if there is any doubt, a repeat TVUS should be performed in 7-10 days.

Misoprostol is a prostaglandin E1 analogue. It is used off-label for treatment of miscarriage in Australia and endorsed by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)[14]. Success rates are dependent on the type of miscarriage and duration of follow-up, dose and route of administration; a meta-analysis of 13 studies showed an overall success rate of 81% for misoprostol to manage missed miscarriage and 99% for incomplete miscarriage[15].

Correct patient selection is crucial to reducing risks to patients opting for medical management of miscarriage. Consideration of social factors will also affect patient selection, including access to 24-hour telephone advice and transport, ability to comply with treatment plan and availability of support person(s).

Exclusion criteria

- No immediate access (>30 minutes) to emergency facilities
- Uncertain diagnosis
- Heavy vaginal bleeding
- Maternal anaemia (haemoglobin <100g/L)
- Anticoagulation (including aspirin) or known coagulopathy
- Known or suspected ischaemic heart disease
- Brittle or poorly controlled asthma
- Porphyria

Access to 24-hour telephone advice and emergency facilities within 30 minutes of a woman's place of residence including O negative blood and surgical management are conditions of undertaking medical treatment of miscarriage. SAAS membership is strongly advised.

Prescribing Information

Women assessed as suitable and opting for medical management of miscarriage should be administered:

- 800micrograms of misoprostol sublingually OR vaginally.

Misoprostol is usually well-tolerated. Side-effects may include nausea, vomiting, diarrhoea and fever. Vaginal administration may cause less gastrointestinal side-effects and less pyrexia with similar efficacy if this is an acceptable route of administration for the woman[16]. More than 70% of patients who had sublingual misoprostol experienced diarrhoea[17]. Pyrexia secondary to misoprostol administration should not last more than 24 hours after last dose.

There is no difference in blood loss, transfusion rate, risk of infection, duration of convalescence or analgesia requirements compared to expectant management[18].

Oral anti-emetics and pain relief (paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs)) should be prescribed or provided.

Anti D immunoprophylaxis should be administered to Rhesus negative women.

A recent study has shown pre-treatment with mifepristone to significantly increase the success rate of medical treatment misoprostol at 3 days (84% vs. 67%)[19]. Mifepristone is currently restricted to certified prescribers (www.ms2step.com.au) and has not previously been recommended for medical management of miscarriage; practitioners should adjust their practice in accordance with site-specific guidelines and access to mifepristone.

Follow-up

Women opting for medical management of miscarriage with misoprostol should be given advice, preferably written, about what to expect, where and when to represent and to keep POC for histopathology.

Medical review is indicated at any time after administration of misoprostol if there is excessive blood loss, pain or fever.

If bleeding has not started within 24 hours, the patient should represent to their coordinating centre for either a repeat dose of misoprostol or otherwise individualised care.

If POC have not been expelled after 7 days, the patient should represent to their coordinating centre and surgical management should be considered.

Once POC have been passed and bleeding has ceased, the woman should perform a urine pregnancy test after 3 weeks to confirm resolution of the pregnancy; if vaginal bleeding persists and/or the urine pregnancy test is positive, the woman should return to her coordinating centre for medical review.

Surgical Management of Miscarriage

Surgical management of miscarriage offers the shortest time to complete evacuation of uterine contents and the lowest representation and retreatment rates (8%)[20]. Surgical management with suction, dilatation and curettage can be offered as first line management of miscarriage and is indicated when there is evidence of sepsis, maternal haemorrhage, significant pain or patient preference. Surgical management should be utilised as a second-line option when other expectant or medical management options have failed and there are retained POC.

Suction, dilatation and curettage is performed under general or regional anaesthesia. The woman will need surgical consent, detailing in particular the risks of:

- Perforation (1:300) and the possible need for subsequent laparoscopy and/or laparotomy, as well as possible recommendation for future delivery by caesarean section should such an injury occur, and;
- Asherman's syndrome (1:1000) which is less common with the modern use of suction curettage.

Except in cases of life-threatening maternal haemorrhage, the woman should be fasted and cervical ripening effected with:

- 400micrograms misoprostol sublingually 2 hours prior to cervical dilatation

This assists in cervical dilatation and minimises the risk of false passage creation and uterine perforation. POC should be routinely sent for histopathology and followed up in a systematic fashion. Where the woman has experienced 3 consecutive early pregnancy losses, some of the POC should be sent in normal saline for karyotyping, along with referral to a recurrent pregnancy loss clinic. Anti D immunoprophylaxis should be administered to Rhesus negative women shortly after the procedure and prior to discharge.

Ectopic Pregnancy

An ectopic pregnancy occurs when a conceptus implants outside of the endometrial cavity, most commonly (>95%) in one of the Fallopian tubes[21]. Rarer ectopic pregnancies can be sited on the cervix, within caesarean section scars, the interstitium, ovaries or indeed anywhere in the abdominal cavity and can occur concurrently with an intrauterine pregnancy (heterotopic pregnancies; 1:10,000). Management of these rarer types of ectopic pregnancy is outside the scope of this guideline and they should be referred for specialist care in a tertiary centre.

Risk factors for ectopic pregnancy include smoking and previous infection with Chlamydia trachomatis, both of which are thought to affect cilial beat frequency in the Fallopian tube and thus transport of the conceptus from its site of fertilisation in the tube to the endometrial cavity. Adnexal surgery, previous ectopic pregnancy, failure of contraception (especially current intrauterine device) and artificial reproductive methods also increase the risk of ectopic pregnancy[22].

Diagnosis of ectopic pregnancy requires a positive serum hCG, an empty uterus or pseudo sac on TVUS as well as visualisation of an adnexal mass: either a GS with yolk sac and occasionally a live fetus, or more commonly, an inhomogeneous mass with associated free fluid (‘blob’ sign). Once an ectopic pregnancy is diagnosed, the woman and her carers should be counselled about the risk and signs of rupture, namely severe abdominal and/or shoulder tip pain with syncope/ pre-syncope. The woman should present to the nearest emergency facility should she experience these symptoms at any time in the course of her treatment and follow-up. Membership of the SAAS is strongly advised.

The majority of ectopic pregnancies are managed surgically with a laparoscopic salpingectomy. This is mandated if there are any signs of haemodynamic instability. If the woman is haemodynamically stable and depending on her serum hCG level at diagnosis, medical or even expectant management may be considered. The recurrence rate of ectopic pregnancy is 10%[23] and rises to 30% after two or more ectopic pregnancies[24].

Surgical Management of Ectopic Pregnancy

A laparoscopic salpingectomy is the mainstay of treatment of ectopic pregnancies. It is mandatory when there is significant intra-abdominal bleeding as indicated by maternal haemodynamic instability or demonstrated on ultrasound with free fluid above the level of the uterus and/or in Morrison’s pouch. A laparotomy may rarely be performed where laparoscopic equipment or expertise is not available or the woman is *in extremis*.

Where a woman is assessed as stable, she should have a laparoscopic salpingectomy if:

- That is her preference, and/or she is also seeking sterilization;
- The serum hCG is >5000IU/L;
- There is a live fetus;
- The adnexal mass is greater than 35mm in size, or;
- If a subsequent ectopic pregnancy has affected an ipsilateral tube after previous medical or expectant treatment.

A recent multi-centre international trial comparing laparoscopic salpingectomy with laparoscopic salpingostomy showed no difference in subsequent fertility outcomes; however, persistent trophoblastic tissue requiring further treatment was more common in the salpingostomy group. The majority of women should therefore have a salpingectomy, except in cases where there is contra-lateral tubal damage or absence, when salpingostomy should be considered[25].

Surgical consent requires a discussion of:

- Injury to surrounding organs such as the bladder and bowel (1:1000);
- Risk of catastrophic bleeding and death from vascular injury (1:100,000).

The patient should ideally be fasted, except in cases of haemodynamic instability. The tube and its contents should be sent for histopathology and the woman given Anti-D immunoprophylaxis if Rhesus negative. Follow up with weekly hCG is required when a salpingostomy is performed and all women should be reviewed in gynaecology clinic with results and counselling about future risks and contraception if required.

Medical Management of Ectopic Pregnancy

Medical management of ectopic pregnancy can successfully treat stable women with ectopic pregnancies and should be considered as an alternative to surgical management where:

- The serum hCG is <5000IU/L
- The gestational sac/adnexal mass size is less than 35mm in maximal diameter
- There is no fetal heartbeat demonstrated on TVUS
- There is no intrauterine (heterotopic) pregnancy
- The woman has access to 24-hour transport and telephone advice and is able to comply with the treatment plan and follow-up

By contrast, contraindications to medical management include:

- Haemodynamic instability or free fluid demonstrated above the level of the uterus/in Morrison's pouch
- Presence of an intrauterine pregnancy (in cases of heterotopic pregnancy)
- Immunodeficiency
- Sensitivity to methotrexate
- Pre-existing liver disease, haematological abnormalities, pulmonary disease, peptic ulcer disease or immunodeficiency.
- No access to 24-hour telephone advice and unable to comply with treatment plan

Access to 24-hour telephone advice and emergency facilities within 30 minutes of a woman's place of residence including O negative blood and surgical management are conditions of undertaking medical management of ectopic pregnancy. SAAS membership is strongly advised.

Prescribing Information

Medical management of ectopic pregnancy utilises the anti-folinic agent methotrexate. The use of pre-drawn syringes of methotrexate with rounding of the dose to the nearest 5mg increases access to medical treatment of ectopic pregnancy after hours and in regional centres. The required dose is:

- $50mg/m^2$ of methotrexate given intramuscularly (see below)

  Maximum dose is capped at 100mg

The recommended formula for determining the body surface area of a patient is as follows:

$$\text{BSA, } m^2 = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

BSA equation is the square root of (height in centimetres x weight in kilograms divided by 3600).

Example of Methotrexate dose calculation:
Height =165cm, weight =65kg
165 x 65 = 10725
Divide 10725 by 3600 = 2.979
Take the square root of 2.979 = 1.726
Multiply 1.726 by 50 = 86mg
Round calculated dose to nearest 5mg = 85mg of Methotrexate

The following methotrexate pre-filled syringes are available to SA Health sites:
5 mg / 0.2 mL
65 mg / 0.65 mL
75 mg / 0.75 mL
85 mg / 0.85 mL
95 mg / 0.95 mL

Women should cease their folate containing supplements and are advised to avoid ultraviolet light exposure and ingestion of high FODMAP foods to minimise photosensitivity and abdominal discomfort. Paracetamol and judicious use of NSAIDs (where the creatinine is normal) are recommended for pain relief. Should the woman require stronger analgesia, medical review is indicated.

Subsequent pregnancy should be avoided for 3 months to minimise the risk of congenital abnormalities after gamete exposure to methotrexate. Contraception should be provided.

Breastfeeding should be considered a precaution for methotrexate. Women should be advised to express and discard their breast milk for 4 days after a single dose of methotrexate for an ectopic pregnancy.

Baseline blood tests should include:

- Blood group and antibodies;
- Full blood examination;
- Urea, electrolytes and creatinine;
- Liver function tests and;
- Quantitative serum hCG.

Cytotoxic handling precautions should be followed and the methotrexate administered by appropriately trained staff. Anti-D immunoprophylaxis should be administered to Rhesus negative women at diagnosis/day 1 of treatment.

Success rates of medical treatment with methotrexate range between 65-95% and between 3-27% of women will require a second dose at day 7[26]. Predictors of successful medical treatment include lower serum hCG levels, slow-rising, plateaued or falling serum hCG levels prior to treatment and a falling serum hCG level at day 4 of follow up (increases likelihood of treatment success to 88%)[27].

Follow-Up

Women should be provided with written information to assist with what to expect, suggested behavioural modifications and follow-up appointments (see Fact Sheet: Methotrexate for treatment of ectopic pregnancy)

Treatment efficacy is determined by a ≥15% fall in serum hCG between day 4 and day 7 of treatment, where the day of methotrexate administration is day 1. If the serum hCG falls by ≥15%, serum hCG measurements are repeated weekly until negative (serum hCG <2IU/L); if there is a suboptimal response to methotrexate i.e. a rise or <15% fall in methotrexate between day 4 and day 7 (flowchart 3), the woman should be reassessed for suitability for ongoing medical management as based on clinical assessment, serum hCG level and/or repeat TVUS if indicated[28].

Women should be counselled about the ongoing risk of rupture and massive internal bleeding and have a carer with them during follow-up. Women should represent if they experiences any significant abdominal pain or syncope/pre-syncope. SAAS membership is strongly advised.

A phenomenon known as separation pain often occurs on day 3 or 4 of treatment, associated with the separation of the trophoblast from its implantation site. This can be managed with paracetamol and judicious use of NSAIDs where the creatinine is normal[29]. Women should be medically reviewed if they are requiring opioid analgesia, the pain is not responding or increasing and there is any concern of haemodynamic instability.

Expectant Management of Ectopic Pregnancy

A number of recent publications demonstrate that expectant management of ectopic pregnancy can be considered in women who are haemodynamically stable, reliable to follow-up and have a serum hCG of <1500IU/L. Patient selection is crucial in ensuring safety of expectant management and should only be offered after specialist review to women who have access to 24-hour telephone advice and transport, ability to comply with treatment plan and follow up and availability of support person(s).

Access to 24-hour telephone advice and emergency facilities within 30 minutes of a woman's place of residence including O negative blood and surgical management are conditions of undertaking expectant management of ectopic pregnancy. SAAS membership is strongly advised.

Success rates range from 57-100%, and as with medical management, are inversely proportional to the serum hCG at diagnosis and the trend of serum hCG prior[30]. A pre-treatment serum hCG ratio can be used to predict likelihood of expectant resolution of ectopic pregnancy, where a ratio of less than 0.8 is favourable (serum hCG at 48 hours/serum hCG at 0 hours)[31]. There is no set protocol for serum hCG follow up, however, it should be decided on a case-by-case basis and occur no more or less frequently than every 2-7 days. We recommend follow up based on the medical treatment of ectopic pregnancy protocol: if there is a ≥15% fall in serum hCG, weekly hCG follow up can be considered; however, if there is a plateauing or slowly falling serum hCG, more frequent testing and review should be considered.

As in all cases of ectopic pregnancy and PUL follow-up, Anti-D immunoprophylaxis should be administered to Rhesus negative women. Women and their partners should be counselled regarding the risk of rupture and significant intra-abdominal bleeding and advised when and how to present for emergency and follow-up care. Where the serum hCG level plateaus or rises with follow-up, consideration should then be given to medical or surgical management for the condition as detailed above.

Rhesus D Immunoglobulin (Anti-D) Immunoprophylaxis

As per RANZCOG[32] and the National Blood Authority Guidelines[33], all women who are Rhesus negative and have no preformed Rhesus D Antibodies should be offered immunoprophylaxis with 250IU (50mcg) of Rhesus D immunoglobulin (Anti-D) after any sensitising event in the first trimester (up to and including 12 weeks of gestation, including miscarriage, ectopic pregnancy and surgical or medical termination of pregnancy); therefore:

All women experiencing a spontaneous, medical or surgically assisted miscarriage OR an ectopic pregnancy should be administered Anti D after confirming their Rhesus negative and Rhesus D antibody negative status.

There is insufficient evidence to recommend Anti-D to women experiencing a threatened miscarriage.

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Appendices

Appendix 1: Australasian Triage Scale

ATS Category	Response	Description of Category	Clinical Descriptors (indicative only)
Category 1	Immediate simultaneous assessment and treatment	**Immediately Life-Threatening** Conditions that are threats to life (or imminent risk of deterioration) and require immediate aggressive intervention.	Cardiac arrest Respiratory arrest Immediate risk to airway – impending arrest Respiratory rate <10/min Extreme respiratory distress BP< 80 (adult) or severely shocked child/infant Unresponsive or responds to pain only (GCS < 9) Ongoing/prolonged seizure IV overdose and unresponsive or hypoventilation Severe behavioural disorder with immediate threat of dangerous violence
Category 2	Assessment and treatment within 10 minutes (assessment and treatment often simultaneous)	**Imminently Life-Threatening** The patient's condition is serious enough or deteriorating so rapidly that there is the potential of threat to life, or organ system failure, if not treated within ten minutes of arrival or **Important time-critical treatment** The potential for time-critical treatment (e.g. thrombolysis, antidote) to make a significant effect on clinical outcome depends on treatment commencing within a few minutes of the patient's arrival in the ED or **Very severe pain** Humane practice mandates the relief of very severe pain or distress within 10 minutes	Airway risk – severe stridor or drooling with distress Severe respiratory distress Circulatory compromise - Clammy or mottled skin, poor perfusion - HR<50 or >150 (adult) - Hypotension with haemodynamic effects - Severe blood loss Chest pain of likely cardiac nature Very severe pain - any cause Suspected sepsis (physiologically unstable) Febrile neutropenia BSL < 3 mmol/L Drowsy, decreased responsiveness any cause (GCS< 13) Acute stroke Fever with signs of lethargy (any age) Acid or alkali splash to eye – requiring irrigation Suspected endophthalmitis post-eye procedure (post-cataract, post-intravitreal injection), sudden onset pain, blurred vision and red eye. Major multi trauma (requiring rapid organised team response) Severe localised trauma – major fracture, amputation Suspected testicular torsion

			High-risk history: - Significant sedative or other toxic ingestion - Significant/dangerous envenomation - Severe pain or other feature suggesting PE, aortic dissection/AAA or ectopic pregnancy Behavioural/Psychiatric: - violent or aggressive - immediate threat to self or others - requires or has required restraint - severe agitation or aggression
ATS Category	**Response**	**Description of Category**	**Clinical Descriptors (indicative only)**
Category 3	Assessment and treatment start within 30 mins	**Potentially Life-Threatening** The patient's condition may progress to life or limb threatening, or may lead to significant morbidity, if assessment and treatment are not commenced within thirty minutes of arrival or **Situational Urgency** There is potential for adverse outcome if time-critical treatment is not commenced within thirty minutes or Humane practice mandates the relief of severe discomfort or distress within thirty minutes	Severe hypertension Moderately severe blood loss – any cause Moderate shortness of breath Seizure (now alert) Persistent vomiting Dehydration Head injury with short LOC- now alert Suspected sepsis (physiologically stable) Moderately severe pain – any cause – requiring analgesia Chest pain likely non-cardiac and mod severity Abdominal pain without high risk features – mod severe or patient age >65 years Moderate limb injury – deformity, severe laceration, crush Limb – altered sensation, acutely absent pulse Trauma - high-risk history with no other high- risk features Stable neonate Child at risk of abuse/suspected non-accidental injury Behavioural/Psychiatric: - very distressed, risk of self-harm - acutely psychotic or thought disordered - situational crisis, deliberate self-harm - agitated / withdrawn - potentially aggressive

ATS Category	Response	Description of Category	Clinical Descriptors (indicative only)
Category 4	Assessment and treatment start within 60 mins	**Potentially serious** The patient's condition may deteriorate, or adverse outcome may result, if assessment and treatment is not commenced within one hour of arrival in ED. Symptoms moderate or prolonged or **Situational Urgency** There is potential for adverse outcome if time-critical treatment is not commenced within hour or **Significant complexity or Severity** Likely to require complex work-up and consultation and/or inpatient management or Humane practice mandates the relief of discomfort or distress within one hour	Mild haemorrhage Foreign body aspiration, no respiratory distress Chest injury without rib pain or respiratory distress Difficulty swallowing, no respiratory distress Minor head injury, no loss of consciousness Moderate pain, some risk features Vomiting or diarrhoea without dehydration Eye inflammation or foreign body – normal vision Minor limb trauma – sprained ankle, possible fracture, uncomplicated laceration requiring investigation or intervention – Normal vital signs, low/moderate pain Tight cast, no neurovascular impairment Swollen "hot" joint Non-specific abdominal pain Behavioural/Psychiatric: - Semi-urgent mental health problem - Under observation and/or no immediate risk to self or others
Category 5	Assessment and treatment start within 120 minutes	**Less Urgent** The patient's condition is chronic or minor enough that symptoms or clinical outcome will not be significantly affected if assessment and treatment are delayed up to two hours from arrival or **Clinico-administrative problems** Results review, medical certificates, prescriptions only	Minimal pain with no high risk features Low-risk history and now asymptomatic Minor symptoms of existing stable illness Minor symptoms of low-risk conditions Minor wounds - small abrasions, minor lacerations (not requiring sutures) Scheduled revisit e.g. wound review, complex dressings Immunisation only Behavioural/Psychiatric: - Known patient with chronic symptoms - Social crisis, clinically well patient

Fact Sheet

Methotrexate for treatment of ectopic pregnancy

Methotrexate is a drug used to treat a number of conditions including ectopic pregnancy, rheumatoid arthritis, psoriasis, Crohn's disease and some forms of cancers.

An ectopic pregnancy is where the pregnancy grows outside the uterus. Methotrexate is used in South Australia to treat unruptured ectopic pregnancies in appropriately selected women. It is successful in 65-95% of women. The lower your starting level of the pregnancy hormone human chorionic gonadotrophin (hCG) is the better chance of success.

Methotrexate can also be used as a treatment if the hCG hormone has levelled off or is increasing again. In these cases 'left-over cells' continue to grow and release the hormone. Methotrexate blocks an enzyme needed by these cells to stay alive. It interferes with the growth of any cells which are growing rapidly such as in pregnancy tissue, skin and gut cells and cancers.

Side effects

Side effects are generally minimal with a single dose, but may include:

- Reduction in liver function for a short period of time
- 'Colicky' abdominal pain
- Nausea and vomiting
- Diarrhoea
- Increased sensitivity to sunlight

General advice for women

- Remove Band-Aid the next day.
- As methotrexate is excreted by the kidneys, flush toilet twice after use and avoid close skin contact with body wastes for 48 hours.
- Avoid alcohol and folic acid containing vitamins for 48 hours.
- Avoid gas producing foods (high FODMAP foods) such as leeks, cabbage, beans and onions for the first two to three days as they may worsen abdominal pain.
- Minimise exposure to the sun, wear sunglasses and use a sun screen.
- You may experience transient abdominal pain between three and seven days after the injection, known as 'separation pain'. This can be managed with paracetamol or with non-steroidal anti-inflammatory medications (e.g. ibuprofen) if your kidney function is normal.
- If you experience any significant abdominal pain or fainting episodes, you need to return to the hospital as there is a risk of ectopic 'rupture' prior to the pregnancy fully resolving.
- Avoid sexual intercourse for a minimum of two weeks.
- Pregnancy should be avoided for three months to minimise the risk of abnormalities developing in a subsequent pregnancy after exposure to methotrexate. Use of contraception (e.g. condoms or the oral contraceptive pill) during this time is important. The hospital staff can help with this.
- There is no evidence of long term side effects, future pregnancy losses (including miscarriages) or future congenital abnormalities with methotrexate therapy.
- You have an increased risk of another ectopic pregnancy.

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Breastfeeding

Breastfeeding should be considered a precaution for methotrexate.

If you are breastfeeding, express and discard your breast milk for 4 days after a single dose of methotrexate for an ectopic pregnancy. Your baby will need to be fed expressed breast milk (if available) or an age-appropriate infant formula during this time.

Follow-up

The effectiveness of the methotrexate treatment is monitored by measuring your pregnancy hormone (hCG) levels in your blood. A blood test will need to be taken four (4) days and seven (7) days following the methotrexate injection. It is also important to check that your liver and kidneys are not affected by the medication although this is unlikely.

Between 3% and 27% of women will require a repeat methotrexate injection on day 7 as their pregnancy hormone (hCG) levels are not decreasing as expected.

Ongoing testing of hCG levels may be required to ensure the success of the methotrexate treatment. If this is required, the hospital staff will let you know.

Appointments

Day one (1) - Date of methotrexate injection: ___/___/___

Day four (4): ___/___/___ Time: _____am/pm

Day seven (7): ___/___/___ Time: _____am/pm

Additional: ___/___/___ Time: _____am/pm

___/___/___ Time: _____am/pm

___/___/___ Time: _____am/pm

Contact phone numbers

Local hospital (24 hours): _____

Other clinic: _____

SA Ambulance: 000

Emotional wellbeing

If you feel overwhelmed or want to speak to someone about your pregnancy loss, please contact your local hospital or medical provider. Other useful online resources include:

SANDS: https://www.sands.org.au/miscarriage

Pregnancy Loss Australia: https://www.pregnancylossaustralia.org.au/

Pregnancy, birth & baby: https://www.pregnancybirthbaby.org.au/emotional-support-after-miscarriage

For more information

SA Health and Wellbeing
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www.sahealth.sa.gov.au/perinatal

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