CLINICAL PRACTICE GUIDELINE

Pregnancy care: First trimester complications

This document should be read in conjunction with the Disclaimer

Contents

Complications (early pregnancy): Assess / diagnose

Aims

- To obtain information that will enable an accurate diagnosis of the woman's presenting complaint in a timely manner.
- To initiate treatment where necessary.
- To provide the woman with support, a full explanation of the condition and the proposed treatment (including alternatives, likely effects and expected outcome/s).
- To make appropriate referrals for further care where necessary.

Background

Miscarriage and ectopic pregnancy can cause significant maternal morbidity and mortality[3-6]. Miscarriage occurs in at least 10-20% of pregnancies. The risk of miscarriage is reduced to 3% once a viable embryo is visualised[7]. Vaginal bleeding that does not lead to miscarriage has been linked to pre-term birth, stillbirth and low birth weight[4, 6] . Ectopic pregnancy, the most dangerous cause of vaginal bleeding[4]; is increasing in incidence due to earlier diagnosis along with an increased use of assisted conception[3]. Incidence rates for ectopic pregnancy are between 1 in 200-500 pregnancies[5]. Gestational trophoblastic disease or molar pregnancy is rare occurring between 1 in 1000 pregnancies but is important to consider in assessment[5]. Support, follow up and access to counselling is an important part of care for women who experience pregnancy loss. Follow up should be offered to all women after pregnancy loss.[8]

Key points

1. Women commonly present at the Emergency Centre (EC) with a history of amenorrhoea, abnormal vaginal bleeding and/or abdominal pain in the first trimester of pregnancy. Management of these cases begins with a thorough history, clinical examination, followed by appropriate investigations and treatment.
2. **Always consider the possibility of ectopic pregnancy** in a sexually active woman with vaginal bleeding, +/- abdominal pain and positive pregnancy test[3].

Assessment

It is crucial to first assess for haemodynamic stability by recording vital signs and reassess the patient regularly. Symptoms such as unexplained shock, signs of syncope, shoulder pain and tenesmus may suggest a rupture requiring emergency treatment. Septicaemia can occur secondary to retained products of conception and require prompt management.

NB: Knowing the patient's weight can assist with accurate drug dose calculations and avoid toxic reactions.

Aspect	Considerations	Rationale
Pain	• Location, radiation, nature • Constant or intermittent • Provoking or relieving factors • Presence of shoulder tip pain	
Vaginal bleeding	• Onset, nature (heavy/spotting) of bleeding • Last menstrual period – duration and nature • Passage of tissue or products of conception	Vaginal bleeding can be associated with a complication of early pregnancy or identify another cause
Reproductive history	• Sexually active • Current contraception use • History of recent assisted contraception • If possibility of pregnancy – investigations performed, presence of symptoms of pregnancy	
Obstetric and gynaecological history	• Number of pregnancies (gravida) – live births, miscarriages and terminations - details of gestation and treatments • Number and nature of previous births • Previous ectopic pregnancies • Recent dilatation and curettage • Pap smear history • Previous pelvic inflammatory disease (PID) • Previous infertility • Sexually transmitted infections	To identify high risk factors for ectopic pregnancy or other conditions that may require further investigation, observation or intervention. Risk factors for ectopic pregnancy: • Multiple sexual partners • Previous sterilisation or reversal of sterilisation • Early age of sexual intercourse and/or • Presence of IUD and assisted contraception
Complete the assessment with a thorough medical, surgical, social and family history		

Examination and investigations After completing the above history taking it is important to do a physical examination and carry out the appropriate investigations.		
Examination	• Abdominal examination – tenderness and distention • PV blood loss on pad • Vaginal examination 1. Speculum – site and amount of bleeding, cervical os (ectropion, or products of conception visible) 2. Bimanual – cervical excitation, cervix open or closed, adnexal masses, size of the uterus An open cervix can only be assessed by digital examination not speculum **[Recommendation Mar 2019]**	To exclude an acute abdomen that might require urgent surgical intervention Vaginal examination should be individualised as clinically appropriate. If products are visible in the os, they should be removed and sent for histopathology
Investigations	• Obtain IV access with a 14gauge cannula and commence IV therapy if indicated • β-HCG – urine and quantitative β-HCG, serial β-HCG if relevant • FBC, Coagulation Studies, UEC (if significant bleeding is present) • **Check Rhesus D antigen and antibody status if a negative blood group** • Consider history taken and if screening is required for blood borne and infectious diseases i.e. Chlamydia, Hep B/C, HIV • Consider serum progesterone levels with USS as it may assist with PUL	All women of reproductive age with signs of abdominal pain or vaginal bleeding should have a pregnancy test. A single β-HCG indicates when an intrauterine pregnancy should be visualised on USS. Serial β-HCG is useful in the diagnosis of an asymptomatic ectopic pregnancy, or to assess viability of a pregnancy. All women requiring surgical uterine evacuation should be screened for Chlamydia Trachomatis – as it places women at an increased risk of PID. A serum progesterone level <25nmol/L in conjunction with a PUL are confirmed to be

		non-viable pregnancies.
Imaging	Transvaginal ultrasound*****: • Immediate if indicated • Consider referral to EPAS if patient is stable *****Unless a failed pregnancy is confirmed by falling BHCG, visualisation of obvious products of conception or by an open cervix on digital examination by competent assessor, then a diagnosis of failed pregnancy should not be made before an ultrasound is performed as this may cause unwarranted distress. **[Recommendation Sept 2019]**	Transvaginal imaging has been found to be the best single diagnostic modality for: 1. Diagnosing ectopic pregnancy. This should be performed in all cases where early pregnancy complications are being investigated. Sensitivity to diagnosing ectopic pregnancy has been found to be 90.9-99.9%. 2. Determining a live intrauterine pregnancy. NB: When diagnosing an ectopic pregnancy, an empty intrauterine sac may be a pseudo sac in a woman with an ectopic pregnancy. An ectopic pregnancy can co-exist with an intra-uterine pregnancy.

Following assessment

If early pregnancy bleeding or pain:

Refer to the following guideline sections within this document:

- Bleeding (Early Pregnancy) Algorithm
- Bleeding (Vaginal) and a Viable Intrauterine Pregnancy.

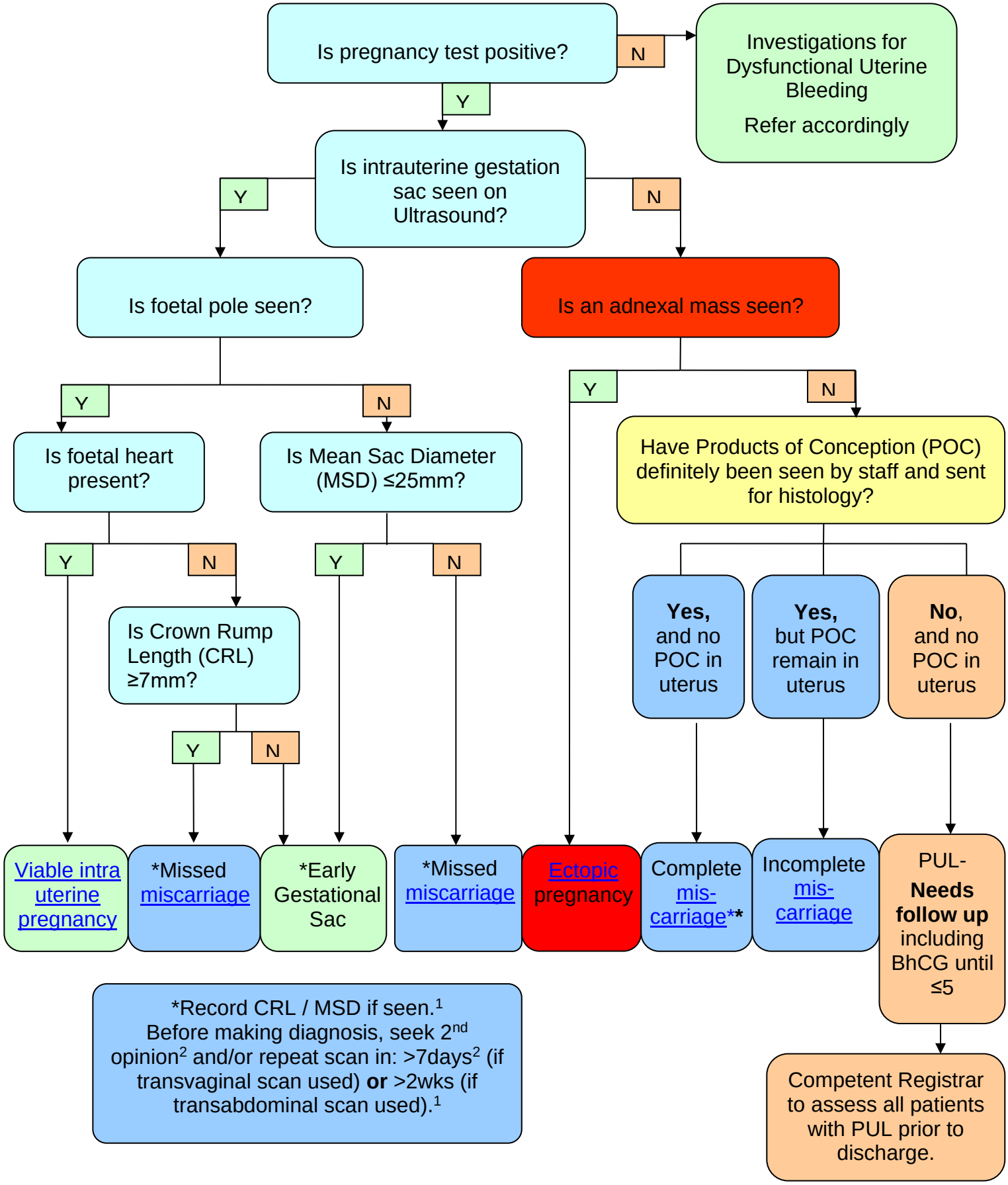
Competent Registrar to assess all patients with pregnancy of unknown location (PUL) prior to discharge. **[Recommendation Mar 2019]**

If ectopic pregnancy suspected or diagnosed:

Refer to following guideline sections within this document: Ectopic Pregnancy for:

- Medical Management using Methotrexate
- Surgical Management of Ectopic Pregnancy
- Expectant Management of Ectopic Pregnancy

Bleeding / pain algorithm (early pregnancy)



** Ultrasound can only diagnose complete miscarriage if an intrauterine pregnancy has been previously proven or products of conception have definitely been identified.

Abbreviation- Pregnancy of unknown location (PUL)

Bleeding (vaginal) and a viable intrauterine pregnancy

Background

Threatened miscarriage is defined as vaginal bleeding with or without abdominal pain, while the cervix is closed and the fetus is viable, inside the uterine cavity[9] . Threatened miscarriage is the most common complication of early pregnancy occurring in 20% of women before 20 weeks gestation[8].

17 % of these women will continue to have further complications in pregnancy and are 2.6 times more likely to experience miscarriage at a later stage in the pregnancy[8].

Threatened miscarriage is associated with adverse maternal and perinatal outcomes[10]. An increased risk of antepartum haemorrhage, pre-labour rupture of membranes, preterm delivery and intrauterine growth restriction has been documented[9]. A UK study reports an association with malpresentation, manual removal of placenta and elective caesarean section[11].

Ultrasound has improved management by rapid confirmation of viability.[9] Transvaginal scanning has a positive predictive value of 98% in confirming diagnosis of complete miscarriage and should be used in assessment. The presence of a fetal heart has the most powerful association with pregnancy outcome. Studies have varied from indicating that at 3 - 5.3mm crown rump length (CRL) a viable fetus can be visualised[1]. A 100% success rate has been found with a CRL of 6mm or more in diagnosing a viable pregnancy[1]. Fetal bradycardia was a sign present in 1 in 3 pregnancies that were subsequently lost, whilst 7% of pregnancies that continued had bradycardia found on ultrasound[12].

Key points

1. Manage all women with early pregnancy complications with respect and dignity, as this can cause significant distress[1]. Provide comprehensive information throughout.
2. Non-sensitised rhesus negative women should receive anti-D immunoglobulin for threatened miscarriages[8].
3. In the case where a heartbeat is absent with a CRL of less than 7.0 mm or a mean gestational sac diameter of less than 25.0 mm measured on a single ultrasound, a repeat scan is recommended in 7 days if using transvaginal ultrasound or 14 days when transabdominal ultrasound is used[1].

Procedure

1. Inform the woman of the assessment findings and diagnosis and provide reassurance.
2. Give the woman the Information Sheet: Bleeding and/or Pain in Early Pregnancy.
3. Refer to WNHS O&G Clinical Guideline: Blood Group Management and Clinically Significant Antibodies (RhD Negative and RhD Positive Women) for guidance on checking the woman's blood group and anti D immunoglobulin if rhesus negative.

4. Advise the woman that if vaginal bleeding gets worse or persists beyond 14 days, she should return for further assessment. If bleeding stops to continue with routine antenatal care[1].
5. Follow up may be required in the following situations:
    - Significant vaginal bleeding and patient refusing to be admitted.
    - A haematoma is noted[13]
    - Fetal bradycardia
    - After IUCD removal
    - For reassurance at woman's request because of previous recurrent miscarriages (3 or more)
6. Discharge to the care of her GP with a formal discharge letter for referral to the antenatal clinic.

For further information on diagnosis and management see section in this document: Bleeding/Pain Algorithm (Early pregnancy).

Early gestational sac: Management of

Aim

- To provide information on the management of an early gestational sac (EGS)

Background

The earliest definitive evidence of pregnancy visible on ultrasonography is the gestational sac. 4 weeks + 3 days is the earliest time to see a gestation sac eccentrically placed within the endometrium by a transvaginal ultrasound (TVS). By 5 weeks + 2 days the sac should be visualised, and should be 2-5 mm in diameter[14, 15]. 78.6% TVS after 49 days of gestation will diagnose pregnancy.[16] Very early gestational sac appears as fluid collection in central echogenic portion of the uterus; sometimes seen as the “double sac sign” or the “intradecidual sign”[15].

Ultrasound features with an empty gestational sac with mean diameter > 25mm and absent yolk sac with mean gestational sac diameter >20 mm are the threshold which has the most precise estimate of specificity for diagnosing early embryonic demise[17]. A biochemical marker such as decline in human chorionic gonadotrophin (hCG) may predict miscarriage but does not preclude laboratory error or a physiological drop in hCG late in the first trimester. It is imperative to have a high specific test with zero false positive rate as diagnosis of fetal demise results in evacuation of the uterus[17]. Ultrasound has lowered threshold values for visualisation of gestational sac[18]. Disproportionately small or non-visible embryo within an enlarged amnion is a good marker for a failed pregnancy[14]. Theoretically cardiac activity should be evident when embryo is over 2mm, but in 5-10% of cases where this has been documented pregnancy outcome was normal[19].

The presentation of women with an “empty sac” is common; with up to 10% of women attending health centres with uncertain viability in pregnancy[8]. Early normal pregnancies always show a gestational sac but no detectable embryo during a brief but finite stage of early development[14]. Once a gestational sac has been documented subsequent loss of viability remain around 11%, there is no difference between gestational sac diameter when compared with pregnancy outcome[19]. If an embryo has developed up to 5 mm length, loss of viability occurs in 7.2% of cases[19]. Persistence of yolk sac has been found inside the gestational sac after embryonic demise[19]. 10-20% of ectopic pregnancies have an intrauterine pseudo gestational sac and it is important to be aware of the rare possibility of concurrent intrauterine and extra uterine pregnancy[20].

Definitions

Intrauterine sac*:*	< 20mm mean diameter with no obvious yolk sac or fetus.
Uncertain viability:	An intrauterine gestational sac (IUGS) of <25mm in mean diameter with no obvious yolk sac, or the presence of a fetus or fetal echo of <7mm CRL with no fetal heartbeat. A repeat scan at a minimum interval of 1 week is necessary[8].
Missed miscarriage:	An empty IUGS with a mean diameter ≥25mm or CRL ≥7mm with no fetal heart is diagnosis of missed miscarriage

Ultrasound features of EGS

- It is seen as a round, anechoic structure with an echogenic rim. When it first appears on ultrasonic imaging, the gestational sac is surrounded by a thickened decidua. This perimeter then becomes a distinct “double ring” (Also known as the “double decidual sign”).
- It is eccentrically placed i.e. it remains within a thickened decidua on one side of the uterine cavity.
- It is typically located in the fundus on the posterior wall.
- Mean Sac Diameter (MSD) is a useful indicator of GA before CRL measurement is available.

Management

1. Early gestation sac needs to be differentiated from a pseudo gestation sac.
2. A follow up scan should be arranged in 7-10 days if there is certainty about the diagnosis of EGS or in 3 days to assess the growth of the sac if the diagnosis is uncertain.

   A healthy gestational sac grows by 1.2mm / day[19].
3. A yolk sac will usually be visible at the next scan in a normal pregnancy.
4. Correlation with quantitative hCG levels will be helpful although it should be remembered that following up every early gestational sac with serial measurements of hCG leads to increased patient anxiety.
5. Give the woman information about when to attend for further medical review.

See also- section: Bleeding/Pain Algorithm (Early pregnancy)

Gestational Trophoblast Disease / Hydatidiform mole

Purpose

- To provide information on the care and management of women presenting with suspected or confirmed gestational trophoblast disease.

NB: These are guidelines and do not preclude the use of clinical judgement and discussion in a tumour board setting for unique cases which may require treatment deviating from this document.

Key points

1. A pregnancy test (Quantitative BhCG) should be performed in all cases of persistent or irregular vaginal bleeding after a pregnancy event (including live birth, miscarriage, termination or ectopic pregnancy) to investigate for undiagnosed gestational trophoblastic disease.[21] [22]
2. Suction evacuation is the preferred initial management for all cases of suspected molar pregnancy.[21, 22] Ideally this should be performed or supervised by an experienced Gynaecologist, under ultrasound guidance, to ensure the uterine cavity is empty at completion and to minimise the risk of perforation.
3. Use of misoprostol to ripen the cervix is appropriate before suction evacuation.[23] There is insufficient data on the safety of prostaglandins for cervical ripening in later gestations (greater than 15 weeks) and therefore should be used with caution in this situation.[21]
4. Molar pregnancies can cause heavy vaginal bleeding. The management for this emergency is uterine evacuation by suction D&C. Oxytocics may be used in theatre ONLY after uterine evacuation has been completed due to the risk of trophoblastic tissue being disseminated throughout the venous system.[21, 22]
5. All products of conception obtained at evacuation should be sent for histopathology and followed up in the EC.[21, 22]
6. Ploidy status and immunohistochemistry staining for P57 may be useful for differentiation between a partial or complete mole.[21, 22]
7. Although complete moles lack the anti-D antigen, there may be a significant delay in histological confirmation, therefore it is recommended that ALL women who are RhD negative receive RhD Immunoglobulin prophylaxis.[21, 22, 24]
8. Patients should be counselled regarding their diagnosis, follow up requirements, and the implications for their future pregnancies. Interpreters should be utilised appropriately for patient education.
9. Unlike the UK, there is no GTD registry in Western Australia. Follow up occurs in the EC at KEMH by the EC Registrar. If a patient's care requires transfer to another practitioner or hospital (i.e. patient moving interstate), a comprehensive and definite handover of care must be completed.
10. Pregnancy should be avoided until after the completion of the surveillance period. Women should be advised to have protected sexual intercourse.

Oestrogen and/or progestogen contraceptives (i.e COCP/implanon) may be used between evacuation of the molar pregnancy and prior to return to normality of BhCG levels. This does NOT appear to increase the risk of invasive mole or choriocarcinoma developing.[21, 25, 26]

11. To minimise the risk of uterine perforation, insertion of an intrauterine device should be delayed for at least 6 weeks after evacuation of the uterus and after the BhCG levels have returned to normal.[21]
12. A diagnosis of persistent gestational trophoblastic disease, gestational choriocarcinoma and placental site trophoblastic tumours (PSTT) requires referral to the Gynaecologic Oncology team.
13. For women who conceive again after having a molar pregnancy, there is a 1:70 chance of recurrence. An ultrasound scan early in pregnancy at 6 weeks gestation is recommended. Also, a BhCG level should be completed 6 weeks after the conclusion of any future pregnancy regardless of the outcome (i.e. miscarriage, termination, or delivery).[21]
14. The patient's general practitioner (GP) should be notified of the diagnosis of gestational trophoblastic disease and a discharge letter should be sent on conclusion of treatment and/or follow up.

Background[27]

Gestational Trophoblast Disease (GTD) is a rare group of placental related disorders derived from a pregnancy. The incidence of molar pregnancies is in the order of 1:200-1000 pregnancies. They form a spectrum of illnesses from hydatidiform mole (complete and partial) to choriocarcinoma and because of their secretion of human chorionic gonadotrophin (hCG), they can be accurately monitored. They have cure rates approaching almost 100%. The types of trophoblast disease range from the usually benign partial and complete molar pregnancy through to invasive mole, malignant choriocarcinoma and placental site trophoblast tumours.[21, 24]

The use of ultrasound in early pregnancy has led to the earlier diagnosis of molar pregnancy, as opposed to the common clinical presentations of irregular vaginal bleeding, hyperemesis, excessive uterine enlargement, early failed pregnancy or persistent vaginal bleeding following a completed pregnancy. Rarer presentations may include hyperthyroidism, early onset pre-eclampsia or the presence of theca lutein cysts. HCG levels greater than two multiples of the median may also contribute to the diagnosis.[21, 22]

Gestational trophoblastic neoplasia (GTN) is a term used to describe GTD requiring chemotherapy or excisional treatment because of the persistence of hCG or the presence of metastases. GTN follow hydatidiform mole (60%), previous miscarriage / abortion (30%), normal pregnancy or ectopic gestation (10%).[21]

Risk factors

- Extremes of reproductive age[21]
  - Age 45 years and over
  - Age 16 years and under

- Previous GTD
- Woman from Asia have a higher incidence of GTD (1:390) compared to non-Asian women (1:750).[21] There may be a higher incidence of molar pregnancies in Africa and Asia. However, the varying standards in the frequency and accuracy of histopathology makes it difficult to make accurate comparisons.[28]

Classification

The World Health Organisation classification divides trophoblast disease into the pre-malignant and malignant forms as shown below:

- **Pre-malignant**
  - Partial Molar Pregnancy
  - Complete Molar Pregnancy
- **Malignant**
  - Invasive mole (Persistent Gestational Trophoblastic Disease)
  - Choriocarcinoma
  - Placental site trophoblastic tumours (PSTT)

Pre-malignant trophoblast disease

Hydatidiform moles are separated into complete and partial moles based on genetic and histopathological features. In early pregnancy (less than 8-12 weeks gestation), it may be difficult to separate the complete and partial moles on microscopy alone, and other tests (ploidy, p57) will often be required to make the diagnosis.[21] Historically the relative incidence of partial and complete molar pregnancies has been reported as approximately 3:1000 and 1: 1000, respectively.[24]

Partial mole

Partial moles are usually triploid with 2 sets of paternal and 1 set of maternal chromosomes but may be tetraploid or mosaic in 10% of cases[24].

Macroscopically partial moles may resemble the normal products of conception as they contain embryonic or fetal material such as fetal red blood cells. As a result, the diagnosis of partial mole can often be missed after an apparently straightforward miscarriage or termination.

Partial moles rarely become malignant with an overall risk of 0.5% requiring chemotherapy after a partial mole. [22]

Complete mole

Complete moles are diploid and androgenic in origin with no evidence of fetal tissue. The genetic material is entirely male in origin and results from the fertilisation of an empty ovum lacking maternal genes. The chromosome complement is most commonly 46XX, which results from one sperm that duplicates its DNA, or less frequently 46XX or 46XY from the presence of two different sperm in an empty ovum.[24] In contrast to a partial mole, a complete mole more frequently proceeds to invasive disease with 8-20% of patients requiring chemotherapy.[21, 22]

Malignant Trophoblast Disease

Gestational trophoblastic neoplasm (GTN) may develop after a molar pregnancy, a non-molar pregnancy or a live birth. Any woman who develops abnormal or persistent vaginal bleeding after a pregnancy event is at risk of having GTN. Women may also present with a wide variety of symptoms from distant metastases to the lungs, liver and central nervous system.[29] Locally invasive GTN is most commonly located in the vaginal fornices or suburethrally. Due to their highly vascular nature, biopsy should be avoided.[21]

As this disease crosses the placenta, in all suspected and confirmed cases of postpartum GTN, the neonate should have a urine test for quantitative hCG.[21]

Invasive mole (Persistent Gestational Trophoblastic Disease)

Invasive moles usually arise from a complete mole and is characterised by the invasion of the myometrium, which can lead to perforation of the uterus. Microscopically, invasive moles have a similar benign histological appearance as complete moles but is characterised by the ability to invade in to the myometrium and the local structures if left untreated.

The usual presentation of an invasive mole is with hCG elevation or plateau during surveillance following a molar pregnancy.[30]

Gestational choriocarcinoma

Choriocarcinoma is clinically and histologically overtly malignant.

The diagnosis most frequently follows a complete mole (25-50%) when the patients are usually in a surveillance programme, but can also arise in unsupervised patients within 12 months after a non-molar abortion (25%) or after a normal term pregnancy (25-50%).[21, 30]

HCG levels are always elevated. Diagnosis may be difficult due to frequent haemorrhage and necrosis.[21]

Placental Site Trophoblastic Tumour (PSTT)

Placental site trophoblast tumours are very rare and are the least common form of gestational trophoblast disease comprising less than 2% of all cases.

Women with PSTT usually present later in comparison to other forms of GTD. The average interval between the pregnancy event and presentation of disease is 3.4 years. The clinical presentation of PSTT can range from slow growing disease limited to the uterus, with abnormal uterine bleeding to more rapidly growing metastatic disease with behaviours similar to choriocarcinoma. Other presentations may include amenorrhea, hyperprolactinemia or nephrotic syndrome.[31]

Usually the hCG levels, whilst elevated, are relatively low in PSTT relative to the volume of the disease.[21, 31]

PSTT is diploid and arises from the non-villous trophoblast. The pathology is characterised by intermediate trophoblastic cells with vacuolated cytoplasm, the expression of PLAP rather than hCG and the absence of cytotrophoblast and villi.[32].

Management of GTD

NB: The Gynaecology Consultant rostered in EC at time of presentation must be notified for all suspected or confirmed molar pregnancies.

See GTD Follow-up Flowchart

Initial management for suspected molar pregnancy

1. Perform initial blood tests for
    - BhCG levels
    - Blood group and Hold
    - Full blood count (FBC)
2. Arrange suction dilatation and curettage (D & C). Suction evacuation is recommended for complete and partial molar pregnancies. Consider evacuation under ultrasound guidance due to increased perforation risk with molar pregnancies.
    a. Notify consultant and/or registrar assigned to the theatre list and if possible book case at the beginning of the D&C list due to excessive bleeding risk.
    b. Ensure that there is a current G&H
    c. Misoprostol may be given prior to surgery[23]
3. Avoid the use of oxytocics until after uterine evacuation has been completed. This reduces the risk of causing trophoblastic embolism from the placental bed and disseminated disease.
4. Send all products of conception for histology examination and consider cytogenetics
5. Administer RhD immunoglobulin to Rh-negative patients after surgery
6. Chase histopathology results in EC. This should be done by the EC registrar.
7. Provide initial patient education and provision of information brochures.
8. Provide information about pregnancy loss services and/or referral to psychological medicine if required.

Management of ‘confirmed’ complete and partial mole

1. Ring patient and arrange scheduled review in EC to discuss the diagnosis and provide patient information as well as follow up requirements due to risk of persistent disease (Please refer to; **“Follow Up”**)
2. Advise against pregnancy until end of surveillance period (Please refer to; **“Contraception Advice**”)
3. For **complete moles**; arrange investigations including U&E, LFT, TFT, Coagulation profile and Chest X-ray.

Follow up

Following diagnosis of complete or partial mole (as confirmed on histopathology), patients should be followed with weekly serial serum hCG levels. The blood test can be performed at any Path West collection centre most convenient to the patient.

Ensure an “expect” sticker is placed on their medical files for weekly follow up. The EC registrar must review the hCG level and contact the patient with the result and follow up plan.

A negative (normal) quantitative BhCG level is <5 Iu/L.

Normalisation= three consecutive weekly normal BhCG levels (i.e. three consecutive weekly BhCG levels of ≤5 Iu/L).

If during follow up, there is an increase or plateauing hCG levels, please refer to; “**Management of Persistent Gestational Trophoblastic Disease”**

1. **Complete moles**

   Weekly quantitative hCG levels should be undertaken until 3 consecutive weekly normal levels are achieved. This is called normalisation. Then monthly levels should be performed for a further 6 months following normalisation**. If during follow up and after initial normalisation, any level is > 5iu/L this must be reported to the consultant responsible for the woman’s care and discussed with gynaecology oncology.**

2. **Partial moles**

   Weekly quantitative hCG levels should be taken until 3 consecutive normal levels are achieved. This is called normalisation. If it takes ***less than*** 8 weeks to achieve normalisation the patient may be discharged without any further follow up.

   If normalisation takes **more than** 8 weeks to be achieved, the patient should have monthly quantitative hCG levels performed for a further 6 months **from the time of normalisation**. **If during follow up and after the initial normalisation, any result is > 5iu/L this must be reported to the consultant responsible for the woman’s care and discussed with gynaecology oncology.**

Histopathology “unable to exclude a molar pregnancy”

Manage as per a partial mole with weekly quantitative hCG levels.

Continue follow up while awaiting cytogenetic results. Seek advice from the pathologist and/or treating gynaecologist.

There may be a role for repeat suction D&C in selected cases for histological confirmation in difficult cases which may have problematic bleeding. However, there is an increased risk of perforation and excessive bleeding with repeat D&C. This should be discussed with the consultant Gynaecologist and/or gynaecology oncology.

See GTD follow-up flowchart within this section.

Contraception Advice:

Pregnancy should be avoided in the follow up period, and appropriate contraception can be utilised.

- Women should be advised to use barrier contraception
- Oestrogen and/or progestogen contraceptives may be used between

evacuation of the molar pregnancy and prior to return to normality of hCG levels. This does NOT appear to increase the risk of invasive mole or choriocarcinoma developing.[21, 25, 26]

- Intrauterine contraceptive devices should be avoided for at least 6 weeks following D&C and normalisation of QBHCG levels due to the risk of uterine perforation.[21]

Management of Persistent Gestational Trophoblastic Disease

This diagnosis is usually made in the following situations during follow up:

a. A BhCG increase of >10% over two consecutive weekly levels (i.e. **THREE** hCG results) or;
b. A BhCG decrease/plateau of <10% over three consecutive weekly levels (i.e. **FOUR** hCG levels) or;
c. An elevated BHCG levels (>5iu/L) following initial normalisation during the surveillance period.

These cases MUST be discussed with the treating gynaecologist, and a referral must be sent to gynaecology oncology.

Furthermore, diagnosis of persistent gestational trophoblastic disease requires a metastatic screen, FIGO staging and WHO prognostic risk score.

The metastatic screen should be organized by the EC Doctor after discussion with gynaecology oncology.

The **metastatic screen** for persistent GTD includes*;*

a. Blood tests; FBP, U&E, LFT, TFTs, and coagulation profile
b. CT chest/abdomen/pelvis
c. MRI brain (ONLY if CT chest indicates presence of lung metastases or there are concerning neurological symptoms). Brain metastases in the absence of lung metastases are extremely rare.
d. There is minimal role for repeat pelvic ultrasound in these cases and thus should not be routinely ordered.

The role for repeat D&C is controversial. The procedure may be considered if the HCG level is <5000 IU/L with disease confined to the cavity (no myometrial spread or metastatic disease), however the low efficacy of repeat D&C, the risk of haemorrhage and perforation should be considered in comparison with an almost 100% cure rate and the relative safety of chemotherapy.[21, 22, 24] Consider the use of hysteroscopy to locate the foci of persistent disease.[21]

FIGO anatomical staging of persistent gestational disease[33]

Stage I	Disease localised to uterus
Stage II	Disease localised to the pelvis and adnexa
Stage III	Pulmonary metastases
Stage IV	Distant organ involvement (I.e. brain, liver, kidney, GI tract, spleen)

A modified World Health Organisation (WHO) prognostic system should be calculated to guide chemotherapy regime.

WHO prognostic score[34]

>	**Score**			
Prognostic factors	0	1	2	4
Age (yrs)	<40	>39	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval (months)*	<4	4-6	7-12	>12
Pre-treatment serum hCG (IU/L)	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Number of metastases	0	1-4	5-8	>8
Site of metastases	Lung	Spleen and Kidney	GI tract	Brain and liver
Largest tumour mass, including uterine (cm)	-	3-5	>5	-
Prior failed chemotherapy	-	-	Single drug	Two drugs

* End of antecedent pregnancy to chemotherapy.

The prognostic score predicts the potential for developing resistance to single-drug chemotherapy with MTX or actinomycin D (ActD). A score 0-6 is considered low risk and therefore a single chemotherapeutic agent is indicated. A score of 7 or greater indicates high risk of resistance and requires multi-agent chemotherapy regime[34].

NB: Prescribing of chemotherapeutic agents for GTN is done solely by the Gynaecology Oncology team. Multi agent chemotherapeutic regimes for resistant GTD or WHO high risk scoring patients requires specialised chemotherapeutic regime protocols that is organised by gynaecology oncology.

Methotrexate and folinic acid treatment regime:

- See eviQ https://www.eviq.org.au/medical-oncology/gynaecological/gestational-trophoblastic-disease/668-gestational-trophoblastic-disease-low-risk-met

Management of Gestational Trophoblastic Neoplasm:

1. Inform patient of the diagnosis. Assess for signs and symptoms of metastatic disease
2. All cases MUST be discussed with the treating Gynaecologist and referred to Gynaecology Oncology
3. Arrange a metastatic screen
4. Calculate FIGO staging and WHO prognostic risk score

GTN is very responsive to chemotherapy, and associated cure rates are greater than 90% even in women with metastatic disease[35]. Women who receive chemotherapy are likely to experience menopause earlier by 1 year for single agent, and 3 years for multi-agent chemotherapy.[22, 24, 30]

In circumstances in which women have completed their families and when the disease is confined to the uterus, undergoing a hysterectomy can be an appropriate treatment option followed by close surveillance.[21]

Management of a molar pregnancy with a coexisting viable twin pregnancy:

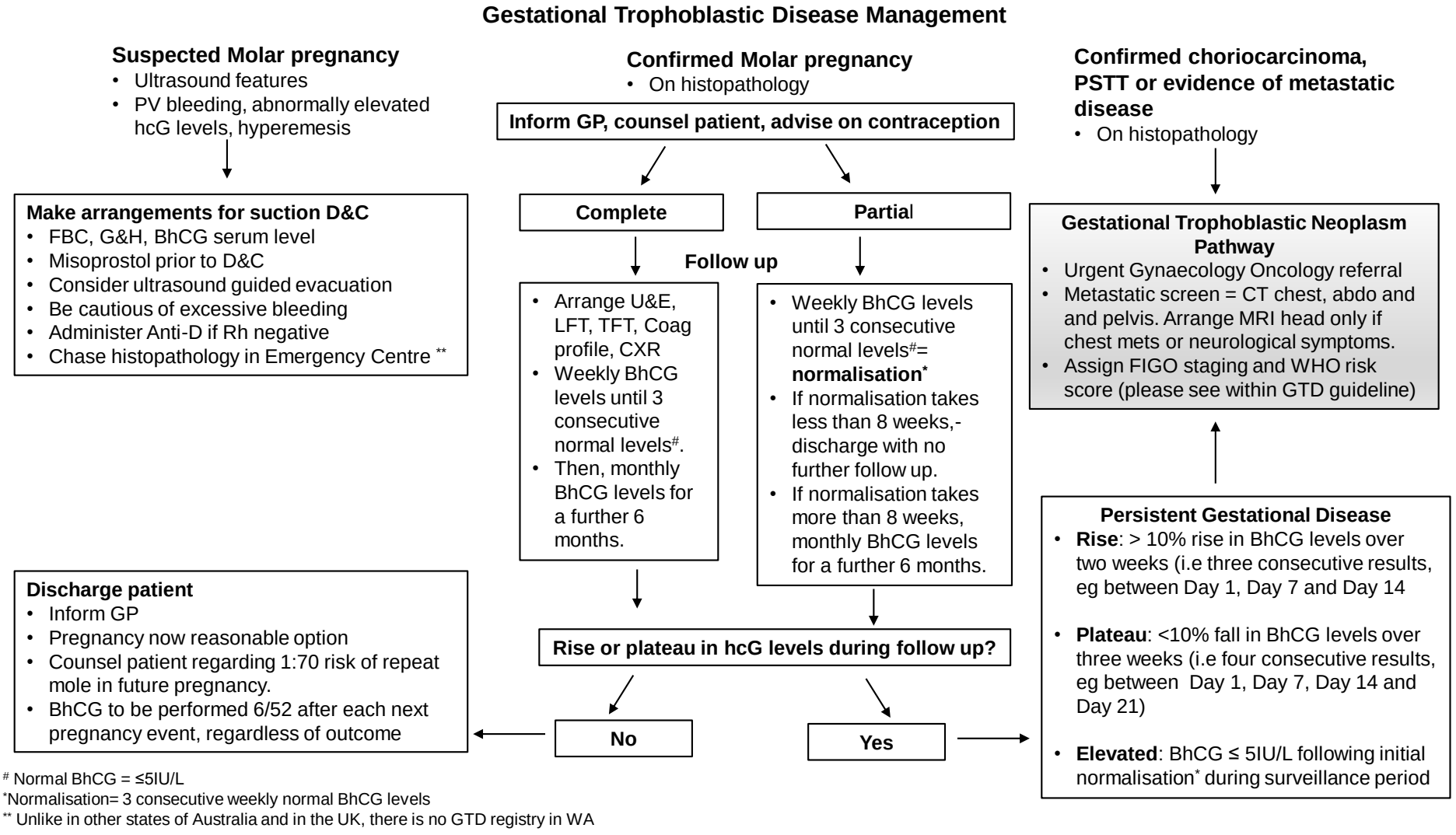
1. Discuss with the Maternal Fetal Medicine (MFM) team and Gynaecology Oncology regarding management.
2. Consider prenatal testing for karyotyping.
3. Pregnancy outcomes in this situation may be poor:[36]
    a. 25% chance of a live birth
    b. 40% chance of early pregnancy loss
    c. 36% chance of preterm birth
    d. Up to 20% of these pregnancies are affected by pre-eclampsia

Post GTD care:

1. Send a discharge letter to the GP. Provide information of discharge, the follow-up management and include management if the woman presents with a future pregnancy.
2. Women should be counselled about what to do in their next pregnancy including an early ultrasound to exclude recurrence of GTD, and a BHCG level 6 weeks after the conclusion of any pregnancy event regardless of the outcome (i.e. miscarriage, termination, or delivery).[21]
3. Following chemotherapy for an invasive molar pregnancy, woman may be at increased risk of miscarriage or stillbirth if they fall pregnant within 12 months of completing multi-agent chemotherapy. Women should therefore be encouraged to avoid pregnancy for 12 months in this circumstance. [21, 22, 30] Fertility rate is not affected following chemotherapy.

See GTD Follow-up Flow chart below.

GTD follow up flowchart



Normal BhCG = ≤5IU/L
*Normalisation= 3 consecutive weekly normal BhCG levels
** Unlike in other states of Australia and in the UK, there is no GTD registry in WA

Absence of chorionic villi in products of conception and negative laparoscopy

Background

Confirmation of pregnancy through histological examination following miscarriage and surgical evacuation of the uterus is recommended in the rare instance that an ectopic pregnancy or molar pregnancy continues. The risk of ectopic pregnancy diagnosed following surgical treatment for miscarriage was found to be 0.42%[8]. When treating ectopic pregnancy by surgical management failure rates are significantly higher when a salpingostomy is performed[37, 38]. The failure rate is reported to be between 5-20% with this procedure[38].

Key points

- Quantitative hCG levels should fall following removal of all trophoblastic tissue.
- If histology of the products of conception does not demonstrate chorionic villi, ectopic pregnancy must be excluded.

In the absence of chorionic villi in products of conception: Refer to section: Ectopic Pregnancy.

Negative laparoscopy

Rarer forms of ectopic pregnancy such as interstitial/corneal implantations can be missed at laparoscopy. Tubal abortion is another cause of a negative laparoscopy.

Management

1. The woman must be contacted and if pain is present, prompt medical review should occur.
2. Serial quantitative hCG measurements should be performed weekly to determine demise or continuation of the pregnancy[39].
    - A plateau or rise in hCG level >5% signifies a persistent ectopic; hCG <5% of preoperative value indicates resolution of ectopic pregnancy. hCG measurements should continue until the level is ≤5 IU/L.
3. If the hCG rises further USS should be performed when the level reaches 1500IU/l or if pain develops[39] (an intrauterine pregnancy should be identified by transvaginal ultrasound when is >1500 IU/l hCG).
4. The woman should be warned of the risks of on-going ectopic pregnancy and the need for closely monitored follow-up. If pain develops the woman should be advised to seek medical attention urgently.

For treatment options refer to section in this document Ectopic Pregnancy for:

- Medical Management of Ectopic Pregnancy using Methotrexate
- Expectant Management of Ectopic Pregnancy
- Surgical Management of Ectopic Pregnancy

Nausea and vomiting in pregnancy / hyperemesis gravidarum

Aim

- To provide information on the care of a woman with nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum (HG).

Key points

1. Intervention is supportive, using antihistamine and antiemetic medications. Ordinarily treatment is not indicated unless symptoms are severe. Safety and efficacy of antiemetic medications should be discussed with women if symptoms are severe. Cochrane Review of Interventions for NVP and HG concluded that although antiemetic medications were effective, there is insufficient high quality evidence to support any intervention over another.[40, 41]
2. Consultation with a Dietitian is useful to obtain an accurate dietary history, elucidate possible nutritional avenues to pursue, and to counsel the woman. Dietary and lifestyle changes should be encouraged. Women should be advised about appropriate foods and fluids to prevent dehydration and minimise aggravation of symptoms. All repeat admissions require referral to the Dietitian.
3. Clinical Psychologists and Social Workers are also available to provide multi-disciplinary care for this condition.
4. Complementary therapies have been used including ginger (*Zingiber officinale* – **not** stocked in KEMH pharmacy) and acupuncture/acupressure. However, there is currently insufficient high quality evidence to support a particular choice of complementary therapy. See WNHS Clinical Guideline, Obstetrics and Gynaecology: Discomforts: Symptoms or Disorders (Minor) of Pregnancy.
5. Iron supplementation may worsen symptoms. Discontinuing iron containing multivitamins and supplements (where appropriate) may improve hyperemesis symptoms.
6. Women admitted to hospital with hyperemesis should be considered for thromboprophylaxis with a Low Molecular Weight Heparin (enoxaparin). This can be discontinued when the hyperemesis resolves.

Background

Nausea and vomiting affects up to 80% of women in the first trimester of pregnancy.[42] The peak severity for hyperemesis is around 12 weeks and whilst most will resolve by 20 weeks, 10% will continue throughout pregnancy.[40] Hyperemesis gravidarum is a severe form of nausea and vomiting which occurs in 0.3% to 2.0% of pregnancies and is the most common reason for hospitalisation in the first trimester.[42] It is a diagnosis of exclusion and is given when intractable vomiting is associated with weight loss of ≥ 5% of pre-pregnancy weight, electrolyte imbalance and dehydration with ketonuria. Severe HG with limited pregnancy weight gain is associated with intra-uterine growth restriction, low birth weight, preterm birth and low Apgars.[43]

The most likely cause of NVP is rising β-hcg and oestrogen levels although the pathogenesis is multifactorial.[44] Higher levels of β-hcg seen with molar or multiple pregnancies are associated with more severe symptoms. If nausea and vomiting starts after 12 weeks gestation then other causes need to be excluded and the cause needs to be evaluated fully for serious obstetric and medical complications.

Note*:* β-hcg can cause gestational thyrotoxicosis through cross reaction with the TSH receptor. BHCG is a glycoprotein similar in structure to TSH thus the circulating levels of free T4 and T3 are elevated and TSH suppressed. The biochemical hyperthyroidism is more significant in hyperemesis gravidarum. This is usually self-limiting and normalises in the second trimester but occasionally anti-thyroid medication is required.[44]

Predisposing factors for NVP

- Multiple pregnancy
- Molar pregnancy
- Previous hyperemesis
- Young age
- *Helicobacter pylori*
- Depression or anxiety
- Eating disorders
- Raised BMI
- Unplanned pregnancy
- Gastric reflux
- Inflammatory bowel disease
- Restrictive diet (e.g. lactose-free, vegetarian, or nutritional deficiency
- Financial and other situational stresses
- Cultural isolation, removal from country of origin, separation from spouse/family.

- NVP can affect a women's quality of home and work life, relationships and use of healthcare resources.
- Depression is common, either preceding or resulting from hyperemesis.
- Dehydration increases the risk of Diabetic Ketoacidosis in those with Type 1 Diabetes Mellitus.
- Electrolyte disturbances as seen in any patient with persistent vomiting – hypochloraemic alkalosis, hypokalaemia and hyponatraemia.
- Protein-calorie malnutrition, muscle wasting and accompanying ketosis, anaemia, hypoalbuminaemia.
- Vitamin / mineral deficiencies and accompanying problems – e.g. Wernicke's encephalopathy from thiamine deficiency, folate deficiency, iron deficiency.
- Thyroid dysfunction – e.g. "pseudothyrotoxicosis" – suppressed TSH with high free thyroxine resulting from thyroid stimulation by HCG.
- Renal dysfunction– (reversible) elevated urea and creatinine. Rarely, acute tubular necrosis.
- Hepatic dysfunction accompanying hyperemesis – elevated ALT, AST, low albumin, elevated bilirubin, subsequent to malnutrition and catabolic changes.
- Ulcerative oesophagitis.
- Mallory Weiss tear

Management

History

1. Obtain details of current pregnancy.
    - Determine first day of the last menstrual period.
    - Check whether an ultrasound has been performed in this pregnancy, at what gestation and where it was performed. If this was performed outside KEMH, arrange for the report to be faxed to KEMH and following review and initialling, a copy filed in the woman's digital medical record (DMR).
    - Confirm single or multiple pregnancy of what gestation.
    - Determine whether there has been any vaginal bleeding.
    - Seek information regarding the woman's anxiety about progress of her pregnancy – some cases require ultrasound to confirm fetal viability.
2. Obtain a specific history of nausea and vomiting pattern and dietary history to ascertain state of nutrition and recent intake.
    - At what gestation did vomiting start?
    - What is being kept down after ingestion?
    - Can she keep down fluids?
    - Does anything precipitate the nausea?
    - Is the appetite normal/decreased?
    - Ask specifically what she is eating?

3. Determine the presence of other symptoms. The following is a list of differential diagnoses or factors that aggravate hyperemesis:

• Urinary tract infection	• Cholelithiasis	• Gastro-enteritis
• Pyelonephritis	• Hepatitis	• Gastric ulcer/ dyspepsia
• Pancreatitis	• GI obstruction	• Thyroid disease
• Inflammatory bowel disease	• *Helicobater Pylori*	• Vestibular neuronitis
• Raised intracranial pressure	• Recurrent Migraine	• Positional vertigo

Ask about:

- Bowel habits and the presence of diarrhoea and/or constipation
- Urinary symptoms such as dysuria, frequency and suprapubic pain
- Presence of abdominal/pelvic/back pain
- Fevers, rigors or shivering
- Past surgical, medical and psychiatric history (diabetes, depression/ anxiety)
- The dose and frequency of use of alcohol, smoking and other recreational drugs
- Social circumstances
- Current medications and allergies
- Anxiety, low mood and negative thoughts towards herself and the baby

Examination

A full examination is required as there are a large number of differential diagnoses.

Investigations

- Patient weight
- Urinalysis: To look for ketonuria or signs of infection
- Blood glucose
- Blood tests: FBC, UEC's, LFT's, TFT's
- Ultrasound Scan: Arrange if this has not already been performed to exclude molar or multiple pregnancies which precipitate hyperemesis
- Other investigations in severe vomiting or electrolyte abnormality:
    - Serum magnesium, phosphate and calcium
    - Bicarbonate level
    - Blood gases if required
- Women with diabetes should be monitored carefully as dehydration increases the risk of diabetic ketoacidosis

Treatment

Management of hyperemesis is supportive, using vitamins, antihistamines, antiemetic medications and IV fluid therapy. It is important to reassure women that symptoms will subside by 20 weeks in 90% of cases. [40]

Dietary and lifestyle changes

- It is important to stay hydrated and try to have small meals regularly. Eating something before getting out of bed or before you get hungry is helpful.
- Avoid fatty and spicy foods
- Have small sips of water, carbonated or sweet drinks every 15 minutes
- Try and identify nausea triggers and avoid them (eg perfumes, smoke)
- Referral to a dietitian may be necessary in moderate to severe NVP. See WNHS Clinical Guideline, O&G: Discomforts (Minor) in Pregnancy for further dietary advice.
- Adequate sleep is important in the first trimester as the need for sleep increases. Fatigue may aggravate symptoms.
- Getting outside for fresh air and exercise is good for relieving physical symptoms and also for improving mental health.
- It is beneficial to have a supportive family member or close friend who is aware of the patient's symptoms and is able to help around the house/ with kids and look out for their general wellbeing.
- It is common for women to suffer from low mood and anxiety and referral for counselling may be appropriate.

First-line pharmacotherapy

Ginger (*Zingiber officinale*)

Ginger is a natural product shown to be safe and effective in reducing nausea in pregnancy by increasing gastro-duodenal motility.[45, 46]

It is a flowering plant and the root is commonly used as a fresh ingredient, dried or as a tea. Pharmaceutical grade ginger can be bought over the counter and the recommended dose is 250mg orally four times per day. Maximum 1g in 24 hours.

Use of ginger as an antiemetic should be avoided in women with a history of miscarriage or antepartum hemorrhage as it may increase the risk of bleeding.[47]

- 500mg capsule orally twice daily

Pyridoxine (*Vitamin B_6*)

The therapeutic mechanism of B_6 for hyperemesis is unknown but it can reduce nausea and is safe to use in pregnancy. There is limited data to support the monotherapy of pyridoxine.[40, 48]

- 25mg tablet: 50mg orally up to four times per day or 200mg at night. Maximum 200mg in 24 hours. Toxicity may occur with prolonged treatment at high doses.

Doxylamine

A sedating antihistamine. Evidence shows that a combination of pyridoxine and doxylamine reduces the severity and duration of NVP in patients with a past history or risk factors for hyperemesis.[41, 49, 50] It must be taken regularly and not used for acute nausea and vomiting. Once NVP has improved a dose reducing regime should be adopted rather than ceasing medication immediately.[51]

- 25mg tablet: Start with 12.5mg (half a tablet) orally at night. Increase as tolerated to 12.5mg morning and midday and 25mg at night.

Note: Use caution when taking sedating antihistamines if working or driving.

Second-line therapy

If nausea and vomiting persists then a second sedating antihistamine should be added. H_1 antagonists are safe for use in pregnancy.[52]

Promethazine

H_1 antagonist but also has a weak dopamine agonist effect.

- 10-25mg tablet orally three to four times per day. Maximum 100mg in 24 hours
- 12.5mg by IM injection three to four times per day

Note*:* Use caution when taking sedating antihistamines if working or driving.

Third- line therapy

Metoclopramide

An antiemetic and gastroprokinetic drug. It is safe for use in pregnancy.[53]

- 5-10mg tablet orally or by IM/IV injection three times per day. Maximum 30mg in 24 hours.
  - Maximum treatment duration of **5 days**[54]
  - **Note:** The TGA has recently updated guidelines on the duration of use of metoclopramide to reduce the risk of potentially serious neurological adverse events, including extrapyramidal disorders and tardive dyskinesia, as well as rare cardiac conduction disorders.[54, 55]

OR

Prochlorperazine

A sedating antihistamine that is effective for treating nausea and vertigo. For short term use only, prolonged use can increase risk tardive dyskinesia.

- 5-10mg tablet orally three times per day
- 12.5mg by IM/IV injection 8 hourly

Note: Use caution when taking sedating antihistamines if working or driving

Fourth-line therapy

Ondansetron

A $5HT_3$ antagonist and an effective antiemetic in HG. It should only be used with protracted vomiting when other therapies have failed to improve symptoms or there has been recurrent hospitalisation.

- 4-8mg wafer or tablet orally or by IV injection 12 hourly. Maximum 16mg in 24 hours.

Note: Large cohort studies on the safety of Ondansetron in pregnancy have provided conflicting results with some showing as increase in oral clefts. Ondansetron should be considered as a non-first line agent for the treatment of nausea and vomiting in pregnancy. An alternative medication should be used in first trimester when possible.

Fifth- line therapy

Steroids should only be used if antiemetic medications and IV hydration have failed. Glucose levels should be monitored for hyperglycemia which has adverse effects on the fetus.

Hydrocortisone

- 100mg IV twice daily followed by oral steroid once tolerated

Prednisolone

- 50mg orally daily for 3 days. 25mg tablet orally daily for 3 days then reduced by 5mg daily as tolerated.
- **Plus** consider histamine H2-receptor antagonists e.g. famotidine, where appropriate.

Note: Most studies describing the use of maternal corticosteroids have not reported an increased risk of major malformations.[40-43] Early reports have suggested an association between corticosteroid use and increased risk of cleft lip and palate.[40, 44] but more recent data have shown no increased risk of orofacial clefts or preterm birth. [43, 45, 50]

IV Fluid therapy

Dehydration can exacerbate nausea, cause headaches, muscle aches and lethargy. Even if urinalysis and UEC do not suggest dehydration; history, examination and clinical judgement should determine whether IV fluids are necessary.

- 0.9% Sodium Chloride 1000mL. Rate as per clinician
- In hypokalaemia oral supplementation is preferred. However if the patient has ECG changes or cannot tolerate oral supplements then KCl can be given IV.

Do **not** exceed 10mmol per hour.

- IV multivitamins may be needed if the patient has a history of malnutrition.

Note: Do **not** administer IV Glucose. If the patient is thiamine deficient this can worsen hyponatraemia and cause Wernicke's encephalopathy. Symptoms include: ataxia, confusion or ophthalmoplegia.[44]

Admission to hospital

- Admit if the woman continues to vomit or remains dehydrated after initial treatment in emergency/ hospital in the home.
- Rehydrate with IV fluids. Where possible, provide warmed fluids and blankets to reduce caloric loss from shivering.
- Correct electrolyte abnormalities.
- Fast the woman until the mode of treatment has been determined. If she is not to be fasted, offer dry crackers, lemonade and ginger beer. Provide advice on oral hygiene as vomiting affects oral health.

- Administer IV anti-emetics and change to oral when tolerated.
- Provide compression stockings and LMWH for thromboembolism prophylaxis.
- Commence a fluid balance chart.
- Do not rush oral intake. It may help to keep the woman fasted or suck ice cubes for the first 24 hours until the anti-emetics become effective.
- Seek dietitian review and provide dietary education.
- Seek clinical psychology and social work review.
- Perform a daily ward urine test for ketones.
- Assess bowel function daily.
- Weigh patient weekly
- Thiamine (Vitamin B1) 100mg once daily to prevent Wernicke's encephalopathy.
- Folic acid and multivitamins.
- H2 antagonist or PPI for prophylaxis/ treatment of gastritis.
- Patients can be discharged once urine is free of ketones, they are tolerating oral fluid and diet and electrolytes have been corrected.
- They must have weekly follow up arranged.

Enteral feeding

- Consider enteral feeding in extreme cases of intractable vomiting that do not respond to any of the above interventions.[56]
- Effectiveness is not well established and a recent trial showed that early enteral feeding had no effect on maternal or neonatal outcomes.[57]
- There is no set criteria but indications are:
    - Significant weight loss or failure to achieve an appropriate gestational weight gain
    - Inability to tolerate oral feeding despite antiemetic treatment
    - Multiple hospital admission for hyperemesis gravidarum
    - Poor nutritional status
    - Significant vitamin deficiencies
    - Persistently abnormal LFTs.

Parenteral feeding

- Total parenteral nutrition is a complex high-risk intervention
- Maternal complications associated with PICC line placement are substantial and the use of PICC lines for the treatment of hyperemesis gravidarum should not be routinely used.[58]
- If a PICC line is used consider VTE prophylaxis
- 100mg IV thiamine twice daily should be given before starting TPN

For consideration

Iron supplementation

Oral iron supplements can worsen the symptoms of nausea and vomiting. Iron absorption increases in the second trimester of pregnancy so unless the woman is anaemic, iron supplements or supplements containing iron can be stopped or swapped for a lower does in the first trimester.[59] Ferrous fumarate (Ferro F tab®) products cause less GI side-effects than ferrous sulphate (Ferro-grad C®). Iron polymaltose (Maltofer®) products have the least GI side-effects but they are expensive and not available through KEMH pharmacy. If oral iron cannot be tolerated due to nausea and vomiting, an iron infusion is available.

Folic acid should be encouraged throughout pregnancy. Taking supplements at bedtime may be better tolerated than in the mornings on an empty stomach.

Gastro-oesophageal reflux and *H. pylori* infection

Gastric reflux is common in pregnancy due to relaxation of the lower oesophageal sphincter and delayed gastric emptying. It can worsen symptoms of NVP.

- Antacids should be used as first line therapy. Aluminium and calcium based products are safe. Bicarbonate products should be avoided as they may cause metabolic alkalosis and maternal and fetal fluid overload.[59]
- If antacids are ineffective, consider H_2 receptor antagonist (e.g. famotidine), where appropriate.
- There is a strong association between *H. pylori* and hyperemesis. Where there is intractable vomiting or reflux, investigation should be considered for *H. pylori* infection.[60]

Quality of life

NVP can have a profound effect on a woman's quality of life. Persistent nausea is debilitating and can lead to feelings of isolation from partners, friends and family. The inability to complete simple daily tasks and look after children may lead to strained relationships at home and being unable to attend work may also lead to further tension and financial stress. Women commonly feel that friends and family lack understanding surrounding the condition and that clinicians are reluctant to treat NVP due to belief that it is psychogenic.

NVP can result in feelings of grief for the pregnancy. Women may also feel guilty that they are unable to eat healthily and that taking medications may harm their baby. It is important for medical practitioners to be empathetic, offer reassurance and explain the condition to the patient and partner and explain that most anti-emetics are safe during pregnancy. Referral to clinical psychology should be considered.

Hyperemesis: Management in the home

Silver Chain home management

Out-patient management for women with uncomplicated hyperemesis requiring:

- Intravenous (IV) hydration
- Oral or IV antiemetic medication

Exclusions:

- Co-existing medical conditions requiring hospital admission.
- Electrolyte abnormalities.
- Uncontrollable nausea and vomiting.

Referrals

- Complete Hospital in the Home Referral Form (on Silver Chain website).
- Copy the UEC and FBC results with the referral.
- You MUST call Silver Chain to confirm the referral request. They are available out of hours.
- Hydrate the woman with IV fluids before transferring them to Hospital in the Home– leave an IV cannula in situ on discharge.
- On the referral form the emergency doctor needs to order:
    - IV fluids with date, time, type and volume of IV fluids required.
    - Antiemetic medication with date, time and dose as per guideline.
    - Women prescribed IV antiemetic medication will need a script.
    - Vials of ondansetron need to be given to the patient to take home if being discharged from KEMH EC.

Follow up

- Women should be discharged with a detailed and individual management plan.
- Patients should be followed up weekly to assess their wellbeing, the effectiveness of their medication regime and for signs of dehydration.
- Antiemetic medications should be provided and continued on discharge. They should be continued for a whole week after nausea and vomiting has stopped.
- If vomiting has continued into the second and third trimester serial scans should be organised to monitor fetal growth.

Ectopic pregnancy

Aim

To provide information on risk factors, symptoms, signs and diagnosis of an ectopic pregnancy.

Key points

1. Ectopic pregnancy should be considered in all pregnant women who present to the EC with abdominal pain or vaginal bleeding.[61]
2. Untreated ectopic pregnancy in a fallopian tube can rupture and cause intra-abdominal bleeding.[62]

Background

Ectopic pregnancy occurs when the developing blastocyst becomes implanted at a site other than the endometrium of the uterine cavity and the most common extra-uterine location is the fallopian tube,[62] which accounts for 91-95% percent of all ectopic pregnancies[63]. Other locations (and rates, out of all ectopic pregnancies) include the caesarean / hysterotomy scar (<6.1%), ovary (1-6%), rudimentary horn of a unicornuate uterus (2%), cervix (<1%), and abdomen (0.9-1.4%).[63] Contemporary management, associated with earlier diagnosis of ectopic pregnancy, involves (where possible) a conservative approach that attempts to save the fallopian tube, rather than salpingectomy.[64, 65]

Ectopic pregnancy is an important cause of maternal morbidity and mortality.[39, 66, 67] Although deaths associated with ectopic pregnancy have declined with earlier and improved diagnosis,[39] the majority (80%)[63] of maternal first trimester deaths, and 10-15% of all pregnancy related deaths, are related to haemorrhage from ectopic pregnancy.[67]

Incidence

Of all reported pregnancies 1 to 2% are ectopic.[61, 66, 68-70] The prevalence of ectopic pregnancy among women who go to an emergency department with first trimester bleeding, pain, or both, ranges from 6 -16%.[71] Over the past three decades, in many countries, the rate of ectopic pregnancy increased by a factor of three to six, and has remained stable.[66]

Risk factors

Some factors have been associated with an increased likelihood of ectopic pregnancy, however risk factors are only found in approximately 50 % of cases.[66]

See Table 1 below for risk factors.

Table 1: Risk Factors

Degree of additional risk	Risk factor	Odds ratio [72]
High	Previous ectopic pregnancy[61, 66]	9.3 - 47
	Previous tubal surgery[61, 66, 67, 73]	6.0 - 11.5
	Failed tubal ligation[61, 66]	3.0 - 139
	Documented tubal damage or pathology[61]	3.5 - 25
	Failed IUCD[61, 66, 67]	1.1 - 45
Moderate	History of infertility[67, 73]	1.1 - 28
	Previous pelvic[66, 67] / genital infection[61, 73]	2.1 - 3.0
	Cigarette smoking[61, 66, 67, 73]	2.3 - 3.9
	Multiple sexual partners[61]	1.4 - 4.8
	Assisted reproductive technology[66, 67]	2.3 - 3.9
Low	Previous pelvic/ abdominal surgery	0.93 - 3.8
	Early age at first sexual intercourse[73]	1.1 – 2.5
	Vaginal douching	1.1 – 3.1

Other factors include increased maternal age,[66, 73] pelvic inflammatory disease[73], and in-utero exposure to diethylstilbestrol.[61, 67]

Symptoms / signs

Symptoms

Clinical manifestations typically appear six to eight weeks after the last normal menstrual period, but can occur later, especially if the pregnancy is not in the fallopian tube. Normal pregnancy discomforts (e.g., breast tenderness, frequent urination, nausea) are often present in addition to the symptoms described below.[1]

The typical triad of symptoms are:

- Bleeding (75% of women[66])
- Abdominal pain (80-90% of women[66])
- Amenorrhoea.[1, 66, 70]

When the woman's pain is disproportionately more severe than her bleeding, then ectopic pregnancy is likely, and if the bleeding is more severe than the pain, then intrauterine pregnancy is more likely.[66]

But

- No symptoms before rupture[67] - in 9%
- A third of women – No clinical signs
- Amenorrhoea is not universal

- Other presenting symptoms could be dizziness/fainting, shoulder tip pain, passage of tissue or gastrointestinal symptoms[61] like diarrhoea or pain on defaecation[1].

Signs

The clinical presentation and natural history of evolution of an ectopic pregnancy are unpredictable. It could range from complete absence of symptoms to shock/collapse. The physical examination is often unremarkable in a woman with a small, un-ruptured ectopic pregnancy.

Findings on physical examination may include[1]:

- Lower abdominal / pelvic / adnexal tenderness or mass[61]
- Cervical motion tenderness[70]
- Pallor / tachycardia / hypotension / shock / collapse / orthostatic hypotension.[1, 61]

Diagnosis

The recommended diagnostic tests include:

- Trans vaginal ultrasound scan alone (TVS)
- Diagnostic algorithms (TVS + quantitative hCG).[70]

The combination of tests with ultrasound scan +/- quantitative hCG estimation will permit a definitive diagnosis in almost all cases at a very early stage of pregnancy, thereby permitting treatment options less invasive than surgical excision.[74, 75] Although progesterone concentrations can be used to predict a viable intrauterine or failed pregnancy, they do not assist clinicians to locate a pregnancy of unknown origin.[66, 70] Currently, other diagnostic tests (e.g. Doppler or 3D ultrasound, curettage, laparoscopy, culdocentesis, magnetic resonance imaging) have not demonstrated improvement in current diagnosis sensitivity or specificity, and do not provide additional clinically useful information.[66]

Ultrasound scan alone

Transvaginal ultrasound examination (TVS) is the most useful and primary investigation for determining the location of a pregnancy.[61] If an ectopic pregnancy is present, the use of TVS should visualise 73-93% of cases.[66] Visualisation of an adnexal mass separate from the ovary, on TVS, has been shown to have high sensitivity (84.4%) and specificity (98.9%) for diagnosing ectopic pregnancy.[61]

The most appropriate diagnostic criteria include a combination of[66]:

- Positive pregnancy test
- Empty intrauterine cavity
- Complex adnexal mass +/- extrauterine gestation sac.[66]

Other ultrasound features that may be suggestive of ectopic pregnancy are[66]:

- Bagel sign (a fluid filled adnexal mass surrounded by a hyperechogenic ring)
- Pseudo sac (collection of variable amount of fluid within the uterine cavity). They tend to be located in the middle of the uterine cavity and conform to the contour of the cavity unlike an IUGS embedded in the decidua.

- Pelvic free fluid.[66]

Note: If the woman declines the TVS, offer a trans-abdominal ultrasound scan and explain how findings will be limited, with the low specificity of the test making an ectopic diagnosis difficult.[1]

Diagnostic algorithms (TVS + quantitative hCG)

Ultrasound is inconclusive in 8-31% of women, in whom one or more measurements of hCG concentration is necessary to guide the assessment.[61]

- TVS + discriminatory zone hCG titre
- TVS + serial hCG +/- discriminatory zone hCG.

Discriminatory zone hCG – 1500 IU/L

It is defined as the serum hCG level above which a gestational sac should be visualised by ultrasound examination if an intrauterine pregnancy is present.[66] At KEMH, this serum hCG level is 1500 with TVS (the level is higher [6500 IU/L] with transabdominal ultrasound). The absence of an IUGS at hCG concentrations above the discriminatory zone strongly suggests an ectopic pregnancy.[66]

hCG above the discriminatory zone (>1500 IU/L)

If no intra or extra uterine pregnancy is visualised on ultrasound scan in the Emergency Department/ EPAS clinic, a Consultant review or a formal USS in the department should be organised.

The diagnosis of ectopic pregnancy is less certain if no complex adnexal mass can be visualised, since there is variability in the level of expertise among sonographers. Furthermore, a serum hCG greater than 1500 IU/L without visualisation of intrauterine or extra uterine pathology may represent a multiple gestation, since there is no proven discriminatory level for multiple gestations. For these reasons, in the absence of features suggestive of ectopic pregnancy on formal USS, the next step is to repeat the TVS examination and hCG concentration 48 hrs later in EPAS.

- If an intrauterine pregnancy is still not observed on TVS, then the pregnancy is abnormal.
- A rise or plateauing in the serum hCG concentration in the absence of ultrasound evidence of intrauterine pregnancy is diagnostic of ectopic pregnancy.
- A falling hCG concentration is most consistent with a failed pregnancy (intrauterine or extra uterine). Expectant management will be an option if the woman is stable, there is no fetal cardiac activity, and the levels are dropping steadily[63] (ideally less than 50% of its initial level within seven days). These women should be observed closely for rupture or clinical deterioration.[63] Weekly hCG concentrations should be monitored until the result is 5 or less for pregnancy.

hCG below the discriminatory zone

A negative ultrasound examination at hCG levels below the discriminatory zone (1500IU/L) is consistent with an early viable intrauterine pregnancy, an ectopic pregnancy, or a nonviable intrauterine pregnancy. A serum hCG concentration less

than 1500 IU/L should be followed by repetition of hCG in 48 hrs to follow the rate of rise (99% will have a 53% increase in 2 days, with 66% doubling).

- If the hCG rises normally, then a TVS should be performed when hCG reaches / expected to reach the discriminatory zone[66]
- A falling hCG concentration is most consistent with a failed pregnancy (intrauterine or extra uterine). Expectant management will be an option if the woman is stable and the levels are dropping steadily[63] (ideally less than 50% of its initial level within seven days). Weekly hCG concentrations should be monitored until the result is 5 or less for pregnancy.

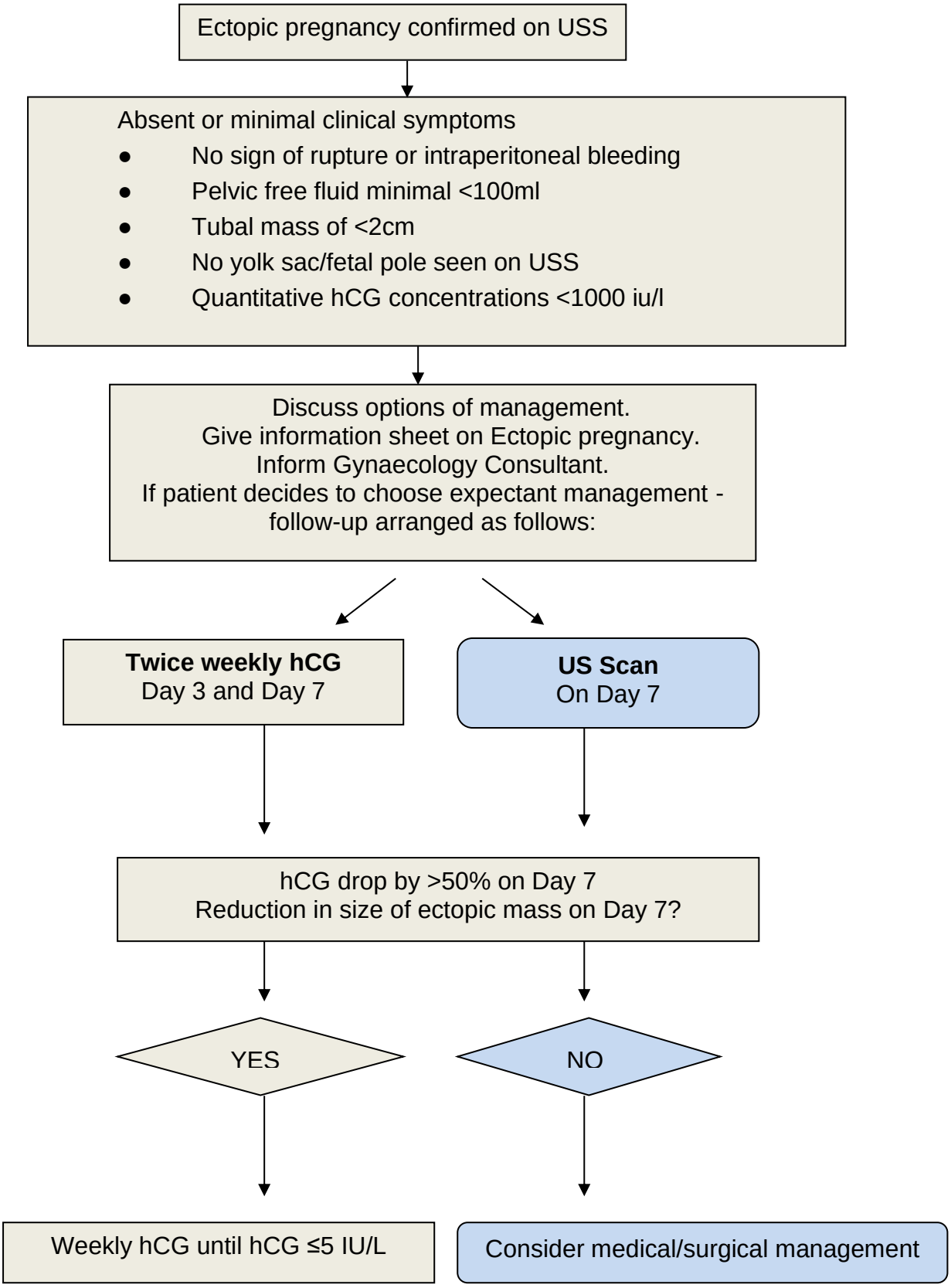
Serial hCG

More than one measurement of hCG is needed if TVS + Discriminatory zone hCG is not conclusive. Studies in viable intrauterine pregnancies have reported the following changes in serum hCG[74]:

- The mean doubling time for serum hCG ranges from 1.4 to 2.1 days in early pregnancy.[70]
- In 85% of viable intrauterine pregnancies, the hCG concentration rises by at least 66% every 48 hours during the first 40 days of pregnancy; only 15% of viable pregnancies have a rate of rise less than this threshold.[74]
- The slowest recorded rise over 48 hrs associated with a viable intrauterine pregnancy was 53%.[66, 70, 74]

Ectopic pregnancy: Expectant management

Flowchart



Background

Ectopic pregnancy is a gynaecologic emergency usually requiring urgent treatment. However, in a selected small number of cases in which the risk of tubal rupture is minimal, expectant management may be appropriate after discussion with the gynaecology consultant on call.

Historically, observation studies reported success rates of 48-100%[76]. The criteria between these studies varied considerably. A recent study has reported success rates from 77% when women were treated expectantly, compared with medical management[76]. The success rates of expectant management have been reported to be inversely related to lower hCG levels at diagnosis of ectopic pregnancy. Success rates when the initial hCG level was <1000mIU/ml has been found to be between 80-90% by two different studies. In addition, a rapidly decreasing hCG level appears to predict a favourable outcome[77 37]. Higher hCG levels have been related to lower success rates with expectant management, with one study reporting only 21% of cases were successful when the initial hCG was>1500mIU/ml[78, 79]. Other studies, that focused on declining hCG levels rather than an absolute value, found that, in 25% of ectopic pregnancies with declining hCG levels, almost 70% will resolve without any treatment[77]. Fertility rates have not been found to be significantly different between surgical, medical and expectant management[80].

An initial hCG level of <1000mIU/ml has been demonstrated to be the best single factor in predicting a successful outcome with expectant management[78]. Trans-vaginal ultrasound has also been found to be a useful tool in predicting success[81]. Cacciatore et al found trans-vaginal ultrasound had an 84% sensitivity and 100% specificity in predicting the resolution of ectopic pregnancy by serial ultrasounds demonstrating decreasing ectopic size.[77] The lack of an identifiable extra-uterine gestational sac on trans-vaginal ultrasound increased the odds of a spontaneous resolution by 5.6 times[37]. Expectant management for atypical ectopic gestations is not recommended due to a lack of available literature.[77]

The use of more stringent selection criteria results in an increase in the efficacy of expectant management.[79] In expectant management, no treatment is given and the patient is followed twice weekly with serial hCG measurements and weekly by trans-vaginal examinations to ensure a rapidly decreasing hCG level (ideally less than 50% of its initial level within seven days) and a reduction in the size of adnexal mass by seven days.[77] Thereafter, weekly hCG measurement is advised until serum hCG levels are ≤5 IU/L.

Inclusion criteria for expectant management

- Absent or minimal clinical symptoms
- No sign of rupture or intra-peritoneal bleeding
- Pelvic free fluid minimal (<100ml)
- Tubal mass of <3cm
- No yolk sac/fetal pole seen
- Quantitative hCG concentrations <1000 iu/l and declining progressively

The risk of rupture in a woman with an ectopic exists until the hCG level has fallen to

≤5 IU/L. It often involves multiple visits for follow up. Both the physician as well as the patient must be well motivated to accept the long recovery time.

Contraindications

Expectant treatment should not be attempted or should be abandoned in women with known or suspected ectopic pregnancy with the following characteristics:

- Haemodynamically unstable
- Signs of impending or ongoing ectopic mass rupture (i.e. severe or persistent abdominal pain or >300 ml of free peritoneal fluid, or fluid outside the pelvic cavity)
- An hCG that is greater than 1000 IU/ml, is increasing, or is not declining
- The woman is unwilling or unable to comply with monitoring
- The woman lives more than 30 minutes away from the hospital

Follow-up

- Twice weekly serum hCG measurements

(Expect to have a level less than 50% of its initial level within seven days).

- Thereafter, weekly hCG measurements until the levels are ≤ 5 IU/L
- Weekly Trans-vaginal Scans

(Expect to have a reduction in the size of adnexal mass by seven days)

- When the expected results (as mentioned above) are not achieved in a week, consider medical/surgical management.

Ectopic pregnancy: Medical management

Aim

To outline the medical management of tubal ectopic pregnancy.

Background

The routine use of an ultrasound scan for women, who present with early pregnancy symptoms like pain or bleeding, facilitates an early diagnosis of ectopic pregnancy and medical treatment can be administered in most cases. Methotrexate is the drug used for medical management of ectopic pregnancy at King Edward Memorial Hospital. Methotrexate is a folic acid antagonist (anti-metabolite) which prevents the growth of rapidly dividing cells including trophoblasts and fetal cells by interfering with DNA synthesis. The dose of methotrexate used to treat ectopic pregnancy is relatively low, safe and well tolerated[82]. In some protocols folinic acid (Leucovorin Calcium®), is given to bypass the metabolic block induced by methotrexate and thus rescue the normal cells from toxicity [83].

Candidates for medical treatment

Inclusion criteria [62, 84]

- Haemodynamically stable.
- Indications
  - Unruptured tubal or other ectopic pregnancy.
  - Persistent trophoblast after salpingotomy.
- Serum quantitative hCG < 5000 IU/L
- Size of ectopic mass < 3.5cm
- Normal LFT's, U & E's, and FBC[62]
- Patient compliance for regular follow ups (average follow up 35 days) [62]

Exclusion criteria [62, 69, 84, 85]

- Clinically unstable
- Severe or persistent abdominal pain or evidence of significant haemoperitoneum on ultrasound scan (>300mL)
- The presence of cardiac activity in an ectopic pregnancy
- Coexistent viable intrauterine pregnancy (heterotopic pregnancy)
- Ectopic mass >3.5 cm (Not an independent predictor of treatment success)
- Non-compliant patient / patient living far away from the hospital
- Clinically significant renal, hepatic or haematological impairment
- Known hypersensitivity to methotrexate
- Breast feeding
- Immunodeficiency / concurrent use of corticosteroids

Management

Pre-treatment checks

- Discuss the options for treatment – expectant / medical / surgical – provide the woman with information leaflets.
- FBC, U&Es, LFTs, hCG, Group & Hold
- Satisfy inclusion and exclusion criteria
- Obtain written consent
- Calculate the Patient Body Surface Area from height and weight (Refer to chart 1)
- Prescribe methotrexate as per the dosage regimen (Refer to chart 2)

Methotrexate administration

- **Methotrexate is given as an outpatient treatment. Patients do not need to be admitted to a ward after methotrexate administration for observation.**
- **WNHS Guideline: Pharmacy: Cytotoxic Agents: Safe Handling of must be followed when handling methotrexate.**

1. Methotrexate is provided by pharmacy as patient and dose specific prefilled syringes
2. Methotrexate should be ordered the day prior to administration from pharmacy before 9.30 am.
3. For out of hours and weekend use, there are methotrexate prefilled syringes. These syringes are available in the Emergency department, Ward 6, and Theatre. It may be acceptable to round the calculated patient dose up or down to the nearest 5mg.

Methotrexate prefilled syringes	
5mg/0.2mL	Only on EC
10mg/0.4mL	Only on EC
50mg/0.5mL	
75mg/0.75mL	
80mg/0.8mL	Only on EC
100mg/1mL	

4. Intramuscular methotrexate administration is the predominant and preferred route for treatment of tubal pregnancy although it can also be given by direct local injection into the ectopic pregnancy sac transvaginally ultrasound guided or laparoscopically [84].
5. Methotrexate is given intramuscularly in the buttock or lateral thigh. The empty syringe or needle should be placed in a separate purple Sharps Safe, labelled “Cytotoxic waste for special incineration”.
6. Monitor the woman in the EC for 30 minutes for the immediate hypersensitivity reactions. Check for any local reaction. If local reaction is noted consider anti-histamine or steroid cream (very rare).
    - Side effects usually present 2-7 days after the administration of the drug.

Dosage regimen

- In this commonly used protocol, Day 1 is the day of methotrexate treatment.
- On Days 4 and 7, a serum hCG concentration is checked and if the decrease in hCG is less than 15 percent between Days 4 and 7, a second dose of methotrexate is administered.
- A 15% decrease in serum hCG between day 4 and day 7 is a very good indicator of the likely success of methotrexate[86].

Single/ variable dose regimen:

Day	Management
1	Serum hCG, FBC, U&Es, LFTs, G&H
1	Intramuscular methotrexate 50 mg/m^2
4	Serum hCG
7	Serum hCG, FBC, U&Es, LFT If hCG decrease > 15 % day 4-7, repeat hCG weekly 2nd dose of methotrexate 50mg/m^2 if hCG decrease < 15 % day 4-7 Repeat FBC and AST if further methotrexate is required [84]
14	Serum hCG, FBC, U&Es, LFT If hCG decrease > 15 % day 7-14, repeat hCG weekly 3rd dose of methotrexate 50mg/m^2 if hCG decrease < 15% day 7-14 Repeat FBC and AST if further methotrexate is required [84]
Monitoring	The hCG is followed weekly until the level is ≤5 mIU/L.
Laparoscopy: • If 3 doses have been given and there is a <15% hCG decline from day 14 to 21. • If severe abdominal pain or signs suggestive of tubal rupture	

Post treatment management

- hCG – weekly serial hCG follow up needed until ≤5 IU/L
- USS – There appears to be no clinical benefit from routine serial ultrasound examinations[11]. After treatment, the ectopic pregnancy is often noted to increase in size and may persist for weeks on serial USS examinations. This could represent a haematoma, rather than persistent trophoblastic tissue, and is not predictive of treatment failure. However, USS evaluation for peritoneal free fluid is indicated for women with severe abdominal/ pelvic pain.[84]
- Advise the woman to:
  - Avoid vaginal intercourse until hCG is undetectable
  - Avoid pregnancy for three months due to the theoretical risk of teratogenicity with methotrexate
  - Avoid pelvic exams during surveillance of methotrexate therapy due to the risk of tubal rupture
  - Avoid sun exposure to limit risk of methotrexate dermatitis
  - Avoid foods and vitamins containing folic acid

- Avoid nonsteroidal anti-inflammatory drugs, as the interaction with methotrexate may cause bone marrow suppression, aplastic anaemia, or gastrointestinal toxicity. Paracetamol with or without codeine is recommended for pain relief

Efficacy

- Overall success is 88-90% with a single / variable dose regimen.
- 14% of patients on single / variable dose regimen will require a second dose and less than 1% of women will require more than two doses.[12]
- When evaluating treatment, studies have found that a decline in hCG on day 0-4 is predictive of an 88% success rate in medical management. This can be used as a good biomarker test for predicting successful treatment. A rise in hCG on day 0-4 is a less reliable indicator, indicating that there is a 42% probability of treatment success. [87]

Side effects

Drug related

Adverse reactions to methotrexate are usually mild and self-limited. Approximately 30 % of patients in the single dose protocol will have side effects[12]. The most common are stomatitis and conjunctivitis. Rare side effects include gastritis, enteritis, dermatitis, pneumonitis, alopecia, elevated liver enzymes, and bone marrow suppression. All of these side effects resolve as methotrexate exposure wanes.[83]

Separation pain

Up to 75% of patients may complain of pain on days 2-7 after receiving the medication[14]. The pain may be due to tubal miscarriage or tubal distension from haematoma formation and can usually be managed with simple analgesia. Nonsteroidal anti-inflammatory drugs should be avoided because a clinically significant drug interaction with methotrexate may occur in some patients taking both drugs.

Occasionally pain may be severe, but women with severe pain who are haemodynamically stable often do not need surgical intervention.[88] They may be further evaluated with transvaginal ultrasonography. Findings suggestive of significant (>300mL) haemoperitoneum should raise clinical suspicion of tubal rupture. Women with severe pain should be closely observed for haemodynamic changes which may accompany a tubal rupture. If tubal rupture is suspected, immediate surgery is required.

Subsequent reproductive performance

- There is no evidence of adverse effects of methotrexate treatment of ectopic pregnancy on future pregnancies[82, 85].
- Treatment with methotrexate does not appear to compromise ovarian function[80].
- Ectopic pregnancy happens as a result of abnormal tubal function due to clinical or subclinical endosalpingitis which is bilateral and irreversible. Hence there is a risk of recurrent ectopic pregnancy and infertility for women who have had an ectopic pregnancy irrespective of the type of treatment they received to treat their

first ectopic pregnancy. This highlights the need for women with a history of ectopic pregnancy to have fertility follow up if they plan to conceive.[82]

- The incidence of recurrent ectopic pregnancy is approximately 15% and rises to 30% following two ectopic pregnancies. The risk of recurrence appears to be the same for both medical and surgical treatments.[80]
- Observational studies have shown a subsequent intrauterine pregnancy rate of 58 – 89 % [89].

Single/variable versus multiple dose regimen[62]

- Similar success rates for single/variable dose and multiple dose regimens.
- More side effects/ less patient satisfaction with multiple dose regimens.
- No difference in future tubal patency/intrauterine pregnancy/or recurrent ectopic
- Single/ variable dose regimen is less expensive, needs less intensive monitoring and does not require folinic acid rescue.

Medical versus surgical treatment[62]

- Approximately 35% of women with ectopic pregnancy will satisfy the criteria for medical management[18]
- In these women, systemic treatment with variable dose methotrexate regimen is as effective as laparoscopic salpingotomy (82 – 95% MTX Vs 80-92% Salpingotomy).
- Similar Post treatment tubal patency and intrauterine pregnancy rates.
- Similar risk of recurrent ectopic pregnancy.
- More side effects with medical treatment especially so with multiple dose regimen.
- The period of post treatment monitoring is longer for medical treatment.

*If surgical treatment is required at a later time RhD immunoglobulin for Rhesus negative women is recommended to be given. Evidence has found it is not required for medical or expectant management.[1]

In patients who are eligible for either medical or surgical treatment, the choice of therapy should be guided by the patient's preference after a detailed discussion of risks, benefits, outcomes, and monitoring requirements of both medical and surgical approaches.

Chart 1: Body surface area

Weight (kg)	Height (cm)													
	70	80	90	100	110	120	130	140	150	160	170	180	190	200
10	0.42	0.46	0.50	0.54										
15	0.49	0.54	0.59	0.64	0.69	0.73	0.77							
20	0.56	0.62	0.67	0.72	0.78	0.83	0.87	0.92	0.97					
30	0.66	0.73	0.80	0.86	0.92	0.98	1.04	1.10	1.15	1.21	1.26			
40					1.04	1.11	1.17	1.24	1.30	1.37	1.43	1.49		
50							1.29	1.36	1.43	1.50	1.57	1.63	1.70	
60							1.40	1.47	1.55	1.62	1.69	1.77	1.84	1.91
70								1.57	1.65	1.73	1.81	1.89	1.96	2.04
80									1.75	1.83	1.92	2.00	2.08	2.15
90										1.93	2.01	2.10	2.18	2.27
100										2.02	2.11	2.20	2.28	2.37
110											2.19	2.29	2.38	2.47
120											2.28	2.37	2.47	2.56
130											2.35	2.45	2.55	2.65

Taken from: Du Bois,D and Du Bois, E. A formula to estimate the appropriate surface area if height and weight be known. Arch Int Med 1916; vol17:863-871.

Chart 2: Dose of methotrexate in milligrams

(50MG/M^2 Body Surface Area)

Weight (kg)	Height (cm)												
	70	80	90	100	110	120	130	140	150	160	170	180	190
10	21	23	25	27									
15	24.5	27	29.5	32	34.5	36.5	38.5						
20	28	31	33.5	36	39	41.5	43.5	46	48.5				
30	33	36.5	40	43	46	49	52	55	57.5	60.5	63		
40					52	55.5	58.5	62	65	68.5	71.5	74.5	
50							64.5	68	71.5	75	78.5	81.5	85
60							70	73.5	77.5	81	84.5	88.5	92
70								78.5	82.5	86.5	90.5	94.5	98
80									87.5	91.5	96	100	104
90										96.5	100.5	105	109
100										101	105.5	110	114
110											109.5	114.5	119
120											114	118.5	123.5
130											117.5	122.5	127.5

Ectopic pregnancy: Surgical management

Aim

- Outline the surgical management of tubal ectopic pregnancy.

Background

Surgical management remains the first line treatment in ectopic pregnancy and in Caesarean Scar pregnancy (see next section) when a patient's condition is unstable. It should also be considered where there are contraindications to medical and expectant management options. Open laparotomy is indicated in situations where the patient is haemodynamically unstable or the size of the ectopic pregnancy indicates laparotomy is required. Laparoscopic surgery is preferred with the advantage of less adhesion formation along with shorter hospital stay; lower cost, less blood loss and lower analgesia requirements[37, 90]. Haemoperitoneum is not a contraindication for performing laparoscopic surgery[37, 90]. There is limited research demonstrating a proven significant advantage of salpingotomy compared to salpingectomy. Risks associated with salpingotomy include persistent trophoblast and a small risk of bleeding postoperatively[62]. In the presence of a healthy contra lateral tube there is no clear evidence that salpingotomy should be used in preference to salpingectomy[37]. When there is a desire for future fertility and the presence of contra lateral disease laparoscopic salpingotomy should be considered[37]. Mandatory follow up with hCG serial monitoring is required where salpingotomy has been performed[37]. Fertility rates have been found to be comparable between salpingotomy or salpingectomy in the situation of a normal contra lateral tube[80]. Pregnancy rates following surgery or methotrexate treatment have not been found to be significantly different[80].

Key points

1. Surgical treatment becomes a necessity when a patient is:
    - Haemodynamically unstable
    - Confirmed impending or ongoing rupture of the ectopic pregnancy
    - Co-existing intrauterine pregnancy
    - Contraindication of medical treatment
2. In a patient who is haemodynamically unstable immediate resuscitation and the surgical procedure which prevents further blood loss quickly should be used [37]- usually this involves a laparotomy. **Transfer to theatre should not be delayed by attempts to establish a normal circulating plasma volume.**
3. A laparoscopic approach to the surgical management of tubal pregnancy in the haemodynamically stable patient is preferable. Experienced operators may be able to safely manage women laparoscopically - even those with a large haemoperitoneum.
4. Salpingectomy is the standard procedure. However laparoscopic salpingostomy should be considered when managing tubal pregnancy in the

presence of contra lateral tubal disease and the desire for future fertility[37]. Follow up for salpingotomy should include mandatory serial hCG.[62]

Follow up

1. All patients investigated for possible ectopic pregnancy should be advised to seek medical attention immediately if symptoms change**.**
2. Negative laparoscopies should be followed up with serial serum hCG.
3. All women treated for ectopic pregnancy should be counselled regarding the risk of recurrence.
4. Ensure Anti D immunoglobulin is given to all non- sensitised women who are Rhesus Negative[37].
5. If histology shows no chorionic villi or fetal tissue, the case should be reviewed by the consultant and the patient advised for follow up.
6. Following conservative surgery, hCG should be monitored weekly (this may take up to 10 weeks to return to normal). If hCG is rising, request ultrasound scan and consider further treatment (either laparotomy or methotrexate).
7. Refer to Diagnosis of Ectopic Pregnancy for hCG screening levels.

Ectopic pregnancy: Caesarean section scar

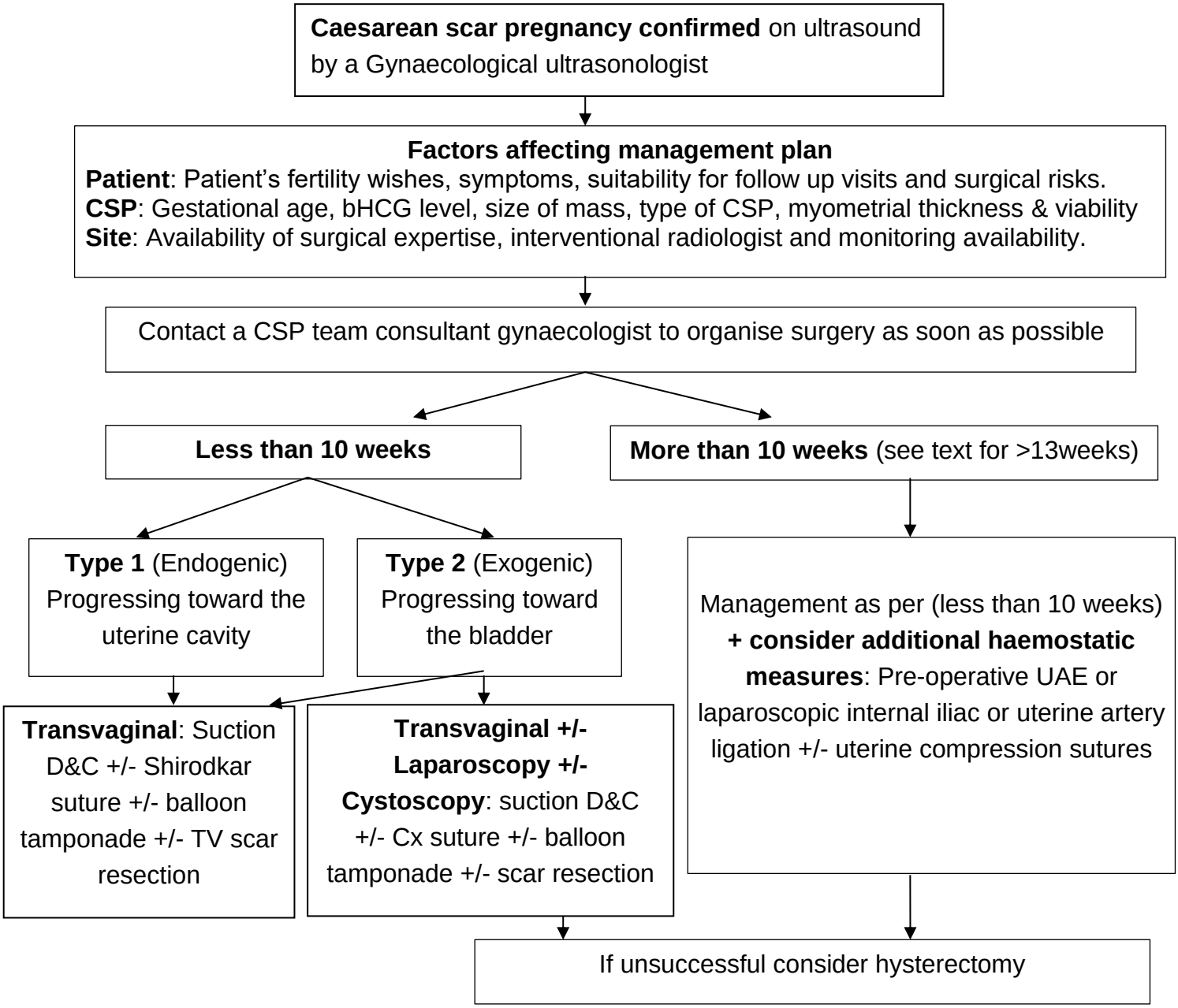
Key points

1. Caesarean scar pregnancy (CSP) exposes women to a high risk of life threatening haemorrhage. The risk increases as the gestational age increases.
2. Avoid delay to minimise surgical morbidity/mortality.
3. Establish an accurate diagnosis early (see Ultrasound diagnostic criteria below). Ultrasounds performed external to KEMH may need to be confirmed by KEMH ultrasound department.
4. On determining the diagnosis of CSP, discussion between a Gynaecological ultrasonologist and a gynaecologist in the CSP Team is desirable.
5. Expectant management is not recommended as it is associated with a high complication rate including placenta accreta spectrum and hysterectomy.
6. Surgical management is preferable to medical as it has a higher success rate and a lower complication rate.
7. Medical management (methotrexate) alone is associated with a low success rate (75% in the literature but only 53-62% in the last two KEMH reviews) and prolonged follow up (median 15.5 weeks, range 6-24 weeks in KEMH). Local methotrexate has a 65% success rate with a 13% complication rate but the success rate increases to 84% with similar complication rate when it is administered locally in conjunction with KCl injection and needle aspiration.
8. Dilatation and curettage (D&C) alone has a 48-72% success rate and ideally should be performed in conjunction with ultrasound and in combination with other measures (Shirodkar suture, intrauterine balloon, UAE, misoprostol, oxytocics) which have been shown to increase the success rate up to >95%.
9. For early gestation up to 10 weeks, a variety of surgical techniques with or without haemostatic measures have been reported with >90% success rates (see CSP Flowchart below).
10. For gestations 10-13 weeks, surgical management without additional haemostatic measures is likely to be associated with higher risk of bleeding.
11. For patients above 13 weeks of gestational age, the risk of surgical intervention must be balanced with the risks of allowing the pregnancy to continue with the aim of reaching a potentially viable gestational age. Women with such pregnancies should have a care package put in place for morbidly adherent placenta, with a plan for emergency intervention should haemorrhage or rupture occur.
12. Surgical options are dependent on the type and gestation of CSP (CSP Flowchart). In KEMH, the most common and successful management for early gestations is suction D&C in combination with Shirodkar absorbable cervical cerclage. For later gestations, consider additional haemostatic measures e.g. pre-op Uterine Artery Embolisation (see Checklist of arrangements for arterial embolisation below for arrangements), or

laparoscopic ligation of uterine +/- internal iliac arteries or uterine compression sutures.

13. Consent for surgery to be performed by a senior doctor (include the risk of laparoscopy, laparotomy and hysterectomy).
14. For a list of all doctors in the CSP Team- See WA Health global email 'KEMH, Caesarean Scar Pregnancy Team' or CSP Team list at end of this chapter.

CSP flowchart



Ultrasound diagnostic criteria

1. Empty uterine cavity and closed, empty cervical canal.
2. Gestational sac or solid mass of trophoblast located anteriorly at the level of the internal os or embedded at the site of the previous lower uterine segment caesarean scar.
3. Thin or absent myometrium between the gestational sac and the bladder.
4. Presence of functional trophoblast/placental circulation on colour Doppler.
5. Negative sliding organ sign

Ideal ultrasound report information

1. Size of gestational sac.
2. Size of whole mass inclusive of sac and surrounding trophoblast.
3. Presence of yolk sac, fetal pole (including cardiac activity) and CRL.
4. Thickness of myometrium between trophoblast and bladder.
5. Degree of distortion to anterior serosal contour.
6. Communication with the uterine cavity.
7. Degree of peri-trophoblastic vascularity.

Checklist of arrangements for arterial embolisation

1. Ring SCGH and ask for the interventional radiologist- SCGH direct line is 6001.
2. Get a time for the procedure from the interventional radiologist.
3. Inform the patient and explain the embolisation procedure. Ensure that she consents- formal consent form will be conducted at SCGH.
4. Ensure patient is stable for transfer- have current FBC, coagulation, Group and Hold and consider sending patient with anaesthetic escort, obstetric escort (Senior Registrar (SR) /Registrar) with blood if concerns about bleeding.
5. An obstetric medical escort should always go with the patient (generally Registrar or SR), even when the patient is stable.
6. Inform Anaesthetic Consultant at KEMH of the transfer.
7. Inform KEMH Hospital Clinical Manager of the transfer.
8. Inform the SCGH surgeons on-call of the transfer:
    - They may not need to be involved as the patient routinely returns to KEMH after the procedure. However if the patient does require admission, the patient will be admitted at SCGH under the general surgeons so they need to know.
9. Inform the Consultant in the Emergency Department (ED) at SCGH that the patient will be coming through their ED (so the triage person is aware). The

patient will not stop in ED but the department needs to know they will be coming through.

10. Ensure ASCU staff have the patient prepared for transfer with a nurse escort.
11. Generally the notes will go with the patient.
12. Write a referral letter to the interventional radiologists which is comprehensive in case the patient needs admission- put nominated Consultant at KEMH to be contacted should there be issues with the patient and a contact number.
13. Write a radiology form for arterial embolisation.
14. Get a taxi voucher from the Nurse Manager so that the escort and also the obstetric (plus or minus the anaesthetic personnel) can return to KEMH.
15. Call the ambulance as CAT 1 (or delegate the task). It is vital that it is delegated as a CAT 1 transfer, otherwise the ambulance will not come promptly- thereby will be in a queue which could be long and the radiologist impacted by delayed care when the patient does not arrive promptly.
16. Once you have called a CAT 1 ambulance, be aware they will arrive in 5-10 minutes so be ready to go.

CSP Team contacts

The list below is current as at 22/08/2023. Refer to the list in the WA Health global email 'KEMH, Caesarean Scar Pregnancy Team' for most up to date list.

- Dr Winston Almeida
- Dr Jennifer Beale
- Dr Alexandra Cottam
- Dr Govardhan Das
- Dr Manisha Doohan
- Dr Mathias Epee-Bekima
- Dr Louise Hobson
- Dr Heidi Hughes-D'Aeth
- Dr Panos Maouris
- Dr Lauren Megaw
- Dr Chhaya Mehrotra
- Dr Kristy Milward
- Dr Jenni Pontre
- Dr Nic Tsokos
- Dr Danelle Ward
- Dr Mini Zachariah

Miscarriage

Guidelines relating to 'Miscarriage' are available internally via Department of Health WA, HealthPoint; see Restricted Area Guidelines [Intranet only].

Early Pregnancy Assessment Service (EPAS)

See webpage EPAS Referrals.

Children 13 years and under: Products of conception

(Following pregnancy loss- Including miscarriage or termination of pregnancy)

See WNHS Obstetrics and Gynaecology guideline: Pregnancy Loss in Children 13 and Under: Management of Products of Conception

Related resources
Australian Government, Australian Institute of Family Studies: Responding to children and young people's disclosures of abuse (Practitioners resource) (2015)

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Additional resources

- Department of Health (2020) Clinical Practice Guidelines: Pregnancy Care. Canberra: Australian Government Department of Health. (refer to Section 54- Nausea and vomiting)
- SANDS Miscarriage, stillbirth and newborn death support.
- Women's Hospitals Australasia. (2008). Management of Early Pregnancy Loss: Clinical Practice Guideline.

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Related legislation and policies

Legislation –

- *Children and Community Services Act 2004* Section 124B [Guideline: POC <13 years]
- *Criminal Code Act Compilation Act 1913* Sections 320-321 [Guideline: POC <13 years]
- *Criminal Investigation Act 2006* Section 42 [Guideline: POC <13 years]

Related WNHS policies, procedures and guidelines

WNHS Clinical Guidelines:

- Obstetrics and Gynaecology:
  - Blood Group Management and Clinically Significant Antibodies (RhD Negative & RhD Positive Women)
  - Discomforts: Symptoms or Disorders (Minor) of Pregnancy
  - Sexually Transmitted Infections
  - [Restricted Area Guideline]: Miscarriage: Management [HealthPoint- Intranet only]
- Pharmacy:
  - Cytotoxic Agents: Safe Handling of
  - Medications A-Z: Doxylamine; Famotidine; Folic acid; Hydrocortisone; Methotrexate; Metoclopramide; Ondansetron; Prednisolone; Prochlorperazine; Promethazine; Pyridoxine; Thiamine (Monophosphothiamine)

WNHS Consumer Brochures :

- Pregnancy Loss: In the First 13 Weeks of Pregnancy
- Pregnancy Loss: In the Second and Third Trimester
- Bleeding and/or Pain in Early Pregnancy
- Morning Sickness

WNHS webpage: EPAS Referrals

Keywords:	miscarriage, ectopic, amenorrhoea, pregnancy loss, early pregnancy complications, early pregnancy bleeding, early pregnancy pain, pregnancy bleeding algorithm, missed miscarriage, ectopic pregnancy, early gestational sac, viability of pregnancy, yolk sac, EC, Emergency Centre, referral from GP, molar pregnancy, partial molar, complete molar, invasive mole, malignant trophoblast disease, gestational trophoblastic disease, GTD, gestational choriocarcinoma, placental site trophoblastic tumours, postpartum choriocarcinoma, infantile choriocarcinoma, neoplasia, chorionic villi, products of conception, POC, evacuation of uterus, under 13 years, child pregnancy, hyperemesis, hyperemesis gravidarum, vomiting in pregnancy, morning sickness, referral to silver chain, antiemetics, βHCG, beta HcG, hCG, methotrexate, quantitative hcg, CS scar pregnancy, CSP		
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Endorsed by:	Obstetrics and Gynaecology Directorate Management Committee (Approved OOS by Obstetric Medical Co-director & Nurse Midwife Co-director)	Date:	03/03/2020
NSQHS Standards (v2) applicable:	☒ 1: Clinical Governance ☐ 2: Partnering with Consumers ☐ 3: Preventing and Controlling Healthcare Associated Infection ☒ 4: Medication Safety	☐ 5: Comprehensive Care ☒ 6: Communicating for Safety ☐ 7: Blood Management ☒ 8: Recognising and Responding to Acute Deterioration	
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