Ectopic pregnancy and pregnancy of unknown location

Target audience	Maternity staff
Patient group	Pregnant patints with a suspected ectopic pregnancy (EP) or pregnancy of unknown location (PUL).

Summary

Ectopic pregnancy (EP) affects 1 in 80 pregnancies in the United Kingdom (UK) and remains a significant cause of morbidity and mortality. Most ectopic pregnancies are located within the fallopian tube, however they may also arise in the ovary, cervix and other sites within the pelvis and abdomen.

Contents

Ectopic pregnancy

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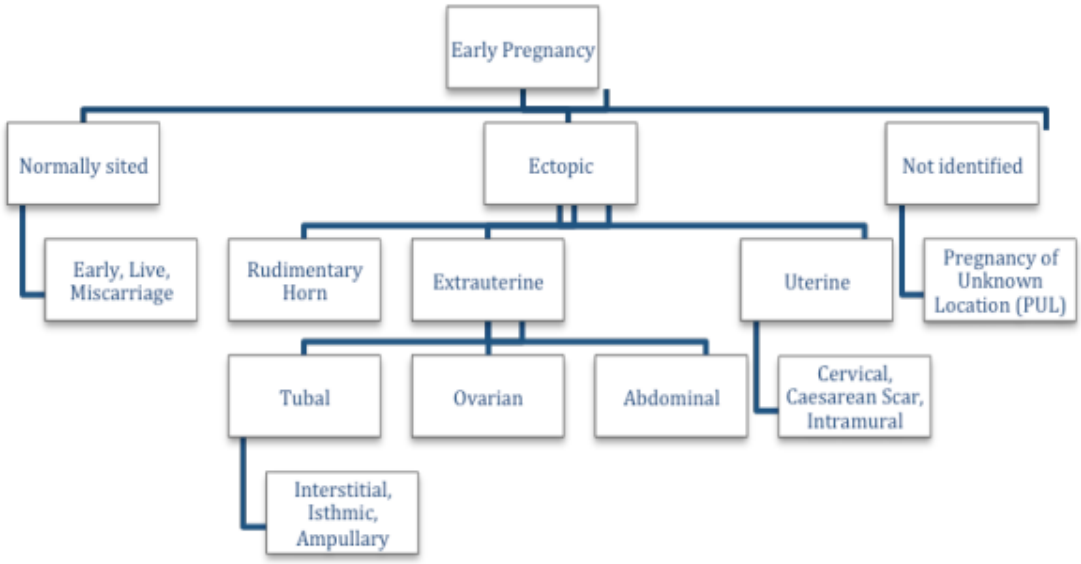


Diagnosis

Initial Assessment

Ectopic pregnancy must always be considered in patients with a positive pregnancy test who present with abdominal pain or vaginal bleeding. Many patients who are symptomatic will self-refer to the Early Pregnancy Assessment Service (EPAS), however referrals may also arise from consultations in primary and secondary care. Patients who have presented to the Emergency Department (ED), and who are clinically unstable, should be reviewed by the gynaecologist on-call in ED.

It should also be noted that most patients having abortion care through the Women's Health Unit will not have had a prior ultrasound in line with national guidance, and this must not affect access to EPAS for medical review if symptoms suggestive of ectopic develop, regardless of whether treatment has been commenced.

A careful history and examination should be taken noting:

- Date of last menstrual period (LMP)
- Contraceptive use
- Date of first positive pregnancy test

- Consideration of risk factors for ectopic pregnancy (eg. previous ectopic pregnancy, history of pelvic inflammatory disease, previous tubal surgery including sterilisation, assisted conception, conception with contraceptive coil in situ – although one-third of patients will have no risk factors)
- Determination of Rhesus status
- A full clinical examination should be performed on all patients attending with pain and/or bleeding in early pregnancy. Those with vaginal bleeding should also have a vaginal examination performed as part of the assessment.

The majority of patients with an ectopic pregnancy present with pain, however there are a variety of symptoms and signs associated with ectopic pregnancy and atypical presentations are common.

Symptoms:

- Abdominal pain
- Vaginal bleeding
- Amenorrhoea (not always)
- Gastrointestinal upset, including diarrhoea
- Shoulder-tip pain
- Urinary symptoms
- Rectal pressure/pain/pain on defaecation
- Dizziness/fainting

Signs:

- Lower abdominal tenderness/rebound
- Adnexal tenderness
- Palpable pelvic mass
- Cervical excitation
- Shock/collapse
- Peritonism

Prioritise assessment of haemodynamic status:

Evidence of haemodynamic compromise:

If signs of haemorrhagic shock are present e.g. tachycardia / hypotension / pale, cold and clammy / prolonged capillary refill > 2 seconds:

1. Notify on call anaesthetist, gynaecology / obstetric registrar & consultant obstetrician/gynaecologist
2. In emergency telephone **2222** and state 'Obstetric Emergency' and current location

3. Obtain intravenous access (2 wide bore cannulas), send full blood count / urea & electrolytes / coagulation screen / cross match **4 units** of blood initially.
4. Resuscitate as per major obstetric haemorrhage guideline but do not delay transfer with protracted fluid resuscitation as the bleeding needs to be stemmed surgically as quickly as possible.
5. Arrange immediate transfer to theatre for definitive treatment
6. Ultrasound is not indicated in this situation and could lead to potentially fatal delay.

No evidence of haemodynamic compromise:

- If ectopic pregnancy is suspected based on history and examination findings and the patient is clinically stable, then an USS should be arranged with EPAS.
- Serum human chorionic gonadotrophin (hCG) should only be measured and interpreted after an ultrasound scan.

If the ultrasound confirms an intrauterine pregnancy:

- Reassure and discharge to community care if fetal heartbeat detected
- Follow appropriate guidance if scan shows non-viable intrauterine pregnancy (IUP) or is inconclusive
- Investigate for other causes of symptoms as appropriate
- Do not check serum hCG

If the ultrasound suggests empty uterus +/- adnexal mass or free fluid:

- Check serum hCG
- Request medical review by gynaecology on call team

Do not routinely check serum progesterone

USS investigation and diagnosis

Transvaginal ultrasound scanning is the diagnostic tool of choice for ectopic pregnancy, however both transabdominal (TA) and transvaginal (TV) ultrasound scanning should be offered to fully investigate for suspected ectopic pregnancy. The scan must be performed by/directly supervised by appropriately trained healthcare professionals with experience of diagnosing ectopic pregnancies.

Where TV USS is unacceptable to the patient, a TA USS should be offered and the limitations of this method of scanning should be explained to the patient and documented in the medical notes.

All USS findings, including the appearance of the adnexae and intrauterine contents, and the presence of free fluid in the pouch of Douglas, should be correlated closely with the clinical presentation and serum hCG levels prior to reaching a diagnosis. A complete USS examination is vital and the possibility of heterotopic pregnancy should be kept in mind (1:40000 chance). The scan should be fully documented in the medical notes and the patient should be reviewed timeously by the on call gynaecology team.

The majority of ectopic pregnancies will be identified on the initial USS. The remainder will be classified as pregnancy of unknown location (PUL) and may later be identified as ectopic as they enlarge and become more visible as the disease process progresses.

- Tubal ectopic pregnancy is identified on TV USS by visualising an adnexal mass, moving separate to the ovary ('sliding sign'), comprising a gestational sac containing either a yolk sac or fetal pole (with or without fetal heartbeat). This is the case in 15-20% of ectopic pregnancies identified on USS.

- There is a high probability of ectopic pregnancy when TV USS identifies an adnexal mass, moving separate to the ovary ('sliding sign') comprising an empty gestational sac ('bagel sign'), or a complex inhomogeneous adnexal mass, moving separate to the ovary.

Signs on TV USS that indicate a possible ectopic pregnancy include an empty uterus or an intrauterine 'pseudo-sac' (-this collection of fluid must be carefully differentiated from an early intrauterine gestational sac which is identified by the presence of an eccentrically located hypoechoic structure with a surrounding double decidual ring in the endometrium). Free fluid is not diagnostic of ectopic pregnancy – it is commonly seen in both intra- and extrauterine pregnancies.

Serum hCG measurement

Blood tests (hCG and progesterone) are not diagnostic and therefore should not be used as the first-line investigation of ectopic pregnancy.

Where an ectopic pregnancy has been confirmed on USS, serum hCG measurement should only be used to assess trophoblastic proliferation to help determine subsequent management if a patient is thought to be suitable for expectant or medical management. It should not be used to determine the location of the pregnancy.

Serial hCG measurements are helpful for investigating patients with pregnancy of unknown location (PUL) – see below for guidance.

Management of ectopic pregnancy

See appendix 1 for a suggested management algorithm for tubal ectopic pregnancy.

All patients with a suspected or confirmed ectopic pregnancy should receive oral and written information regarding:

- the treatment options and what to expect during and after treatment,
- how to access healthcare professionals for advice following their treatment,
- where and when to get help in an emergency

Expectant management

Based on limited evidence, there seems to be no difference following expectant or medical management in the rate of ectopic pregnancies ending naturally, the risk of tubal rupture, or the need for additional treatment (but they may require urgent treatment if their condition deteriorates). Patients should be advised that the time taken for ectopic pregnancies to resolve and future fertility outcomes are likely to be the same with either expectant or medical management.

Obtain written consent for management plan and proposed follow-up.

The **criteria** for expectant management of ectopic pregnancy are:

- Clinically stable and pain-free
- Tubal ectopic measures <35mm with no visible heartbeat on TV USS
- Serum hCG is <1000IU/L
- Able and agreeable to return for follow-up
- **Consider expectant management** if hCG between 1000 IU/L and 1500 IU/L – **senior medical review required**

Planned follow-up

- Repeat hCG on days 2, 4 and 7 following initial test
- If hCG levels drop by 15% or more from the previous value on days 2, 4 and 7, then repeat weekly until a negative result is obtained (<5 IU/L)
- If hCG levels do not fall by 15%, stay the same or rise from the previous value, review the patient's clinical condition and seek senior medical review

Medical management

Medical management of ectopic pregnancy uses systemic methotrexate administered as an intramusular injection, with the dose calculated based on the patient's body surface area. Methotrexate is an antimetabolite that prevents the rapid growth of cells. Side effects arise in 2% of people and include stomatitis, alopecia and haematosalpinx. The serious risks of pneumonitis and life-threatening sepsis secondary to neutropenia are rare. Occasionally patients having treatment

with methotrexate may need a repeat dose, and the treatment may also fail necessitating immediate surgical intervention.

Patients who are considered to be suitable for management with methotrexate must be reviewed by a consultant (includes ST7 (specialty trainee) in consultant role) or specialist doctor, and the discussion and decision must be documented in the medical case notes.

Use the integrated care pathway (ICP) for medical management of ectopic pregnancy.

The **criteria** for systemic methotrexate for management of ectopic are:

- Clinically stable with no significant pain
- Unruptured tubal ectopic with an adnexal mass <35mm with no visible heartbeat
- No significant free fluid in the pouch of Douglas on TV USS
- Serum hCG <5000 IU/L
- Intrauterine pregnancy reliably excluded on USS
- Able and agreeable to return for follow-up, which may continue for several weeks

Situations potentially suitable for methotrexate use:

- May be the preferred option for patients with a cervical / cornual ectopic / persistent ectopic following conservative surgery
- In patients who are medically unfit for surgery or where surgery is likely to be technically difficult
- Patient choice – after appropriate counseling
- Patients with previous salpingectomy

Contraindications to methotrexate (see ICP for complete list):

- Acute infection
- Severe anaemia / haemodynamic instability / blood dyscrasia
- Neutropenia / leucopenia / thrombocytopenia,
- Moderate to severe renal or liver impairment or active pulmonary disease
- Active peptic ulcer or colitis or immunodeficiency
- Significant pain
- Breastfeeding mothers

Prescribing and Administration of methotrexate (MTX)

- Counsel patient on treatment plan
- Obtain written consent for the treatment and proposed follow-up
- Perform full blood count, urea and electrolytes, liver function tests and blood grouping
- Measure height (cm) and weight (kg).

- Using the table below, the consultant obstetrician or speciality doctor should calculate the body surface area and prescribe the dose. Pharmacy will verify the dose prescribed.

  (Dose is 50mg/m^2 but will be banded according as per table below.

  75mg /85mg / 100mg / 125mg injections will be administered accordingly)

- Methotrexate must be prescribed on a cytotoxic prescription and must be signed by senior medical staff (consultant, ST7 trainee or specialty doctor)
- Methotrexate should be administered by intramuscular injection by an appropriately trained healthcare professional

Table indicating dose of methotrexate to be given by patient body surface area*:
***see mdcalc for body surface area calculation**

Body surface Area (m^2)	Dose (mg)	Syringe to be administered (mg) by IM injection
1.4 -1.59	75	75
1.6 - 1.79	85	85
1.8 - 2.19	100	100
2.2 – 2.5	125	100 + 25
>2.5	Contact pharmacy	Contact pharmacy (Use 50mg/m^2 and contact pharmacy for help with rounding the dose to the nearest available syringe combination (max 2syringe/dose)

Patients should be informed:

- Of all emergency contact numbers – EPAS / maternity triage
- They may experience pain and bleeding
- The abdominal pain often worsens 2-4 days after MTX is given secondary to tubal swelling and simple analgesics may be taken
- Avoid non-steroidal anti-inflammatory drugs for 48 hours - can use paracetamol or co-codamol
- Avoid alcohol consumption
- If severe pain experienced, admission is warranted
- Surgery may be required if there is suspicion of tubal rupture
- A second dose of methotrexate or laparoscopy may be need if there is insufficient fall between day 4 and day 7 serum hCG (occurs in 3-8% of patients)
- Avoid sexual intercourse during treatment period

- Avoid pregnancy for at least 3 months after the last dose of MTX.
    - After multiple doses, avoid pregnancy for 6 months as a precaution

Follow up after methotrexate administration:

- Measure serum hCG on days 1, 4 and 7.
- Serum hCG usually rises up to day 4 post-MTX and then declines.
- The day 7 serum hCG should have **declined by at least 15%** from the day 4 level
    - If not, repeat treatment protocol if clinically stable
- **Review weekly in EPAS – assess clinical condition and measure serum hCG**
- Serum hCG represents trophoblastic proliferation, hence should fall each weekly
- Serum hCG should be tracked until <5 IU/L
- If serum hCG begins to plateau during follow-up, a repeat dose of methotrexate may be administered

Surgical management of ectopic pregnancy

Surgical management of tubal ectopic is the treatment of choice for -

- Haemodynamically unstable / symptomatic patients
- Live tubal ectopic
- Tubal ectopic mass >35mm
- Significant free fluid within the pelvis
- Heterotopic ectopic
- hCG ≥5000 iu/l
- Failed medical treatment
- Those who are unable or deemed unsuitable to return for follow-up monitoring after methotrexate
- Patient choice

Surgical Approach

- Ideally should be performed laparoscopically by suitably trained surgeons
- In the event of a haemodynamically unstable patient laparotomy may be the fastest route to control the bleeding.
- Salpingectomy is the preferred option.

- Patients should be advised to perform a high sensitivity home pregnancy test 3 weeks after salpingectomy, and notify EPAS if the result is positive
- Salpingotomy may be considered in cases, such as unhealthy contralateral tube
- In cases where salpingotomy is performed:
    - Inform patient there is up to a 1 in 5 chance further treatment in the form of methotrexate +/- salpingectomy may be needed, due to the risk of persistent trophoblast
    - Emphasise close follow-up is needed
    - Serum hCG to be taken 7 days post salpingotomy then weekly hCGs until <5 IU/L

Pregnancy of unknown location (PUL)

See appendix 2 for a suggested management algorithm for PUL.

The term 'pregnancy of unknown location' (PUL) is used whenever there is no sign of intra- or extra-uterine pregnancy or retained products of conception on TV USS, despite a positive pregnancy test. There are 4 possible outcomes of PUL: failing PUL, intrauterine pregnancy, ectopic pregnancy and persisting PUL.

Patients presenting with suspected miscarriage and empty uterus on USS must have serial hCG to exclude the diagnosis of ectopic pregnancy, unless products of conception have been seen or prior USS confirmed the presence of an intrauterine pregnancy.

Patients with PUL who are asymptomatic should be followed-up appropriately with hCG and TV USS until the pregnancy is located accurately or until intervention becomes necessary. Greater importance should be placed on clinical symptoms rather than on hCG results, and the patient should be reviewed if symptoms change regardless of previous assessments and results. Patients attending for hCG monitoring should have observations recorded at each attendance.

Where the diagnosis remains uncertain after 3 hCG's, then consultant or specialty doctor review is required. An individualised care plan will be agreed, taking into account the risk factors, past history, symptoms and patient's wishes.

Methotrexate or surgical intervention can be considered as treatment of PUL after no fewer than 3 static hCGs, bearing in mind that half of PULs are failing intrauterine pregnancies. There must be no intrauterine findings on USS and if there is a delay greater than 48 hours in administering methotrexate then a repeat USS should be performed.

HCG < 1500iu/L

- Arrange repeat hCG in 48 hours
- Serum hCG should rise by 63% with a continuing intrauterine pregnancy - in most cases it will double
- Suboptimal rise may suggest an ectopic or a failing intrauterine pregnancy

- Management should be discussed with the gynaecology on-call team
- Serial test and/or repeat ultrasound will usually be arranged

HCG >1500iu/L: level suggested by the National Institute for Clinical Excellence (NICE) for higher risk of ectopic:

- Suggestive of a possible ectopic pregnancy
- There is however the possibility of a continuing intrauterine pregnancy within this group
- Repeat hCG and USS in 48 hours
- If clinically well, a conservative approach should be adopted initially particularly if levels appear to be rising appropriately
- If significant pain is present, a diagnostic laparoscopy should be considered

HCG > 2500iu/L

- Usually indicative of an ectopic pregnancy; offer definitive treatment

Contraception

All patients who have experienced an ectopic pregnancy or PUL should have a sensitive discussion with an appropriately trained healthcare professional regarding their contraceptive needs, which should be clearly documented in the medical case notes.

An individualised contraceptive plan should be devised with the patients using UK MEC (United Kingdow Medical Eligibility Criteria for Contraceptive Use) to assess suitability. A wide variety of contraceptive methods should be available for patients prior to discharge from the EPAS setting, such that it may be commenced as soon as possible to minimise the risk of unplanned pregnancy.

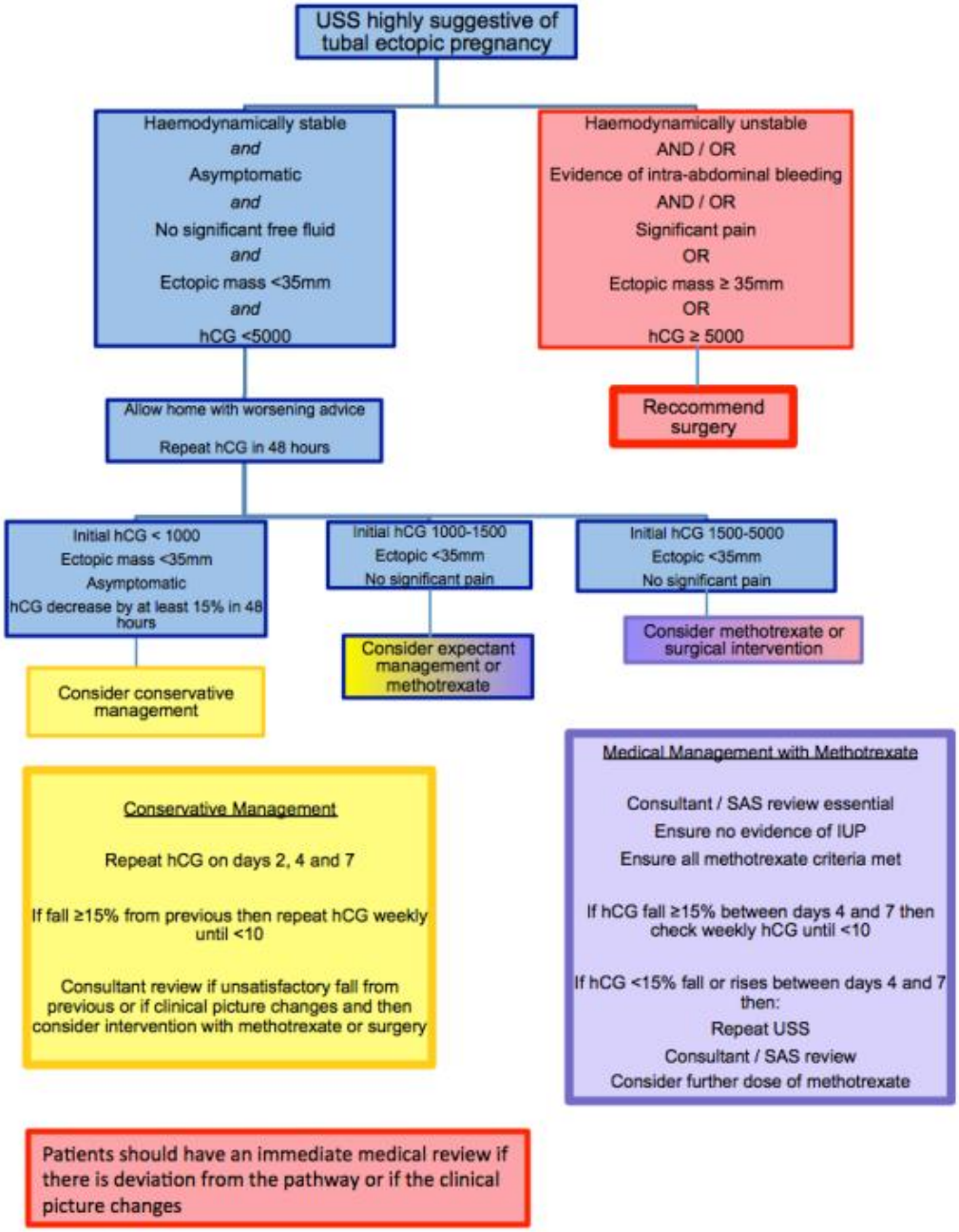
Anti-D rhesus prophylaxis

Offer anti-D Rhesus prophylaxis at a dose of 250 IU to all rhesus-negative patients who have a surgical procedure to manage an ectopic pregnancy.

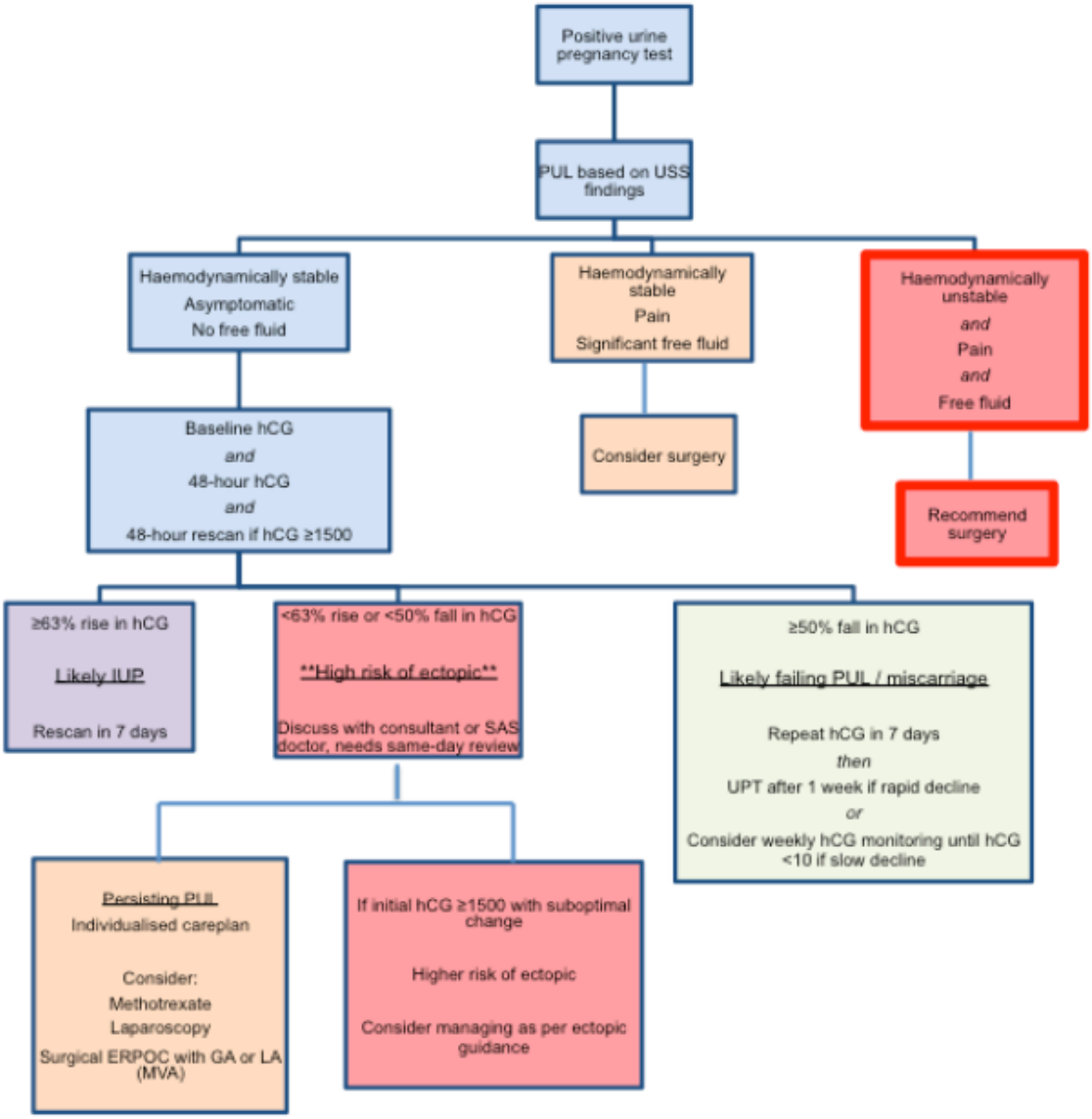
Rhesus-negative patients who have solely expectant or medical management of ectopic pregnancy or PUL should not receive anti-D rhesus prophylaxis.

Do not use a kleihauer test to quantify feto-maternal haemorrhage.

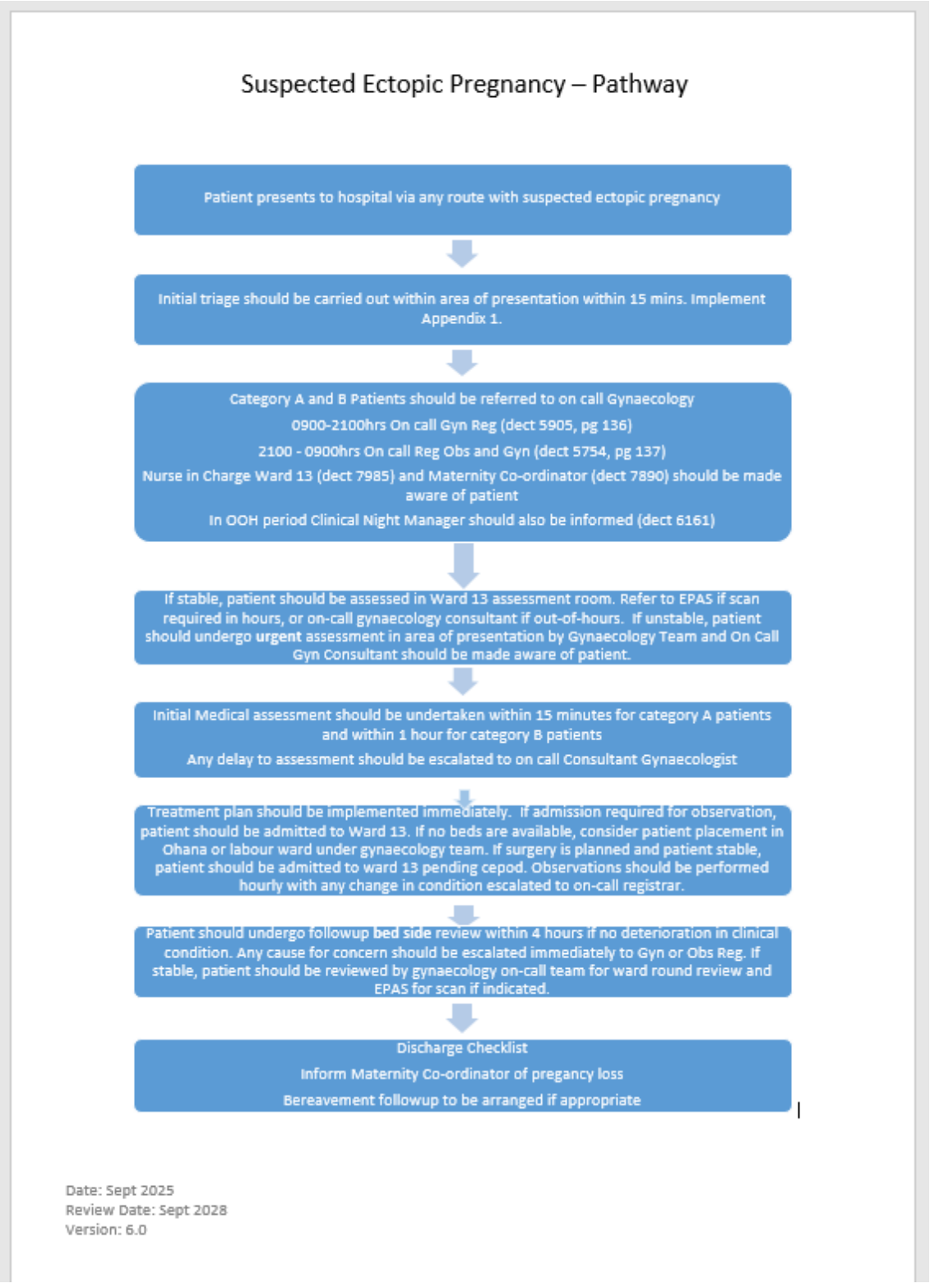
Appendix 1 – suggested management for EP



Appendix 2 – suggested management for PUL



Appendix 3 – suggested pathway for EP



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Useful documents

Patient information leaflets

- Ectopic pregnancy – Ectopic pregnancy
- Blood tests used to exclude ectopic pregnancy – Blood test to exclude Ectopic Pregnancy
- Medical management - Methotrexate for treatment of ectopic pregnancy
- Surgical management - Surgical Management of Ectopic Pregnancy

Consent forms

- Medical management – available on the Clinical Records page via Firstport
- Surgical management – available on the Clinical Records page via Firstport

Integrated care pathways

- Acute EP management – available on the Clinical Records page via Firstport
- Medical management - Integrated Care Pathway - Medical Management of Ectopic Pregnancy-Pregnancy of Unknown Location SAMPLE.pdf

Clinical governance

Lead author:	L Beaton
Current responsible author:	L Beaton
Endorsing body:	MCEG
Version number:	2
Approval date:	13.8.25
Review date:	13.8.28

Consultation/distribution record	
Contributing authors:	L Beaton (Specialty Doctor O&G), E O'Connor (Cons O&G)
Consultation process:	MCEG
Distribution:	All in maternity via RDS app

Change record			
Date	**Lead author**	**Change**	**Version**
May 2022	L Beaton	Initial document	1
13.8.25	L Beaton	New formatting, insertion of appendix 3 and links to other ectopic-related documents	2