Clinical Practice Guideline	**Management of Ectopic Pregnancy**
Peninsula Care Goal	**Safe**

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Target Audience

Obstetrics and Gynaecology HMOs & Registrars
GP Obstetricians working in EPPAS
Obstetrics & Gynaecology Consultants
ED Medical Staff
Registered Nurses
Ultra-sonographers
Pharmacy Staff

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Purpose.

1. To provide information on risk factors, symptoms, signs and diagnosis of ectopic pregnancy.
2. To support clinicians in the management of women who have a diagnosed ectopic pregnancy.
3. To aid consistent information sharing and counselling of women on management options for ectopic pregnancy.
4. To aid clinicians in making decisions about management of Pregnancy of Unknown Location

Guideline.

This guideline reviews recent information related to the diagnosis and clinical management of women with PUL and ectopic pregnancy, defined as a pregnancy located outside of the uterine cavity.

Please refer to the following appendices as required:

Table 1 Risk factors for ectopic pregnancy
Table 2 Success rates of MTX therapy for ectopic pregnancy based on initial β-hCG level.
Table 3 Treatment & follow up schedule for single dose MTX
Table 4 Multi-dose MTX regime for non-tubal ectopic pregnancies
Table 5 Rare types of non-tubal ectopic pregnancies
Appendix A Flow chart: Investigation and Differential Diagnosis for Early Pregnancy Bleeding and Pain in EPPAS.
Appendix B Flow chart: Investigation and Management of Pregnancy of Unknown Location
Appendix C Flow chart: Expectant Management of Ectopic Pregnancy
Appendix D Flowchart Surgical Management of Ectopic Pregnancy

Definitions Used In this Guideline

- **Early pregnancy:** pregnancy up to 12+0 weeks of pregnancy

- **Expectant management:** A management approach in which treatment (pharmacological or surgical) is not administered, with the aim of monitoring spontaneous resolution of the condition.

- **Methotrexate:** Methotrexate (MTX) is the drug used for the medical management of ectopic pregnancy. Methotrexate is a folic acid antagonist which prevents the growth of rapidly dividing cells including trophoblasts and fetal cells by interfering with DNA synthesis and cell replication.

- **Pregnancy of unknown location (PUL):** refers to cases in which the hCG level is higher than 2 IU/L but the location of the pregnancy cannot be found with transvaginal ultrasound. **See Appendix B**

- **Ectopic pregnancy:** is a pregnancy that develops outside the uterine cavity. The fertilized egg implants and grows in any location other than the endometrial lining of the uterus. The large majority (90%) of ectopic pregnancies occur in the fallopian tube. This is referred to as a ***tubal ectopic*** pregnancy. However, rarely (1-3%) can occur in other locations, such as the cornua of the uterus, ovary, cervix, caesarean scar and abdominal cavity. These are collectively referred to as ***non-tubal ectopic*** pregnancies.

- **Heterotopic pregnancy:** where an ectopic pregnancy co-exists with an intrauterine pregnancy. A heterotopic pregnancy is exceptionally rare when the pregnancy is spontaneously conceived, 1 in 4,000 to 1 in 30,000, but more commonly associated with in vitro fertilization; 1 in 100 (Barrenetxea et al., 2007).

- **Anti D:** Immunoglobulin that binds to, and causes the removal of, any Rhesus D positive red blood cells that have passed from the fetus into the maternal circulation.

1.0 Human Chorionic Gonadotrophin βhCG

1.1 Urine measurements

The urine test is simple and reliable enough to be used routinely to establish whether or not a woman is pregnant. It is positive when βhCG is ≥ 25 IU/L.

1.2 Serum measurements

Measurement of βhCG in serum permits more accurate quantification which may be useful in the following:

- Screening in women at high risk of ectopic pregnancy
- Determining the appropriate treatment for women with suspected ectopic pregnancy.
- Monitoring during expectant management or medical management of women with ectopic pregnancy
- Evaluation of conservative surgical treatment of ectopic pregnancy

1.3 βhCG doubling time

It refers to the time taken for the βhCG level to double its original value. A βhCG value of <5 IU/L is considered to be the non-pregnant or negative value. The doubling time is particularly useful in early pregnancy i.e. before 6 weeks or when the plasma βhCG level is < 5000 IU/L.

Serum βhCG levels double approximately every two days in early (< 8 weeks) normal intrauterine pregnancy; a lesser increase (< 63% over 48 hours) is associated with ectopic pregnancy and miscarriage.

However, 15% of normal pregnancies will have abnormal doubling time and 13% of ectopic pregnancies will have a normal doubling time.

Caution

- In multiple pregnancies the βhCG level would be a little higher, requiring an extra two or three days for a sac to become visible.
- The possibility of a heterotopic pregnancy should be kept in mind (1 in 3000 cases of spontaneous conceptions and between 1% to 3% of assisted conceptions).

2.0 Management of Pregnancy of Unknown Location (PUL)

2.1 Definition

- No evidence of intrauterine or extrauterine pregnancy in women with a positive pregnancy test.
- A PUL can be an early intrauterine pregnancy, an ectopic pregnancy or a spontaneous miscarriage.

- The outcome of a PUL is declared with close monitoring of hCG and clinical presentation; intrauterine pregnancy, ectopic pregnancy, failing PUL with uneventful fall in hCG to <2 or persistent PUL. **See flowchart, Appendix B**
- Assume women with a PUL have an ectopic pregnancy until proven otherwise.

2.2 Initial assessment.

- Clinical history: the presence of risk factors for ectopic pregnancy, gestational age calculation
- Clinical symptoms and signs e.g. abdominal or pelvic pain, vaginal bleeding, shoulder tip pain
- TVS (Transabdominal scan TA) can be offered if women find TVS unacceptable explaining the diagnostic limitations).
- Serum β-hCG
- Provide patient education and counselling and clear plan for follow-up.

2.3 Follow up

- Close surveillance with serum βhCG measurements every 48 hours
- Can repeat TVS when βhCG >1500 IU/L to look for an IUP or ectopic pregnancy.
- Provide support and contact numbers for Early Pregnancy and Perinatal Assessment Service (EPPAS)
- Follow up until:
  - Intrauterine pregnancy identified
  - Miscarriage confirmed
  - Ectopic pregnancy diagnosed
  - Level of serum βhCG spontaneously decreases (failing PUL)

3.0 Ectopic Pregnancy

An ectopic pregnancy is any pregnancy implanted outside the endometrial cavity. The incidence of ectopic pregnancy in women attending early pregnancy units is 2–3%.

Unfortunately, women still die from ectopic pregnancy. It is an important cause of pregnancy-related morbidity and mortality. However, the case fatality rate has decreased over recent years, suggesting that earlier diagnosis and treatment may have made an impact.

Ectopic pregnancy can be a devastating experience for the woman; confronted with the loss of a baby, possible loss of fertility and life. The psychological impact can be significant. The emotional as well as the clinical needs of individual women should be assessed and managed in a sensitive way.

Sites of ectopic pregnancy include:

- The fallopian tube (the most common site: 91 – 95% of ectopic pregnancies)
- Other possible sites are:
  - Interstitial (2%)
  - Cervical (<1%)
  - Ovarian (0.01%)
  - Caesarean or hysterotomy scar.
  - An abdominal pregnancy can be primary or secondary resulting from a tubal miscarriage.

3.1 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.

Table 1: Risk Factors

Degree of additional risk	Risk Factor	Odd Ratio
High	Previous ectopic pregnancy	9.3 – 47
	Previous tubal surgery	6.0 – 11.5
	Failed tubal ligation	3.0 – 139
	Documented tubal damage or pathology	3.5 – 25
	Failed IUCD	1.1 – 45
Moderate	History of infertility	1.1 – 28
	Previous pelvic infection	2.1 – 3.0
	Cigarette smoking	2.3 – 3.9
	Multiple sexual partners	1.4 – 4.8
	Assisted reproductive technology	2.3 – 3.9
Low	Previous pelvic/abdominal surgery	0.93 – 3.8
	Early age at sexual intercourse	1.1 – 2.5
	Vaginal douching	1.1 – 3.1

3.2 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.

The classic triad of common symptoms are:

- Vaginal bleeding with or without clots (75% of women)
- Abdominal or pelvic pain (80 – 90% of women)
- Amenorrhoea.

Be aware that

- 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.
- The classic symptoms and signs such as severe abdominal pain and hypotension are associated with advanced or ruptured ectopic pregnancy.
- Atypical presentation for ectopic pregnancy is common – **30% of women will have no clinical signs**
- Be aware that ectopic pregnancy can present with a variety of symptoms.
- Even if a symptom is less common, it may still be significant.

Other reported symptoms include:

- Breast tenderness

- Gastrointestinal symptoms
- Dizziness, fainting or syncope
- Shoulder tip pain
- Urinary symptoms
- Passage of tissue (likely decidual cast)
- Rectal/pelvic pressure on defecation

3.3 Signs.

The clinical signs of ectopic pregnancy can be quite varied ranging from a total absence of signs (33% of cases) to shock and maternal collapse. Hypotension and tachycardia are late signs in the evolution of clinical signs.

Common signs include:

- Pelvic tenderness
- Abdominal tenderness
- Adnexal tenderness

Less common signs are:

- Cervical excitation
- Rebound tenderness or peritoneal signs
- Pallor
- Abdominal tenderness and distension
- Enlarged uterus
- Tachycardia
- Hypotension or orthostatic hypotension
- Abdominal distension
- Shock/collapse

3.4 Making a Diagnosis.

- Refer women who are haemodynamically unstable, or in whom there is significant concern about the degree of pain and bleeding, directly to the Emergency Department (ED).
- Have a high index of suspicion for ectopic pregnancy:
  - May not be symptomatic until rupture occurs (9% of cases)
  - May experience vague and mild symptoms early in the course of the disease.
  - The clinical presentation and natural course of an ectopic pregnancy are unpredictable.

The diagnosis of ectopic pregnancy is made using either:

- Transvaginal ultrasound (alone or supplemented by transabdominal ultrasound)
- Diagnostic algorithms: transvaginal ultrasound + quantitative βhCG

Laparoscopy is no longer the gold standard for diagnosis. False-negative laparoscopies (3.0 – 4.5%) have been reported when the procedure is performed too early in the development of an ongoing ectopic pregnancy.

Comment on progesterone. 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.

3.4.1 Transvaginal Ultrasound

Transvaginal ultrasound (TVS) is the primary diagnostic tool of choice for tubal ectopic pregnancies. TVS can be used to diagnose up to 90% of tubal pregnancies with a sensitivity of 85% and specificity of 98%.

Ideally tubal ectopic pregnancies can be positively identified by visualising a hypoechoic adnexal mass that moves separately to the ovary.

Other ultrasound features suggestive of an ectopic pregnancy are a combination of uterine and adnexal findings in the presence of a positive pregnancy test.

Uterine findings are:

- An empty uterus
- A variable degree of non-specific thickening of the endometrium
- An intrauterine pseudo sac (collection of variable amounts of fluid within the uterine cavity present in approximate 20% of ectopic pregnancies). Its presence alone cannot be used to diagnose an ectopic pregnancy.

Adnexal findings are:

- A fluid filled adnexal mass surrounded by a hyperechoic tubal ring (doughnut or bagel sign)
- A mixed adnexal mass which can either be a tubal miscarriage or tubal rupture
- A gestational sac with or without fetal heart beat
- Fluid in the pouch of Douglas (POD), present in 25 – 50% of ectopic pregnancies. It may signify tubal rupture, but most commonly is due to blood leaking from the fimbrial end of the fallopian tube. It is, however, not diagnostic of an ectopic pregnancy and may also be present in normal intrauterine pregnancies.

3.4.2 Diagnostic algorithms: transvaginal ultrasound + quantitative βhCG

An ectopic pregnancy is more likely when the βhCG is >1000IU/L and the ultrasound scan fails to identify an intrauterine pregnancy. In the absence of any significant pain, the patient's serum βhCG is to be repeated in 48hrs time.

If the βhCG is falling it is suggestive of a resolving intra or extra-uterine pregnancy. The rate of fall of βhCG tends to be slower in ectopic pregnancy than with a complete miscarriage.

A serum βhCG level that is increasing or plateaued may either show an ectopic pregnancy at a subsequent scan or remain as a PUL.

If the ultrasound findings are non-specific follow diagnostic algorithm for ectopic pregnancy.

Comments about βhCG

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

- TVS + discriminatory zone β-hCG titer
- TVS + serial hCG +/- discriminatory zone β-hCG.

3.4.2.1 Discriminatory zone β-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. 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.

β-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 β-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 or PUL.
- 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 (ideally less than 50% of its initial level within seven days). These women should be observed closely for rupture or clinical deterioration. Weekly hCG concentrations should be monitored until the result is 5 or less for pregnancy.

β-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 β-hCG rises normally, then a TVS should be performed when hCG reaches / expected to reach the discriminatory zone
- A falling β-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 (ideally less than 50% of its initial level within seven days). Weekly β-hCG concentrations should be monitored until the result is 5 or less for pregnancy.

3.4.2.2 Serial β-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.

- The mean doubling time for serum hCG ranges from 1.4 to 2.1 days in early pregnancy.
- 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.
- The slowest recorded rise over 48 hours associated with a viable intrauterine pregnancy was 53%.

3.5 Expectant Management (see flowchart, Appendix C)

Not all ectopic pregnancies progress and pose a risk to the mother. Spontaneous resolution of tubal ectopic pregnancies with minimal risk of tubal rupture has been well documented in a number of reports.

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 β-hCG was < 1000 IU/ml has been found to be 80 – 90% by two different studies.

Higher β-hCG levels are related to lower success rates with expectant management, with one study reporting only 21% of cases were successful when the initial β-hCG was >1500mIU/ml.

Studies have shown no difference in fertility rates between expectant, medical and surgical management.

3.5.1 Selection criteria (ALL INCLUSIVE) for expectant management.

- Absence of clinical symptoms
- No signs of rupture or intraperitoneal bleeding
- Absence of or minimal haemoperitoneum
- No yolk sac or fetal pole seen at ultrasound
- Adnexal mass < 2cm in diameter
- Serum β-hCG < 1000IU/L at initial diagnosis and declining progressively
- The patient will comply with treatment and follow-up

The risk of rupture in a woman with an ectopic mass exists until the β-hCG level has fallen to <5 IU/L. It often involves frequent hospitalisation and /or follow-up. Both the clinician and the patient must be well motivated to accept the long recovery time.

3.5.2 Predictors of success of expectant management.

- Beta-HCG level <1000 IU/L at diagnosis (best single predictor of success)
- Rapidly declining beta-hCG levels at follow up (>50% drop by day 7 of follow up)
- Decreasing ectopic pregnancy/adnexal mass size at follow up ultrasounds
- PUL i.e. no intra or extrauterine gestational sac seen at ultrasound.

3.5.3 Contraindications for expectant management

- Extra tubal ectopic pregnancy e.g. CS scar, ovarian, interstitial, abdominal
- 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)
- β-hCG that is greater than 1000 IU/ml, is increasing, or is not declining
- The woman is unwilling or unable to comply with follow up requirements.
- The woman lives more than 30 minutes away from the hospital

3.5.4 Follow-up

- Monitor serum β-HCG levels twice a week in the first 7 days.
- If β-HCG drop is ≥ 50%, then monitor β-HCG levels once per week till less than 5 IU/L
- Rescan weekly expecting 50% reduction in size of adnexal mass.
- If expected drops in β-HCG levels and adnexal mass are not seen, offer medical or surgical management.

3.6 Management of Ectopic Pregnancy with Methotrexate.

The routine use of ultrasound scans for women with early pregnancy symptoms of pain and bleeding facilitates early diagnosis of ectopic pregnancy and medical treatment can be administered in most cases.

The psychological impact of an ectopic pregnancy should be appreciated and counselling offered.

Methotrexate is the drug used for the medical management of ectopic pregnancy. It 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.

Intramuscular methotrexate (MTX) is given as a single dose calculated from the patient's body surface area (50 mg/m2). For most women this will be between 75 mg and 90 mg. This dose is relatively low, safe and well tolerated. In some protocols where multidose MTX is used, folinic acid (Leucovorin Calcium®), is given to bypass the metabolic block induced by methotrexate and thus rescue the normal cells from toxicity.

Systemic Methotrexate should never be given at first presentation, unless the diagnosis of tubal ectopic pregnancy is absolutely clear on ultrasound and a viable intrauterine pregnancy has been excluded. Treatment must be discussed with and approved by the gynaecology consultant on call.

3.6.1 Indications for Methotrexate Use in Early Pregnancy

- Confirmed ectopic pregnancy
- Pregnancy of unknown location
- Persistent trophoblastic disease following salpingotomy; if β-hCG levels are > 65% of the initial level 48 hours after surgery
- Persistently elevated HCG levels after surgery e.g. salpingostomy, ruptured ectopic pregnancy.

3.6.2 Selection Criteria (ALL INCLUSIVE) for Medical Management.

- Haemodynamic stability with no signs of peritonism
- Absence of intrauterine pregnancy
- β-hCG less than or equal to 3,000 IU/L

- Gestational sac < 3cm in diameter
- Early unruptured ectopic pregnancy as indicated by;
  - Less than 8 weeks pregnant by ultrasound date
  - Absence of significant free fluid seen on ultrasound
  - Absent fetal cardiac activity
- Patient compliant for regular follow up including clinical review and blood tests (average 35 days)
- Patient compliant to avoid conception for 3 months following methotrexate therapy
- No hypersensitivity or reaction to methotrexate.

Patients who don't fit these criteria e.g. high-risk surgical candidates – gross obesity, multiple previous laparotomies or multiple bowel surgery with high risk of adhesions may still be suitable for treatment but a second opinion must be sought from a second Gynaecology Consultant or the Clinical Director.

3.6.3 Exclusion Criteria for Methotrexate Use

- Haemodynamic instability
- Severe or persistent abdominal pain or evidence of significant haemoperitoneum on ultrasound
- Immunodeficiency or concurrent use of steroids
- 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 function tests
- Known hypersensitivity to methotrexate
- Immunodeficiency
- Peptic ulcer disease
- Blood dyscrasias

3.6.4 Predictors of Successful Treatment with Methotrexate

- Initial β-hCG at diagnosis (< 3,000 IU/L)

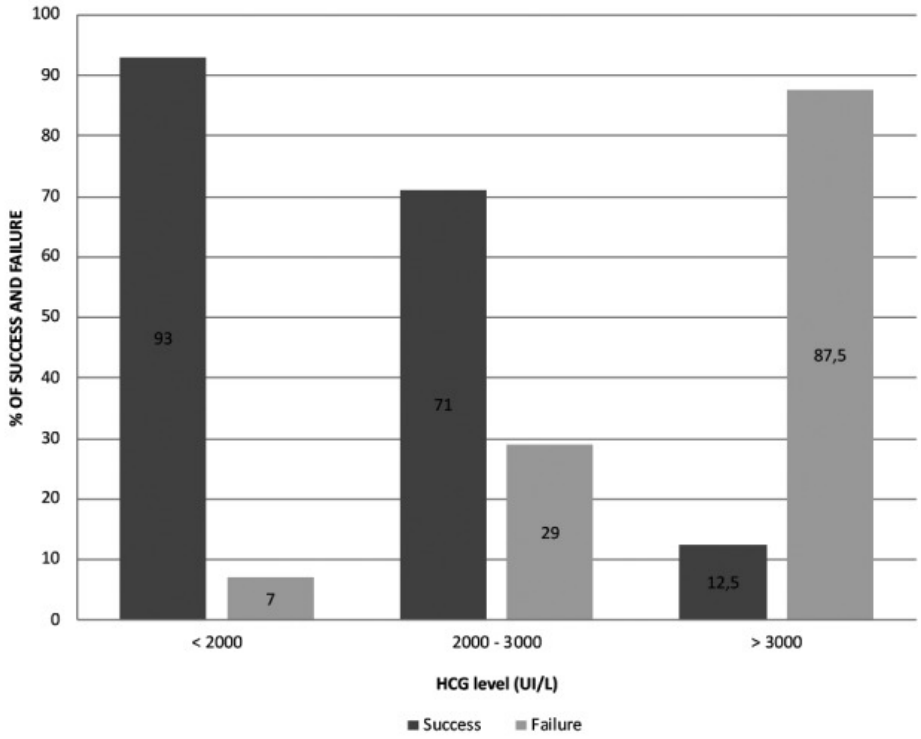
Initial β-hCG level	Success rate (%)
< 1,000 IU/L	88
1,000 to 2,000 IU/L	71
2,000 to 3,000 IU/L	59
3,000 to 4,000 IU/L	50
>4,000 IU/L	42

Table 2: Success rates of MTX therapy based on initial β-hCG level.

- β-hCG of < 3,500 IU/L at day 4 of follow up
- β-hCG drop greater than 15% between day 4 to 7 of follow up.
- Absence of subchorionic tubal haematoma in the ectopic gestation or haemoperitoneum
- Absence of an embryo in the ectopic gestation

- Adnexal mass size less than 3cm at day 0 of MTX treatment
- ≥50% reduction in βhCG levels by day 7 of MTX treatment

- A retrospective single-center study of 61 women receiving single dose methotrexate therapy for ectopic pregnancy (tubal or pregnancy of unknown location) found that the risk of failure is higher when the hCG level on D0 is >3000 IU/L than when it is <2000 IU/L (OR 100.3). When comparing hCG levels between 2000 and 3000 with levels <2000 IU/L, the OR was 5.73.
- This same study concluded that gestational mass size, reported patient symptoms and presence of fluid in the Pouch of Douglas did not have a significant influence on the success of MTX treatment.
- Overall, the success rate of single dose MTX for the treatment of ectopic pregnancy was 80% and rose to 84% when hCG >5000 IU/L were excluded. Surgery was required for 20% of patients due to pain, increased mass size and/or suboptimal hCG response to MTX.
- Whilst the limitations of this study are its retrospective nature and small sample size, it is important to emphasize the increasing risk of failure of MTX therapy with a hCG level increasing beyond 2000 IU/L.



Success and failure rates according to hCG level at Day 0. Chances of success are higher when hCG level is < 2000 IU/L and risks of failure are higher when hCG level is > 3000 IU/L. Beguin et al, 2019.

3.6.5 Potential Side Effects:

- Mild stomatitis, gastritis, enteritis, diarrhoea
- Photosensitivity
- Transient elevation in liver enzymes (in 3%)
- Rare side effects – alopecia, bone marrow suppression, hepatotoxic effects.

Adverse reactions to methotrexate are usually mild and self-limiting. All of these side effects resolve as methotrexate exposure wanes.

3.6.6 Patient counselling

- Method of action (blocks folate action in the growth of fetal tissue)
- 10% cases may require a second dose of treatment or surgical management.
- 75% women experience abdominal pain on days 2 – 7 after injection. Can be managed with analgesia but if refractory to simple analgesia, urgent medical review is advised.
- 7 – 10% risk of tubal rupture requiring emergency surgery.
- Mild and self-limiting side-effects (conjunctivitis, stomatitis, gastritis) can occur in 30% cases. Rarely dermatitis, liver damage, bone marrow suppression or alopecia occur.
- Post treatment follow-up is required to confirm resolution of the ectopic pregnancy. Average 28 – 35 days.
- Conception within 3 months following methotrexate is contraindicated owing to the cytotoxic/teratogenic nature of methotrexate. In addition, a new pregnancy makes interpretation of β-hCG surveillance difficult to interpret.
- Avoid sun exposure to limit the risk of methotrexate related dermatitis.
- Avoid NSAIDs as their interaction with methotrexate may cause GIT toxicity, aplastic anaemia and bone marrow suppression. Paracetamol with or without codeine is recommended for pain relief.
- Discontinue folic acid supplementation as this may interfere with the effectiveness of methotrexate.
- Avoid alcohol for 7 days following administration as this may increase the risk of side-effects.
- Reassure that methotrexate does not compromise ovarian function or future fertility.
- Recurrence risk of ectopic pregnancy is 15% irrespective of the treatment modality
- Present for medical attention if heavy vaginal bleeding, shoulder tip pain, fever, severe abdominal pain, dizziness or fainting occurs.
- Methotrexate can remain in bodily fluids (urine, faeces, saliva) for 7 days following administration – be cautious of exposing others to bodily fluids e.g. close the lid of the toilet and use full flush after use.

3.6.7 Pre-treatment checks

- Discuss the options for treatment – expectant / medical / surgical. Counsel and provide the woman with information leaflets.
- FBC, U&Es, LFTs, β-hCG, Group & Hold
- Satisfy inclusion and exclusion criteria
- Obtain written consent explaining the success rate, risks, post treatment advice as detailed below and predictors of success. Document counselling given.
- Calculate the Patient Body Surface Area from height and weight
- Prescribe methotrexate as per the dosage regimen
- Anti D is not required in Rh negative who have medical management

3.6.8 Treatment Schedule

- Single-dose or multi-dose regimens are available.
- Single-dose is primarily used for tubal ectopics (accounting for 95% ectopic pregnancies). Multi-dose is reserved for non-tubal ectopic pregnancies.
- Route: Intramuscular only
- Safety precautions of administering a cytotoxic medication should be followed.
- It is advisable to monitor the patient for 30mins following administration for adverse side-effects.

Single Dose Regime

- Obstetrics and Gynaecology registrar to arrange presentation to an appropriate ward e.g. SSSU/AMSU
- Measure weight and height to calculate the correct dose.
- Prescribe calculated methotrexate dose and arrange preparation with Pharmacy
- Dose of methotrexate: 50mg x BSA **OR** 1mg/kg. For most women this comes to between 75 to 90mg.

Body Surface Area (BSA) equation:

$$BSA\,(m^2) = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$

3.6.9 Administration of Methotrexate

Standard Requirements

It is expected that staff are familiar with the relevant procedures and know when to undertake each step with authorisation for use by the gynaecology consultant on-call.

This procedure only applies to women under the care of the Women's Health Unit. Nursing or Medical Staff are to administer methotrexate in accordance with the Peninsula Health Cytotoxic Administration CPG

- Introduce yourself, discuss the procedure with the patient
- Obtain informed consent. Refer to Consent to Medical Treatment Policy
- Check patient identification at prescribing and administration. Refer to the Patient Identification Policy
- Perform routine hand hygiene. Refer to the Hand Hygiene and Aseptic Technique CPG
- Document medications in the digital medical record
- Each methotrexate dose is supplied as a pre-filled syringe. The syringe is sealed in a clear plastic bag (which is sealed inside another outer bag).
- Pharmacy is responsible for supplying the syringe, packed and sealed in a cytotoxic-labelled plastic box which is placed inside another hard-walled cytotoxic-labelled container for transport to the Early Pregnancy and Perinatal Assessment Service (EPPAS).
- Methotrexate is to be administered in the EPPAS clinic.
- The drug is given as a deep IM injection in the gluteal region or lateral thigh by medical staff or by oncology nurses. An appropriate gown, gloves, mask and eye protection for handling cytotoxic treatment must be worn.
- The syringe and needle, plus the plastic bags housing the methotrexate syringe, is to be disposed of in a purple cytotoxic bin. The gown, gloves, mask and eye protection are also

disposed of in the cytotoxic bin. The hard-plastic box and 'Esky' container are returned to pharmacy.

- The patient is observed for 30 minutes for any hypersensitivity reactions, and can be managed as an **outpatient**. If any local reaction is noted consider antihistamine or steroid cream (very rare)
- Methotrexate is a cytotoxic agent and must be handled and disposed of according to Peninsula Health guidelines. Waste products such as the needle, syringe, wipes, swabs personal protective equipment and plastic bags that have been in contact with the methotrexate must also be disposed of according to the guideline.
- Staff who are pregnant or who are planning an imminent pregnancy must take exceptional care or be able to make an informed choice about the handling and disposal of cytotoxic medication.

Table 3: Follow up schedule for single dose MTX

Day	Management
1	Serum β-hCG, FBC, U&Es, LFTs, G&H
1	Intramuscular methotrexate 50 mg/m2. Administer in EPPAS
4	Serum β-hCG. ▪ Expect a rise in β-hCG levels ▪ Review in EPPAS and discuss with consultant (team leader) in clinic ▪ Request pelvic ultrasound if moderate or significant pain not responsive to simple analgesia to exclude rupture.
7	Serum β-hCG, FBC, U&Es, LFT ▪ If β-hCG decrease > 15% by day 4 – 7, repeat weekly till < 5 IU/L ▪ 2nd dose of methotrexate 50mg/m2 if hCG decrease < 15%, by day 7 and no clinical signs of rupture **OR** offer laparoscopy ▪ Repeat FBC and LFT if further methotrexate is required. ▪ Request pelvic ultrasound if moderate or significant pain to exclude rupture or haemoperitoneum. ▪ Discuss with consultant (team leader) in clinic.
14	▪ Serum β-hCG, FBC, U&Es, LFT ▪ If β-hCG decrease > 15% by day 7 – 14, repeat β-hCG weekly till < 5 IU/L ▪ 3rd dose of methotrexate 50mg/m2 if β-hCG decrease < 15% by day 7-14 **OR** offer laparoscopy ▪ Repeat FBC and LFT if further methotrexate is required
Monitoring	The β-hCG is followed weekly until the level is ≤ 5 IU/L.
Offer 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 at any time.**	

Fixed Multi-dose regime

- The prescribing clinician must discuss this regime with the Gynaecology consultant on call.

- This regime is reserved for non-tubal ectopic pregnancies located in the uterine scar, cervix, interstitial or uterine cornu. It is recommended to discuss these cases with the MFM fellow at Monash Medical Center for a second opinion due to the often-complex nature of diagnosis and management.
- Patients are to remain an in-patient during this regime.
- Measure weight and height to calculate the correct dose.

Table 4: Multidose MTX regime for abnormally located ectopic pregnancies

Day	Management
1	▪ FBE, UEC, LFTs, quantitative beta-hCG ▪ Ensure IV access, blood group and cross-match.
1	Methotrexate 1mg/kg IM
2	Folinic acid 6mg IM
3	Methotrexate 1mg/kg IM
4	▪ Folinic acid 6mg IM ▪ Check beta-hCG
5	▪ Methotrexate 1mg/kg IM ▪ Check beta-hCG
6	▪ Folinic acid 6mg IM ▪ Check beta-hCG
7	▪ Methotrexate 1mg/kg IM ▪ Check beta-hCG, FBE, UEC, LFT
8	Folinic acid 6mg IM

Treatment is discontinued when a decline in consecutive daily quantitative beta-hCG level is observed *after* 4 doses of methotrexate.

3.6.10 Post treatment advice.

- β-hCG – weekly serial hCG follow up needed until ≤5 IU/L
- USS – There appears to be no clinical benefit from routine serial ultrasound examinations. 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 moderate to severe abdominal/ pelvic pain not relieved by simple analgesia**.
- 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. Use non-hormonal contraception.

- Avoid pelvic exams during surveillance of methotrexate therapy due to the risk of tubal rupture
- Avoid sun exposure to limit risk of methotrexate related 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

Further considerations with Medical Management

- **Separation pain.**
  - Up to 75% of patients may complain of pain on days 2 – 7 after receiving MTX (due to tubal miscarriage or tubal distension from haematoma formation). It can usually be managed with simple analgesia. Nonsteroidal anti-inflammatory drugs should be avoided because a clinically significant drug interaction with methotrexate may occur.
  - While routine ultrasound is not required, however, if pain is moderate or severe, not relieved by simple analgesia or vital signs are unstable, then tubal miscarriage or rupture with haemoperitoneum must be excluded by urgent ultrasound. Immediate surgery may be required.

- **β-hCG.**
  - 7 – 10% risk of rupture despite fall in beta-hCG levels. Serum beta-hCG by itself cannot predict whether a tubal ectopic pregnancy is likely to rupture or be ruptured; there is no safe lower limit in hCG titre below which ruptured ectopic is not seen.

- **Future fertility.**
  - There is no evidence of adverse effects of methotrexate treatment of ectopic pregnancy on future pregnancies
  - Treatment with methotrexate does not appear to compromise ovarian function
  - 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
  - Observational studies have shown a subsequent intrauterine pregnancy rate of 58 – 89%
  - Similar risk of recurrent ectopic pregnancy, tubal patency rates and intrauterine pregnancy rates are reported in literature between medical and surgical management.
  - Pre-conceptual counselling for future pregnancy should involve an early ultrasound to confirm a viable intra-uterine pregnancy.

4.0 Surgical Management of Ectopic Pregnancy (see flowchart, Appendix D)

A laparoscopic approach to the surgical management of tubal pregnancy, in the haemo-dynamically stable patient, is best practice and is preferable to an open approach. Experienced operators may be able to safely manage women laparoscopically - even those with a large haemoperitoneum.

In the haemodynamically unstable patient, immediate resuscitation and the surgical procedure which prevents further blood loss quickly, should be used; usually this involves a laparotomy. **Transfer to theatre should not be delayed by attempts to establish a normal circulating plasma volume.**

Advantages of laparoscopic approach include:

- Shorter hospital stays
- Less intraoperative blood loss
- Less adhesion formation
- Lower costs
- Lower analgesic requirements
- Quicker post-operative recovery
- Lower recurrent ectopic pregnancy rate (5%) v laparotomy (16.6%)
- Subsequent IUP rate (70%) similar to laparotomy

Disadvantages:

- Increased risk of inadvertent bowel/vascular damage
- May have to convert to a laparotomy
- Laparoscopic salpingostomy was less successful than an open approach in elimination of the tubal pregnancy reflected in a trend towards higher rates of persistent trophoblast

4.1 Indications for surgery.

- Haemodynamically unstable
- Confirmed impending or ongoing rupture of the ectopic pregnancy
- Co-existing intrauterine pregnancy
- β-hCG > 5,000IU/L
- Adnexal mass >3cm on USS
- Live ectopic pregnancy
- Failed medical treatment
- Contraindication to medical treatment

4.2 Laparoscopic salpingectomy vs. salpingostomy

- The pregnancy rates following salpingostomy or salpingectomy are comparable in the presence of a normal contralateral tube.

Salpingectomy

- Recommended in the presence of a healthy contralateral tube
- Benefit:
  - Reduced risk of tubal bleeding in the immediate postoperative period
  - Less chance of persistent trophoblast needing further treatment
- Disadvantages:
  - Unable to conserve the tube

Salpingostomy.

- To be considered in the presence of any other fertility reducing factors including previous ectopic, previous PID, previous abdominal surgery or contralateral tubal damage
- Benefit:
  - Tube is conserved
- Disadvantage.
  - Higher subsequent ectopic pregnancy (20.5%)
  - Serum β-hCG is taken at 7 days after surgery and then weekly until negative result is obtained.

Fimbrial evacuation (milking) of ectopic pregnancy should be avoided as it predisposes to persistence of trophoblastic tissue.

4.3 Further Considerations.
Persistent trophoblast

- The failure of serum β-hCG levels to fall as expected after initial treatment.
- It is primarily a problem occurring after salpingostomy rather than following salpingectomy.
- βhCG levels may return uneventfully to normal, however, cases of delayed haemorrhage due to persistent trophoblast have been described. Single dose administration of MTX and follow up with serial βhCG measurements till < 5 IU/L may be required.

Factors increasing the risk of persistent trophoblast include

- Higher preoperative serum β-hCG levels (>3000 IU/l)
- A rapid preoperative rise in serum β-hCG
- The presence of active tubal bleeding.

4.4 Anti-D immunoglobulin. Non- sensitized women who are rhesus negative who have a surgical procedure to manage an ectopic pregnancy should receive Anti-D immunoglobulin at a dose of 250IU

4.5 Follow up post-surgery

- 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.
- If histology shows no chorionic villi or fetal tissue, the case should be reviewed by the consultant and the patient advised for follow up.
- Following surgery for ruptured ectopic pregnancy, β-hCG should be monitored weekly (this may take up to 10 weeks to return to normal). If β-hCG is rising, request ultrasound scan and consider further treatment (either laparotomy or methotrexate).

4.6 Unusual types of ectopic pregnancy.
Treatment has to be individualised based on the site, size of the pregnancy and its viability. Second opinion should be requested from the MFM team at Monash Medical Centre.

Table 5: Rare types of Ectopic pregnancy

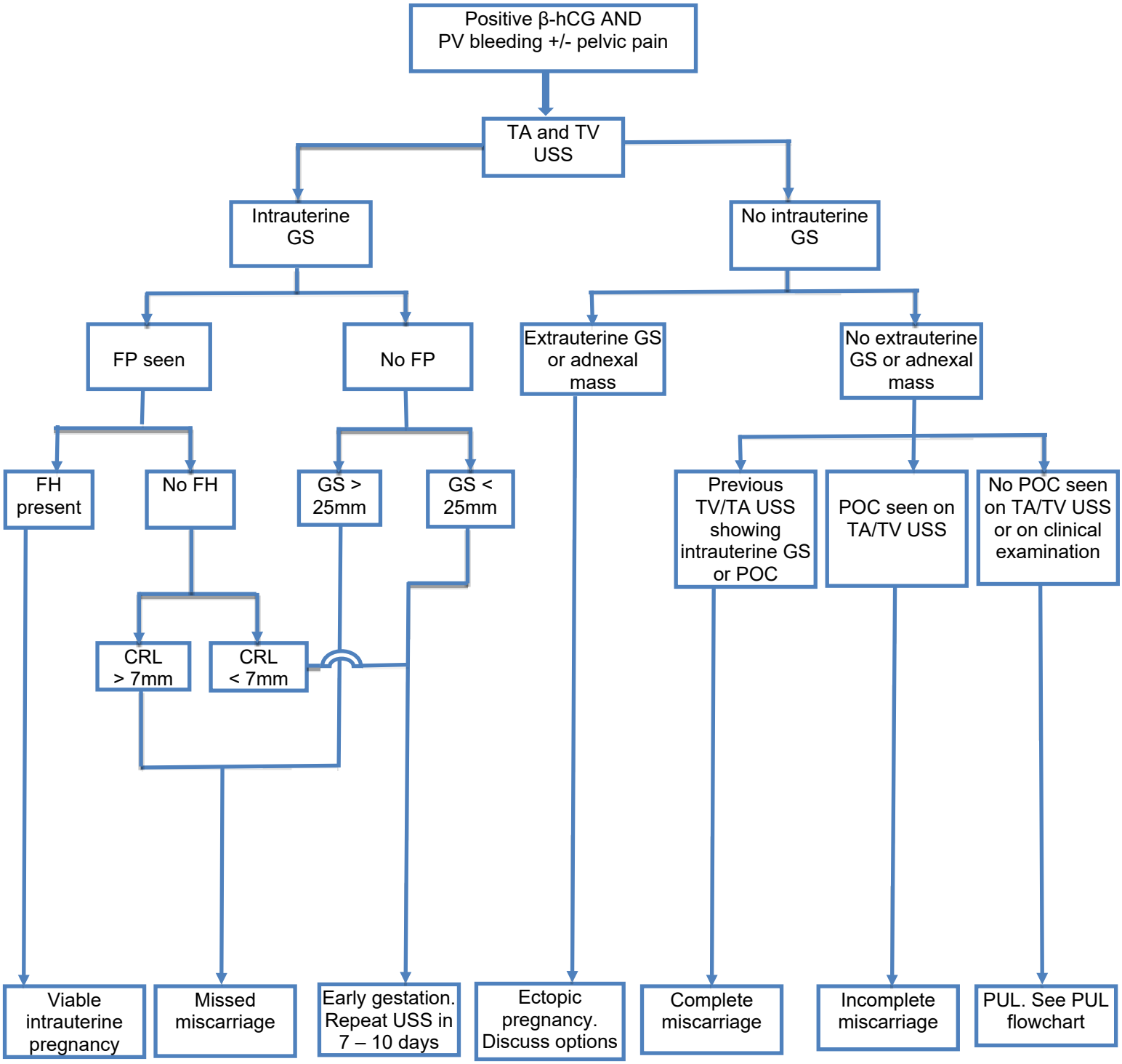
Type	Utrasound Features	Management
Heterotopic	• An intrauterine pregnancy and a concurrent ectopic pregnancy • βhCG is not useful	▪ Laparoscopic salpingectomy if tubal ectopic and unstable. ▪ Intrauterine pregnancy management depends on viability ▪ Local KCl/hyperosmolar glucose injection with aspiration of the sac if clinically stable
Interstitial	▪ Empty uterine cavity ▪ Products of conception in the interstitial part of the tube surrounded by less than 5mm myometrium in all imaging planes ▪ Presence of the 'interstitial line sign' ▪ MRI can be used 2nd line to help aid diagnosis	▪ Conservative/Methotrexate/Surgical ▪ Expectant only suitable if methotrexate is not likely to improve clinical outcome, the patient is stable and the βhCG is falling.
Cervical	▪ Empty uterus ▪ Barrel Shaped Cervix Gestational sac below the level of the internal os ▪ Absence of the 'sliding sign'	▪ Conservative/Methotrexate ▪ Surgical methods should be reserved for those with life threatening bleeding

	▪ Blood flow around the gestational sac using colour doppler	
Ovarian	▪ Hyperechoic mass within the ovary Subcapsular bleeding (must be distinguished from haemorrhagic cyst) ▪ No specific diagnostic criteria	▪ Surgical if laparoscopy required to make diagnosis ▪ Methotrexate if high risk of surgery or persistent trophoblast post operatively
Caesarean scar	▪ Empty uterine cavity ▪ GS is implanted into the scar ▪ Negative sliding sign ▪ MRI can be used as 2nd line if the diagnosis is unclear	▪ Current literature supports surgical over medical approach as the most effective ▪ Associated with high maternal morbidity and mortality
Abdominal	▪ Empty uterus separate from the foetus ▪ Foetus seen without the surrounding uterine mantle ▪ Extremely small amount of liquor ▪ Unusual placental site ▪ MRI can be useful as 2nd line to guide surgical approach in advanced abdominal pregnancy	▪ Laparoscopy if early abdominal pregnancy ▪ US guided fetocide/methotrexate Laparotomy if advanced

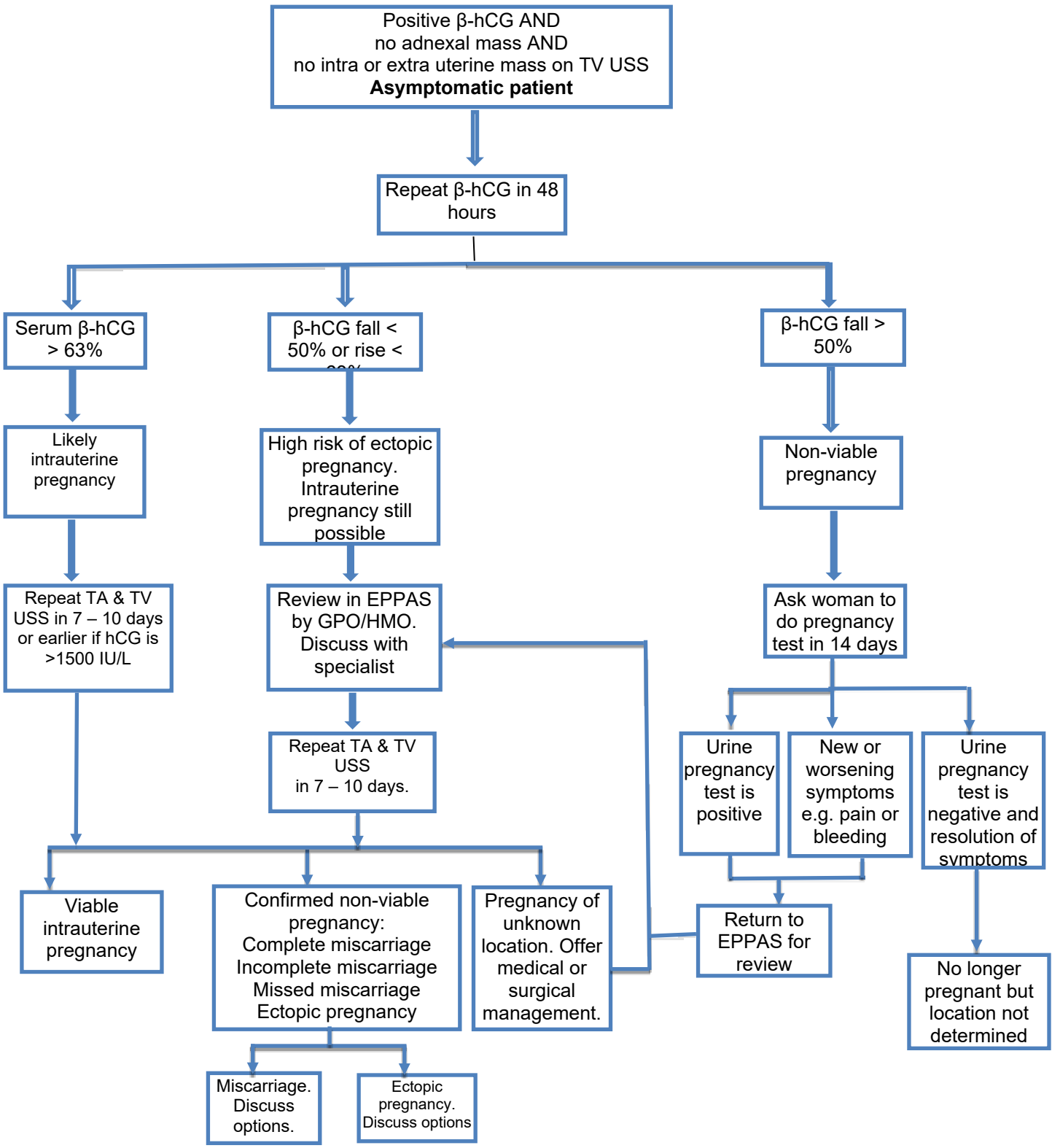
Key Aligned Documents - Standard Requirements

- CPG: Consent to medical treatment procedure
- CPG: Patient identification clinical procedure
- CPG: Hand Hygiene & Aseptic Technique
- CPG: Peninsula Health Cytotoxic Administration
- CPG: PV bleeding and pain in Early pregnancy in ED

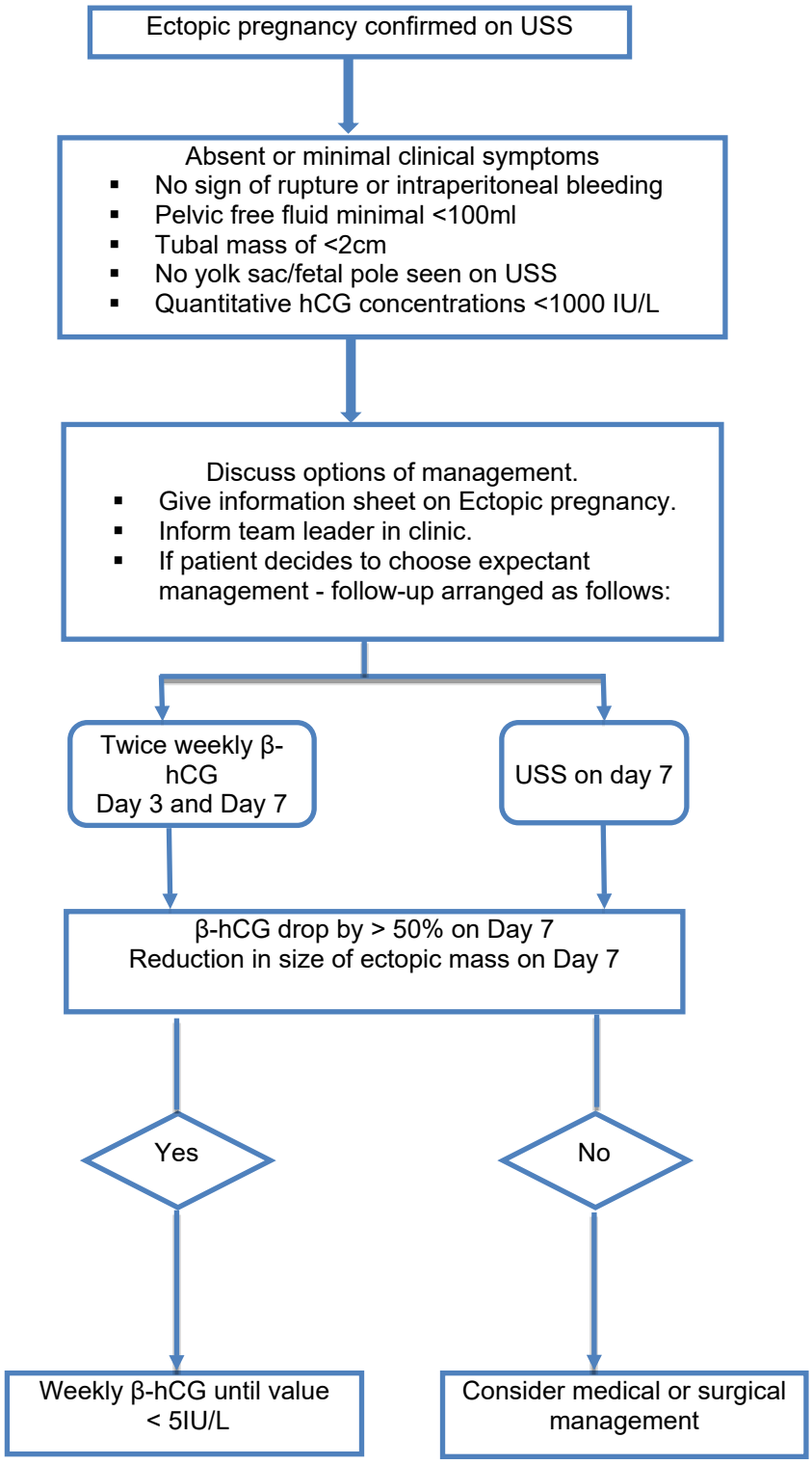
Appendix A: Investigation and Differential Diagnosis for Early Pregnancy Bleeding and Pain in EPPAS.



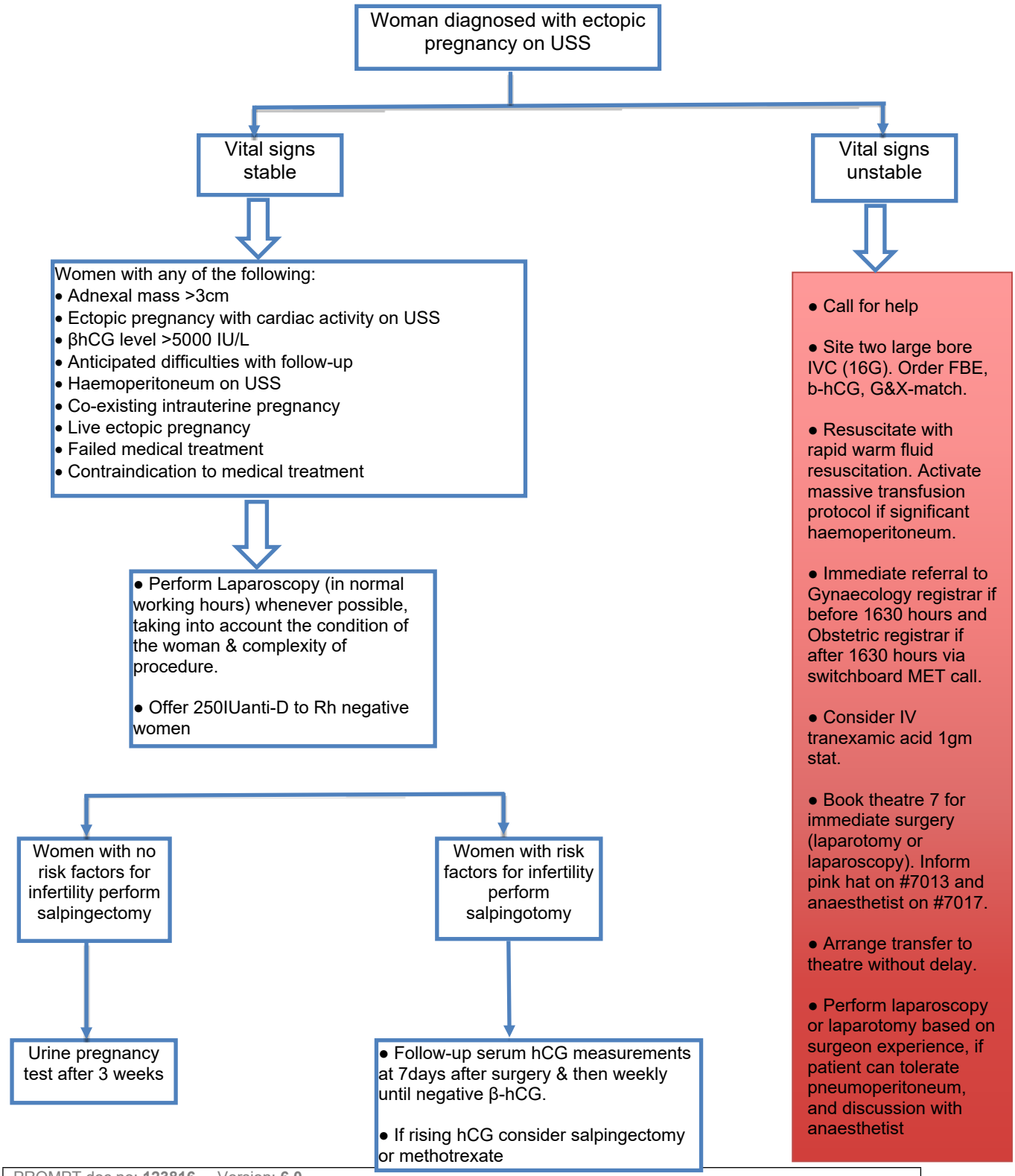
Appendix B: Investigation and Management of PUL



Appendix C: Expectant Management of Ectopic Pregnancy



Appendix D: Surgical Management of Ectopic Pregnancy



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