Bwrdd Iechyd Prifysgol Cwm Taf Morgannwg University Health Board

Diagnosis and Management of PUL and Ectopic Pregnancy including Methotrexate Therapy

Initiated By	Cwm Taf Morgannwg University Health Board Obstetrics and Gynaecology Directorate
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AUTHORSHIP, RESPONSIBILITY AND REVIEW

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CHANGE HISTORY

Version	Date	Author Job Title	Reasoning
1.0	February 2020	Mr Ken Emmanuel Consultant Gynaecologist	
1.1	May 2020	Mr Ken Emmanuel	'Negative' hCG level <20iu as per NICE
1.2	February 2022	Mr Ken Emmanuel	Checking HCG blood test results
1.3	March 2023	Mr Ken Emmanuel	Dr Sophie Giles audit March 2023 • Contraception after methotrexate • Methotrexate checklist for patient notes • Exclusion criteria for methotrexate
1.4	September 2023	Mr Ken Emmanuel	Incorporated NICE 2023 updates
1.5	May 2024	Mr Ken Emmanuel	Amended key message indication when to seek consultant review at Page 8

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BACKGROUND

Guideline Definition

Clinical guidelines are systemically developed statements that assist clinicians and patients in making decisions about appropriate treatments for specific conditions.

They allow deviation from a prescribed pathway according to the individual circumstances and where reasons can be clearly demonstrated and documented.

Purpose

To assist medical and nursing staff in the diagnosis and management of ectopic pregnancy and pregnancy of unknown location.

Many complaints come from poor communication and contradictory advice.

The guideline aims to minimise this by standardising the information, advice and treatment that we provide to those couples who suffer early pregnancy loss and require medical treatment.

Scope

For all staff, medical, nursing and clerical, to provide uniformity in the management of patients diagnosed with a first trimester miscarriage.

Roles and Responsibilities

In seeking further advice on any uncertainties contained in this document, or if you feel that there is new or more updated advice it is your responsibility to contact the guideline author or Approval Group manager so that any amendments can be made.

The guideline Approval Group is responsible for disseminating this guideline to all appropriate staff.

The guideline author or a named alternative is responsible for updating the guideline with any amendments that they become aware of or are highlighted to them.

All health professionals are responsible to ensure that the guideline is utilised effectively, and to ensure that they are competent and compassionate in the implementation of it.

Training Requirements

There is no mandatory training associated with this guideline.

Monitoring of Compliance

- By audit and review of complaints relating to miscarriage diagnosis and management.
- The Governance Department will collate any complaints and distribute to the relevant individuals for comments, and share any learning points.
- The Service Lead will oversee any governance issues, make relevant recommendations to the directorate, and advise the Clinical Director or the directorate of any matters that require implementation.
- The Health Board reserves the right, without notice, to amend any monitoring requirements in order to meet any statutory obligations or the needs of the organisation

Complaints

All complaints should try to be resolved with the patient during any contact to avoid escalation. There concerns should be listened to and documented. If it is not possible to address any concerns at the time, or if the complaint is of a serious nature, the patient's complaint should be discussed with the consultant in charge for the day, or the patient should be given details of how to raise a formal complaint via the local governance department.

ECTOPIC PREGNANCY AND PREGNANCY OF UNKNOWN LOCATION

Related Guidelines

- Diagnosis and Management of First Trimester Miscarriage (<13 weeks)
- Anti-D Prophylaxis Guideline

Definition and Background

The aim of this guideline is to provide advice and care for the patients with possible ectopic pregnancy or pregnancy of unknown location (PUL).

Ectopic pregnancy is any pregnancy implanted outside of the endometrial cavity. In the UK, the incidence is approximately 11/1000 pregnancies, with an estimated 11,000 ectopic pregnancies diagnosed each year. This guideline will cover the following ectopic pregnancies: tubal, cervical, caesarean scar, interstitial, cornual, ovarian, abdominal and heterotopic. **Pregnancy of Unknown Location (PUL)** is said to occur when there is positive pregnancy test but no pregnancy can be found on pelvic ultrasound scan.

Unfortunately, women still die from ectopic pregnancy, with six maternal deaths reported between 2006 and 2008. It remains the leading cause of maternal death in the first trimester. However, the case fatality rate has decreased over recent years, suggesting that earlier diagnosis and treatment may have made an impact.

Ectopic pregnancy risk factors include tubal damage following previous abdominal or pelvic surgery, infection, ectopic, sterilisation/ smoking/ extremes of reproductive age, IVF/subfertility/ IUD failure and known tubal blockage. However, the majority of women with an ectopic pregnancy have no identifiable risk factor.

Poor communication is a recurring cause of complaint from women experiencing miscarriage. All patients must be counselled sensitively, with empathy and patience. The correct terminology should be used when counselling and for documentation. The following topics must be covered during counselling, and should documented in the notes:

- Information on diagnosis and follow-up including oral and written information about what to expect throughout the process and advice on pain relief.
- Ectopic pregnancy and PUL information leaflet given to the patient **https://tinyurl.com/yck7hy5z**
- The patient and partner/companion have no further questions
- When and how to seek help if symptoms worsen or change, and providing a 24 hour contact number(s).
- Advice when conception can next be attempted. There is usually no reason to wait more than one cycle

The Early Pregnancy and Gynaecology Assessment Unit (EPGAU) has experienced nurses who can provide additional counselling if necessary.

Safety Net Advice and Urgent Referral

It is important to provide contact details of the EPGAU, its opening time, and any other emergency contact details so as to allow women to be able to seek advice should they be worried or have worsening symptoms.

Advise all women to seek advice or medical assistance should they have a positive pregnancy test and:

- Lower abdominal pain, particularly unilateral
- Vaginal bleeding - may be absent, light or brown discharge
- GI upset, particularly diarrhoea, or rectal pain on defecation
- Feeling faint or light-headed
- Shoulder tip pain
- Any issue for which they are concerned or worried about
- Risk factors for ectopic pregnancy (as mentioned above)
- Urinary symptoms

CLINICAL ASSESSMENT

Documentation

False positive laparoscopy is a national RCOG auditable standard, and clear records must be kept.

To aid clinicians in the diagnosis of suspected ectopic pregnancy/PUL, The EPGAU must begin a summary sheet record of all women suspected of ectopic pregnancy/PUL that contains information (dataset) on hospital ID, Name, DOB, date seen, ßhCG level and % change in value from the previous scan, main ultrasound scan finding, TV/TAS method, plan of care, and name of person planning care. A copy should be made available 24 hours/day, including in the woman's notes, and filed in an appropriate, accessible manner. (see the *Appendices and Summary* section)

The above minimum dataset information should also be logged on an ongoing spreadsheet and stored on the hospital's shared drive so that prospective audit can be easily carried out and it will also provide a second method of accessing data.

History

- Take a thorough history especially with respect to ectopic pregnancy risk factors and LMP.
    - Do not use gestational age from the LMP alone to determine whether a fetal heartbeat should be visible.
    - Inform women that the date of their LMP may not give an accurate representation of gestational age because of variability in the menstrual cycle.

KEY MESSAGE:

- **Refer women who are haemodynamically unstable, or in whom there is significant concern about the degree of pain or bleeding, directly to A&E.**

Examination and Observations

- Ensure temp/HR/BP/RR are recorded for **all** women presenting to EPGAU, including those reattending.
- Exclude features of acute abdomen, and localised/unilateral tenderness
- Exclude cervical excitation but **avoid deep bimanual examination** as this may cause rupture of the ectopic. Any masses will be picked up by ultrasound scan usually.

KEY MESSAGE:

- **TACHYCARDIA usually precedes a fall in blood pressure**
- **BRADYCARDIA can occur due to the vasovagal effect of rupture**

Investigations

- FBC, G&S, and any relevant other blood tests
- X-match 4 units (if surgery is imminent or patient unstable)
- Transvaginal ultrasound of pelvis (a gestational pseudo-sac (small volume of empty free fluid within the uterine cavity) is seen in about 60% of possible ectopic pregnancies)
    - When carrying out a transabdominal or transvaginal ultrasound scan during early pregnancy, scan the uterus and adnexa to see if there is a heterotopic pregnancy
    - Where a woman declines a transvaginal ultrasound scan, offer a transabdominal ultrasound scan and explain the limitations of this method of scanning. In such cases, uterine contents may not be clearly seen until serum ßhCG is 2000-2500 IU/l, and is dependent on body habitus.

- ßhCG, repeat **after** 48 hours (but no earlier), if surgery is unlikely and the woman is stable *[serum progesterone is not helpful and should not be used]*
    - A suboptimal rise in ßhCG occurs when the rise is <63% in 48 hours, and a suboptimal fall in ßhCG when the fall is <50% .
- The % rise or fall is calculated as follows:

$$\%\ \textbf{rise or fall of hcg level} = 100\,x\left(\left(\frac{[\textbf{Current hCG}]}{[\textbf{Previous hCG}]}\right)-1\right)$$

Usually a combination of pelvic transvaginal ultrasound scan (TVUS) along with ßhCG levels gives a good indication as to the status of the pregnancy. As a rule of thumb, a ßhCG level of 1000-1500 should allow TVUS to see an intrauterine pregnancy if present. However, many ectopic pregnancies never reach these cut off values, and tubal rupture can occur at very low ßhCG levels (<100). Therefore, **do not rely on ßhCG levels alone when making a decision on the diagnosis of ectopic pregnancy**.

Checking hCG Results

KEY MESSAGE:

ßhCG results should be documented in the notes on the day that they are taken (and certainly within 12 hours) by the person taking the test, and a plan of care made directly with the woman, explaining the implication of the result. Where the person taking the test will be unable to 'chase' the result within good time, this should be handed over to a suitable colleague to action, and the hand over documented in the patient's notes.

ALL WOMEN ARE PRESUMED TO HAVE A PREGNANCY OF UNKNOWN LOCATION UNTIL PROVED OTHERWISE.

KEY MESSAGE:

- **Women and clinical staff should understand the importance of follow up.**
- **After 1 serum ßhCG level has been taken, a 2nd ßhCG can only be requested after review by a senior healthcare professional at middle grade or higher. The 1st and 2nd results (providing both numerical values and % ßhCG changes) must be discussed with a middle grade or higher for a plan of care. If there is any deviation of management from the guideline/flowchart OR the guideline suggests ectopic pregnancy, the case must be discussed with the consultant on-call, on the day of the test, explaining the guideline issue.**
- **After 2 or more serum hCG levels have been taken, NO further ßhCG levels may be taken without discussion with the consultant on call. ALL results must be discussed with the consultant on-call on the day of the test (providing both numerical values and % ßhCG changes) so that ongoing plan of care can be made.**

A summary on the interpretation of ßhCG levels please refer to the *Appendices and Flowcharts* section for further advice.

MANAGEMENT OF PREGNANCY OF UNKNOWN LOCATION (PUL)

The term 'pregnancy of unknown location' is used whenever there is a positive pregnancy test, and no evidence of an intra or extra uterine pregnancy, or retained products of conception on transvaginal ultrasound, despite a positive pregnancy test. This occurs in 8-31% of women attending for an ultrasound assessment in early pregnancy. A consensus statement produced by the International Society of Ultrasound in Obstetrics and Gynaecology stated that modern units should try to maintain a PUL rate of <15%.

All PULs being managed expectantly should be recorded in an early pregnancy register and discussed at a weekly Early Pregnancy MDT meeting with the EPGAU staff.

A summary on the interpretation of ßhCG levels please refer to the *Appendices and Flowcharts* section for further advice.

Serial opinions by different consultants on an individual woman are suboptimal and should be avoided if practicable, unless that consultant is unavailable in the hospital. If a different opinion is needed and the consultant is in the hospital, it is important to ensure that the medical notes are available for review.

PUL Pathway

- The management is based on serial βHCG measurements, repeat ultrasound scan findings, and clinical symptoms. Women with a PUL are assumed to have an ectopic pregnancy until the location is determined.
- In a woman with a pregnancy of unknown location, place more importance on clinical symptoms than on serum βHCG results, and review the woman's condition if any of her symptoms change, regardless of previous results and assessments:

KEY MESSAGE:

- **Asymptomatic women may be managed as an outpatient by the EPGAU staff using these guidelines along with safety net advice.**
  - **Expectant management has shown to be safe, reduces the need for unnecessary surgical intervention and is not associated with serious adverse outcomes. However, multiple visits to the early pregnancy unit are often necessary before a diagnosis is made**
- **Symptomatic women require admission and urgent review by an experienced doctor (not junior SHO grade), and subsequent discussion with the consultant on call. Haemodynamically unstable women will require surgery.**

- Use serum βHCG measurements only for assessing trophoblastic proliferation to help to determine subsequent management.
- Take 2 serum βHCG measurements as near as possible to 48 hours apart (but no earlier) to determine subsequent management of a pregnancy of unknown location. Take further measurements only after review by a senior healthcare professional (consultant or senior registrar).
- Regardless of serum βHCG levels, give women with a pregnancy of unknown location written information about what to do if they experience any new or worsening symptoms, including details about how to access emergency care 24 hours a day. Advise women to return if there are new symptoms or if existing symptoms worsen.
- For a woman with an increase in serum βHCG concentration greater than 63% after 48 hours:
  - Inform her that she is likely to have a developing intrauterine pregnancy (although the possibility of an ectopic pregnancy cannot be excluded).
  - Offer her a transvaginal ultrasound scan to determine the location of the pregnancy between 7 and 14 days later. Consider an earlier scan for women with a serum βHCG level greater than or equal to 1500 IU/litre.

  - If a viable intrauterine pregnancy is confirmed, offer routine antenatal care.
  - If a viable intrauterine pregnancy is not confirmed, refer her for immediate clinical review by a senior healthcare professional (consultant or senior registrar).
- For a woman with a decrease in serum βHCG concentration greater than 50% after 48 hours:
  - Inform her that the pregnancy is unlikely to continue but that this is not confirmed **and** provide her with oral and written information (Leaflet M206) about where she can access support and counselling service **and** ask her to take a urine pregnancy test 7-14 days after the second serum βHCG test, **provide her with a pregnancy test kit**, and explain that:
    - If the pregnancy test is negative, no further action is necessary
    - If the pregnancy test is positive, she should return to the early pregnancy assessment unit for clinical review within 24 hours.

For a woman with a change in serum βHCG concentration between a 50% decline and 63% rise inclusive, please refer to the summary on the interpretation of ßhCG levels in the *Appendices and Flowcharts* section for further advice.

Basis of diagnosis

- The level of βHCG produced by a viable intrauterine pregnancy should normally increase by at least 63% every 48 hours.
- The discriminatory level is the level of βHCG at which one should see an intrauterine pregnancy on transvaginal ultrasound. The level depends on expertise, but in our unit we use 1500 IU/l.
- Using the combination of serial βHCG and transvaginal ultrasound, the diagnosis of ectopic pregnancy can be made with a sensitivity of 95-98% and a specificity of 98%.
- Diagnostic laparoscopy is the gold standard for the diagnosis of ectopic pregnancy. It should be considered if the transvaginal scan was not conclusive and βHCG levels are above 1500 IU/L. It should also be considered if there is a strong clinical suspicion.

Cautions

- Around 15% of normal viable intrauterine pregnancies are associated with less than 63% rise in βHCG level in 48 hrs and 13% of ectopic pregnancies will have a normal doubling time. Therefore, impaired or satisfactory βHCG increment will not discriminate sufficiently between normal and abnormal pregnancies.
- In multiple pregnancies the level of βHCG would be slightly higher requiring an extra 2-3 days for a sac to be visible on ultrasound scan and the levels will not rise as in a singleton pregnancy.
- After two serial HCG measurements, a senior opinion (consultant or senior registrar) should be sought if the diagnosis is still not established.

MANAGEMENT OF TUBAL ECTOPIC PREGNANCY

Adnexal masses are presumed to be an ectopic pregnancy unless stated specifically to be otherwise. **Decisions on the ultimate management of likely ectopic pregnancy can only be made by a consultant.**

Surgical

- Surgical management is more likely where the patient has any of the following:
  - an acute abdomen
  - localised pelvic pain
  - appears pale, clammy or faint
  - exhibits cervical excitation on PV exam
  - abnormal MEWS score – heart rate abnormalities, low BP, elevated resp. rate
  - shows evidence of falling haemoglobin levels
- Failed conservative or medical management of ectopic pregnancy is also an indication for surgery.
- Relative contraindications include
  - cornual and cervical pregnancy (due to the higher risk of significant bleeding) – consider methotrexate
  - high risk for intra-abdominal adhesions
  - high anaesthetic risk (e.g. morbid obesity)
- Once the decision has been made by the consultant, keep the patient starved and book an operating theatre
- When consenting a patient for surgery, they should also be consented for
  - the *Sensitive Disposal of Fetal Remains* following histological assessment
  - salpingectomy (if the contra-lateral tube is normal), and salpingostomy (if the woman only has one tube)
- Anti-D is required if the woman is rhesus negative. Follow the *Anti-D Prophylaxis Guideline*

Negative Laparoscopy

If the patient has a negative laparoscopy for a presumed ectopic pregnancy then, as with conservative management of ectopic pregnancy, the ßhCG should be tested on Day 0 and 48 hours later to ensure a significant drop in ßhCG (at least 50%), and then attend EPGAU weekly for serum ßhCG testing until the ßhCG is negative (<20U/l). If there is not a significant decrease in ßhCG levels or the patient becomes/continues to be symptomatic, the patient should be discussed with the consultant with a view to methotrexate therapy.

Salpingotomy and Salpingostomy

If a salpingotomy or salpingostomy is performed, women should be informed about the risk of persistent trophoblast and the need for serum ßhCG follow-up. They should also be counselled that there is a small risk that they may need further treatment in the form of systemic methotrexate or salpingectomy.

To exclude the presence of residual trophoblast, the woman must have the ßhCG checked on Day 0 and 48 hours later to ensure a significant drop in ßhCG (at least 50%). The woman should then follow the *Conservative* management pathway below.

Conservative

Less than 10% of presumed ectopic pregnancies are suitable for conservative management. Conservative management is an option when **all** of the following apply:

- The woman is clinically stable and has no symptoms
- The woman **is** able to be regularly followed up
- The ectopic pregnancy is small and not live
- The is no evidence of intra-abdominal bleeding (i.e. significant free pelvic fluid) on ultrasound scanning

- The initial ßhCG < 1,000 U/l

This pathway may also be considered if there are relative contraindications for surgery (see above).

Management Steps

- If the woman remains clinically well and asymptomatic arrange a clinical review and repeat serum ßhCG every 48 hours in the first week:
    - If the ßhCG level decreases by 50% or more every 48 hours then continue
    - After the first 3 consecutive ßhCG levels, if the woman remains well, move to once weekly clinical review, and ßhCG testing until the ßhCG is 'negative' (less than 20 U/l). Always reiterate safety net advice to the woman at each review.
- **Should home urine pregnancy test be considered, the woman should offered a pregnancy test kit to take home.**
- Arrange for immediate clinical review, transvaginal ultrasound scan, and discussion with the consultant on call or lead consultant clinician for EPGAU if:
    - ßhCG levels DO NOT decrease by 50%
    - the woman experiences any new or worsening clinical symptoms particularly if suggestive of ectopic pregnancy or rupture,

In both of the above situations consider the role of:

- further ultrasound scan
- medical management (see above)
- surgical management (see above)

Medical

Medical management is useful when:

- Surgery is contra-indicated.
- Surgery was unable to locate/remove the entire ectopic pregnancy, and there remain existing concerns about the presence of ongoing pregnancy tissue.
- Conservative management is contra-indicated
- Conservative management or has failed due to ßhCG levels failing to fall appropriately.

Refer to the section *Methotrexate Therapy* below for further details.

KEY MESSAGE:

- **Complications such as rupture of ectopic pregnancy can still arise at low ßhCG levels (e.g . <100)**
- **The woman needs regular clinical review and repeat serum ßhCG testing until the ßhCG is negative (<20U/l).**
- **If suitable for home urine hCG testing, you must provide the woman with pregnancy test kits.**

MANAGEMENT OF NON-TUBAL ECTOPIC PREGNANCY

Pregnancy can occur in a number of unusual locations outside of the fallopian tube. There are specific management options that should be considered

Cervical

A cervical pregnancy is an ectopic pregnancy that has implanted in the uterine endocervix (below the level of the internal cervical os). Such a pregnancy typically aborts within the first trimester, however, if it implants closer to the uterine cavity – a so-called cervico-isthmic pregnancy – it may continue longer.

Clinically the cervix may appear to have a bluish discoloration to it. Cervical pregnancy can be confused with a miscarriage when the pregnancy tissue is passing through the cervix.

- Surgical methods of management are associated with a high failure rate, and risk of major haemorrhage, and should be reserved for those women already suffering life-threatening bleeding. A local injection of diluted vasopressin (0.4 U/mL; 20 units diluted into 50 mL normal saline) may be needed intraoperatively to control any bleeding before attempted resection. The patient should be consented for hysterectomy at the same time as surgical evacuation of cervical ectopic.
- Medical management with methotrexate should be considered to manage cervical pregnancy.

Caesarean Scar

Although technically regarded as a uterine pregnancy, it is considered to be as a rare type of abnormal implantation at the site of a previous caesarean section scar. Poor healing can result in a focal thinning of the scar, excess fibrous tissue, and a susceptibility to implantation of the pregnancy at this point rather than in the endometrial cavity. It is associated with placental invasion into the myometrium and beyond (placenta increta/percreta). It is a rare and life-threatening condition, and must be immediately discussed with the consultant. The consultant may be aided by discussing these types of cases with other consultant colleagues.

- Women diagnosed with caesarean section scar pregnancies should be counselled that such pregnancies are associated with severe maternal morbidity and mortality.
- Medical and surgical interventions with or without additional haemostatic measures should be considered in women with first trimester caesarean scar pregnancy.
- There is insufficient evidence to recommend any one specific intervention over another for caesarean scar pregnancy, but **the current literature supports a surgical rather than medical approach** as the most effective. Options include:
    - dilatation and curettage
    - excision of trophoblastic tissues (laparotomy or laparoscopy)
    - local and/or systemic administration of methotrexate
    - bilateral hypogastric artery ligation associated with trophoblastic evacuation
    - selective uterine artery embolization combined with curettage and/or MTX administration
- Laparotomy followed by wedge resection of the lesion (hysterotomy) should be considered in women who do not respond to conservative medical and/or surgical treatments or present too late. Some consider this as the best treatment option.

Cornual (Interstitial)

Cornual ectopic pregnancy is uncommon. It often poses diagnostic and therapeutic challenges with a significant risk of rupturing and bleeding.

- Non-surgical management is an acceptable option for stable interstitial pregnancies. Expectant management is only suitable for women with low or significantly falling ßhCG levels in whom the addition of methotrexate may not improve the outcome.
- A pharmacological approach using methotrexate has been shown to be effective, although, there is insufficient evidence to recommend local or systemic approach.

- Surgical management by laparoscopic cornual resection or salpingotomy is an effective option. Diluted vasopressin solution (0.4 U/mL; 20 units diluted into 50 mL normal saline) may need to be infused into the uterus around the ectopic site to achieve blanching of the uterus prior to excision, followed by further vasopressin injection at the end of the procedure during knot tying. As with any surgery on the uterus, the scar of a previous laparoscopic cornual resection may become the site of a uterine rupture in future pregnancy, and is an indication for C-section. The patient should be consented for hysterectomy at the same time as surgical evacuation of cervical ectopic.
- Alternative surgical techniques could include hysteroscopic resection under laparoscopic or ultrasound guidance.
- There is insufficient evidence on safety and complications in future pregnancies to recommend other nonsurgical methods.

Ovarian

Ovarian pregnancy refers to an ectopic pregnancy that is located in the ovary. Presence of an IUD is one of contraceptive methods which prevents intra-uterine implantation in 99.5%, if implantation does occurs with IUD, it is implants within the tube in 95% of cases, and will rarely implant in other places such as ovary. The most important risk factor of ovarian ectopic pregnancy is presence of an IUD. Typically, the egg cell is not released or picked up at ovulation, but fertilized within the ovary where the pregnancy implants. Such a pregnancy usually does not proceed past the first four weeks of pregnancy, but where it does continue it generally ends with rupture before the end of the first trimester.

- Definitive surgical treatment is preferred if laparoscopy is required to make the diagnosis of ovarian ectopic pregnancy.
- Systemic methotrexate can be used to treat unruptured ovarian ectopic pregnancy when the risk of surgery is high, or postoperatively in the presence of persistent residual trophoblast or persistently raised ßhCG levels.

Abdominal

An abdominal pregnancy occurs when the embryo or fetus is growing and developing outside the womb in the abdomen, but not in the fallopian tube, ovary or broad ligament. These pregnancies can proceed to term but the risk of haemorrhage and other severe complications is high depending up site of the pregnancy. Management options include:

- Laparoscopic removal for early abdominal pregnancy is preferred.
- Systemic methotrexate with preceding ultrasound-guided feticide.
- Laparotomy for advanced abdominal pregnancy

Heterotopic

A **heterotopic pregnancy** is a multiple pregnancy in which there is a simultaneous development of an intrauterine and extrauterine pregnancy. Although common with assisted reproductive techniques, is very rare in natural conception.

The intrauterine pregnancy must be considered in the management plan. Heterotopic pregnancy , when diagnosed is managed by removal of the ectopic and conservation of the intrauterine pregnancy. The survival rate of the uterine fetus of an ectopic pregnancy in heterotopic gestation is about 70%. Management options include:

- Methotrexate should only be considered if the intrauterine pregnancy is nonviable or if the woman does not wish to continue with the pregnancy.
- Local injection of potassium chloride or hyperosmolar glucose with aspiration of the sac contents is an option for clinically stable women.
- Surgical removal of the ectopic pregnancy is another option depending on the clinical status of the ectopic and the wishes of the woman.
- Expectant management is an option in heterotopic pregnancies where the ultrasound findings are of a nonviable pregnancy.

METHOTREXATE THERAPY

Methotrexate (MTX) is a folic acid-antagonist (anti-metabolite) which prevents the growth of rapidly dividing cells by interfering with DNA synthesis. In relation to early pregnancy management, it is most commonly given as a **single intra-muscular dose of 50 mg/m2** that is well tolerated and effective. Published studies have shown success rates of 81-98% if serum βHCG levels are less than 1000 IU/l, compared to only 38% if βHCG levels are greater than 5000 IU/l.

KEY MESSAGE:

- **Systemic methotrexate should <u>never</u> be given at the first visit, unless:**
  - **the diagnosis of ectopic pregnancy is <u>absolutely</u> clear, and**
  - **a viable intrauterine pregnancy has been <u>absolutely</u> excluded.**

Criteria For Administration

The woman should be told that although MTX is recommended by NICE and is a proven treatment, MTX is not licensed for use in pregnancy. This must be documented on the consent form and in the notes.

A formal consent form must be completed with the woman before administration of MTX.

INCLUSION CRITERIA	EXCLUSION CRITERIA
No significant pain	Clinical or TVS features of intra-peritoneal haemorrhage
No intrauterine pregnancy	Adnexal mass ≥ 35mm diameter
TVS confirmed unruptured ectopic with adnexal mass <35mm and no FH	The presence of cardiac activity (live ectopic) in an ectopic pregnancy
Haemodynamically stable	Haemodynamically unstable
Normal LFT, U&E, FBC	Hepatic dysfunction, severe renal impairment, thrombocytopenia (platelets <100), blood dyscrasia (WCC <2.0), severe anaemia, photosensitivity eg) psoriasis
Failed or incomplete surgical treatment	Active pulmonary disease
ßhCG levels not falling by at least 50%	Peptic ulcer or ulcerative colitis
Patient able to commit to lengthy (average 35 days) follow-up process	Patient **<u>not</u>** able to commit to lengthy (average 35 days) follow-up process
ßhCG values <1500 IU/litre - offer as first line treatment (NB. If ßhCG value <1000 IU/litre consider conservative management and repeat serum ßhCG in 48 hours if the patient remains stable [see *Interpretation of ßhCG Levels]* above)	Clinical issues: • active infection or immuno-suppressed • steroid use • alcoholism • anti-coagulants use
ßhCG level 1500 - 5000 IU/litre - offer MTX or surgery if mass <35mm and No FH (presence of an FH increases the chance of rupture and further intervention)	If ßhCG levels are rising one must exclude intrauterine pregnancy before starting treatment

MTX Treatment Pathway

- The decision to give MTX is a consultant decision, and their agreement must be documented in the notes.
- The patient must be reviewed by at least a middle grade doctor or higher.
- Avoid vaginal examination to reduce the risk of rupture of a known ectopic.
- Ensure that the patient meets the criteria for therapy
- All the options of treatment should be discussed, and an information leaflet provided, so that the woman can make an informed decision.
- Informed written consent should be obtained and documented, including unlicensed ('off label') use of methotrexate

KEY MESSAGE:

- **Explain explicitly that there is a 7% (1/14 women) risk of tubal rupture.**
- **Explain the potential consequences of rupture and provide safety net advice.**
- **Explain that the risk of rupture remains so until the ßhCG is negative (<20 U/l).**
  - **Explain that rupture has been reported with negative levels of serum βHCG.**

- Record height and weight and calculate the body surface area using two methods (formula and Du Bois)

$$\boldsymbol{Body\ Surface\ Area\ (m2)} = \sqrt{\left(\frac{\mathbf{Height[cm]} * \boldsymbol{Weight[kg]}}{\mathbf{3600}}\right)}$$

and then calculate the dose of MTX

$$\boldsymbol{Methotrexate\ Dose(mg)} = \mathbf{50}\ \boldsymbol{x\ Body\ Surface\ Area}$$

KEY MESSAGE:

- **The BSA should be checked by two different methods to confirm similar results.**
- **The MTX dose calculation MUST be independently checked by another clinician and signed on the drug chart. A dedicated Methotrexate prescription chart is available online or in pharmacy.**
- **MAXIMUM METHOTREXATE DOSE 100mg in obese women (higher doses of up to 120mg have been reported, but higher doses are not proportionate to improved success rate per se)**

- Organise baseline blood tests: FBC, G&S, LFT's, U&E's and ßhCG.
- Methotrexate should be given as prescribed by appropriately trained staff in line with hospital policy for the administration of cytotoxic drugs.
- The woman should rest and remain in the hospital for up to one hour post-administration of methotrexate.
- Before discharge home the practitioner giving the MTX should check patient has no local reaction to the drug.

- Before discharge ensure that patient is fully aware of follow-up arrangements, and is provided with 24-hour per contact numbers for the EPGAU, and is given safety net advice.
- **Do not** prescribe anti-D for medical management of ectopic pregnancy.
- Women should be made aware of how to access support via patient support groups, such as the Ectopic Pregnancy Trust, or local bereavement counselling services.
- Advise the woman that:
    - She may experience some vaginal bleeding ranging from dark brown spotting to heavier bright red loss, which may last a few days to weeks. She should contact the EPGAI if it is excessive or the patient is concerned.
    - Side effects of the drug are minimal but may include nausea, vomiting, stomatitis and diarrhoea.
    - Maintain ample fluid intake (> 1.5L/day)
    - She should avoid:
        - Alcohol or folic acid containing vitamins during treatment as they may interfere with the effectiveness of methotrexate treatment.
        - NSAID, aspirin, omeprazole
        - Sexual intercourse until resolution of the ectopic pregnancy
        - Exposure to sunlight
        - Heavy lifting
        - Mouthwashes containing Chlorhexidine
- Muscle relaxation training (to reduce anxiety) may be of use to women undergoing treatment for ectopic pregnancy with methotrexate. Details may be found online.
- It is recommended that women treated with methotrexate wait **at least 3 months** before trying to conceive again using any form of effective contraception. Long-acting reversible contraception would be a good option.
- Should severe side effects occur contact the medical oncology team for further advice.

Follow Up

DAY	PLAN
0	Serum ßhCG, FBC, U&E, LFT, G&S and calculate the body surface area
0	Give Intramuscular methotrexate 50 mg/m2 if suitable to do so. Warn the woman that ¾ women experience worsening) abdominal pain following treatment, which is due to the drug acting on tubal pregnancy. It usually occurs on days 3-7 and normally lasts between 4-12 hours. However the patient should be advised to come in urgently if the pain is severe or there are other symptoms such as dizziness or shoulder tip pain.
4	Serum ßhCG and clinical review Serum ßhCG levels are expected to rise initially between days 1-4 (in 86% of women), and then should decline by at least 15% between Day 4 and Day 7. If it does not decline as expected or plateaus, then consider second dose or surgery after discussion with a consultant.

7	Serum ßhCG and clinical review
	
	• If ßhCG has decreased by MORE THAN 15% then repeat ßhCG weekly until <20 U/l
	• If ßhCG has decreased by LESS THAN 15% give a second dose of MTX (3/20 women)
	  o Consider repeating the TV scan depending on clinical history
	  o Consider role of any surgical options
	
	Repeat serum ßhCG and clinical review every week until <20 U/l
	
	(Rupture has been reported with negative levels of serum ßHCG)

14/21/28/35	Serum ßhCG and clinical review (average time to resolution is 35 days)

Success Rate Factors

- Success rates of 81-98% have been reported if initial serum βHCG levels are less than 1000 iu/l compared to only 38% if initial βHCG levels are greater than 5000 iu/l. Higher doses of methotrexate do not necessarily improve success rates or need for second injection.
- Success rates are higher when no gestational sac is visualised. Presence of yolk sac, fetal pole and / or fetal cardiac activity are significant predictors of failure.
- The smaller the increase in βHCG level (11 – 20% over 48 hours) prior to administration of methotrexate, the higher the chance of successful medical treatment.
- Success rates of 88-100% have been reported if serum HCG level decreases from day 1 to day 4 post administration of methotrexate compared to only 42-62% if the serum HCG level increases.

If the treatment is successful, the tube is conserved with good chance of patency (80%). Subsequent fertility appears to be as good as conservative therapy (>70%), and the risk of recurrent ectopic is the same (10%). In about 10%, surgery will be required as the ectopic ruptures during treatment or ßhCG levels do not drop as expected.

OTHER CONSIDERATIONS

Anti-D Therapy

Offer anti-D prophylaxis as per national protocol to all RhD-negative women who have surgical removal of an ectopic pregnancy, or where bleeding is repeated, heavy or associated with abdominal pain.

Long-term Fertility Outcomes

All women confirmed to have an ectopic pregnancy or PUL should be offered an early scan at 6 weeks gestation in any future pregnancy because of the increased risk, over the background risk, of a further ectopic pregnancy.

- In the absence of a history of subfertility or tubal pathology, women should be advised that there is no difference in the rate of fertility, the risk of future tubal ectopic pregnancy or tubal patency rates between the different management methods.
- Women with a previous history of subfertility should be advised that treatment of their tubal ectopic pregnancy with expectant or medical management is associated with improved reproductive outcomes compared with radical surgery.
- Women receiving methotrexate for the management of tubal ectopic pregnancy can be advised that there is no effect on ovarian reserve.
- Women undergoing treatment with uterine artery embolisation and systemic methotrexate for nontubal ectopic pregnancies can be advised that live births have been reported in subsequent pregnancies.
- Women undergoing laparoscopic management of ovarian pregnancies can be advised that their future fertility prospects are good.

Recommended Standards For ßhCG Review

1. All βHCG results requested in EPGAU during the day must be reviewed before 5.00pm on the same day, ideally by the same clinician who requested them, or it is the responsibility of clinician to hand over any outstanding ßhCG results and the plan of care, including and scan results, so that the context of the test can be determined.
2. All βHCG results from EPGAU available between 09.00hours and 17.00hours on weekdays must be reviewed by the on call middle grade before the end of their on call duty, and any outstanding results handed over to the

oncoming middle grade doctor. Any complicated patients must be discussed with the consultant before finishing their shift.

3. All βHCG results from EPGAU available between 17.00hours and 09.00 hours during the weekdays will be reviewed by the on call middle grade obstetric registrar, or the on call middle grade gynaecology registrar if their shift has not finished. This is particularly the case in women who are clinically unwell. For these cases the results must be seen ASAP.
4. The βHCG results from EPGAU over the weekend should be reviewed by the registrar on call on Saturday and Sunday on a daily basis, whenever the results are available, or handed over to the oncoming middle grade registrar. The on call registrar should discuss any complicated patients with the consultant.
5. All βHCG results have to be written down on the proformas sheet (see *Appendices and* Flowcharts) with a date, clear management plan, signature and printed name.

References

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4. Farquhar CM. Ectopic pregnancy. Lancet. 2005; 366: 583-91.
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7. Verhaegen J, Gallos ID, Van Mello NM et al. Accuracy of single progesterone test to predict early pregnancy outcome in women with pain or bleeding: meta- analysis of cohort studies. BMJ. 2012. 345: e6077.
8. Condous et al. Human chorionic gonadotrophin and progesterone levels for the investigation of pregnancies of unknown location. Int J Gynecol Obstet 2004a;86:351-357.

APPENDICES AND FLOWCHARTS

Summary Table on the Interpretation of ßhCG Levels in PUL

In a woman with a pregnancy of unknown location, place more importance on clinical symptoms than on serum ßhCG levels, and review the woman's condition if any of her symptoms change, regardless of previous results and assessments.

$$\%\ \textbf{rise or fall of hcg level} = 100\,x\left(\left(\frac{[\textbf{Current hCG}]}{[\textbf{Previous hCG}]}\right)-1\right)$$

The table assumes at least 2 ßhCG levels have been undertaken, and the woman is not compromised with significant pain or bleeding.

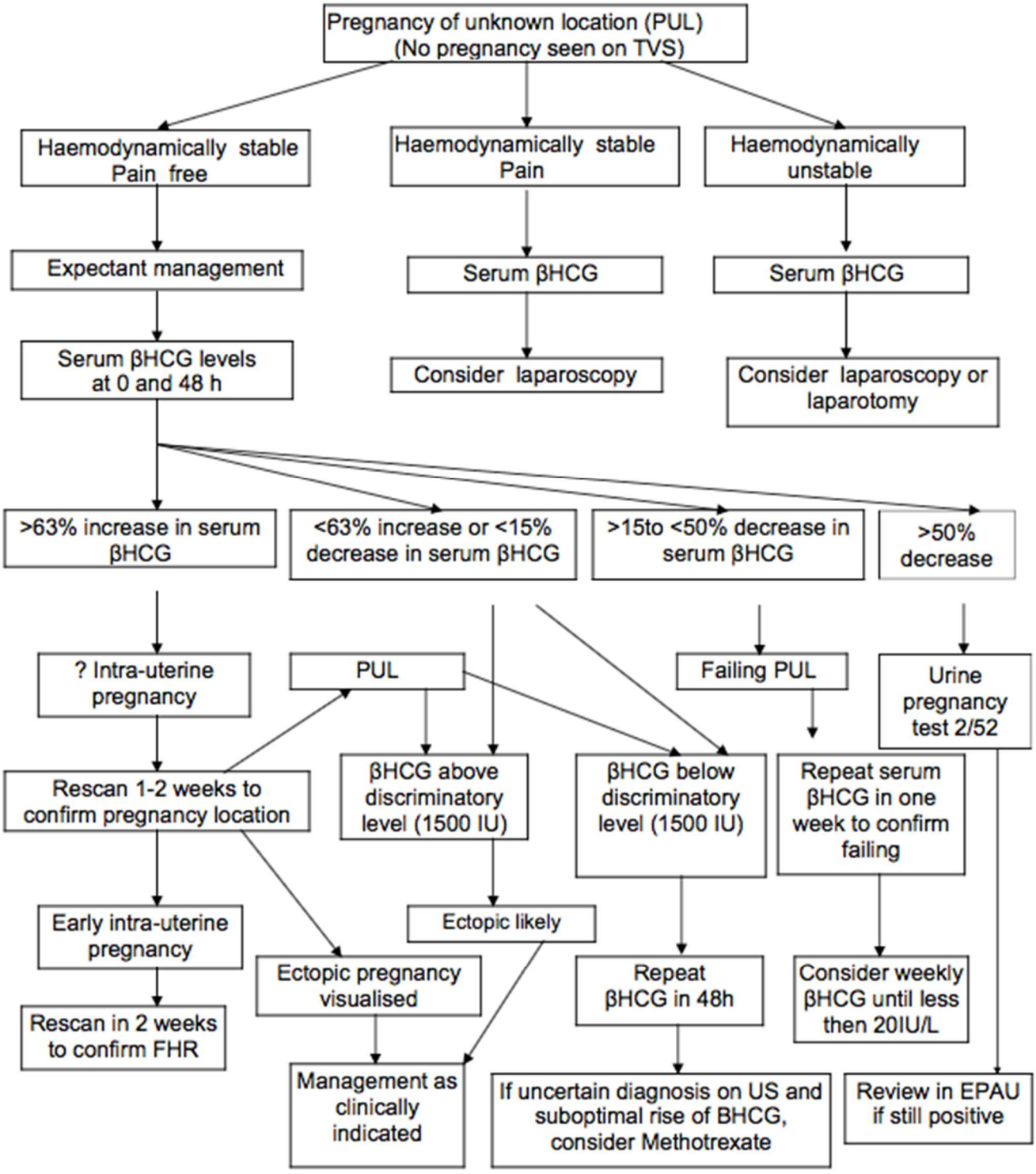
RISING ßhCG			FALLING ßhCG	
< 63% after 48 hours	> 63% after 48 hours		< 50% after 48 hours	> 50% after 48 hours
Probably non-viable	Probably viable		Probably non-viable	Most likely non-viable
Location yet to be determined but probably an ectopic pregnancy	Location yet to be determined but likely intrauterine, but ectopic and PUL not yet excluded.		Location yet to be determined but probably an ectopic pregnancy	Location may never be known
Arrange clinical review in EPGAU	Repeat TV scan in 7-14 days if ßhCG <1500	Repeat TV scan on same/next working day if ßhCG >1500 pregnancy	Arrange clinical review in EPGAU	Provide oral and written support and counselling advice Repeat ßhCG 14 days after the second ßhCG
Up to 15% of early ongoing intrauterine pregnancies have a suboptimal rise in ßhCG BUT also predicts an ectopic pregnancy with a positive predictive value of 43.5 %. If a viable intrauterine pregnancy **is not** confirmed, obtain immediate clinical review by a middle grade doctor or higher **PLAN**: If asymptomatic or has only mild symptoms arrange for a third serum βHCG level 48 hours after the second level and review in EPGAU.	**Up to 15–20% of ectopic pregnancies have serum ßhCG doubling times similar to that of an IUP** If a viable intrauterine pregnancy **is** confirmed, offer routine antenatal care and discharge from EPGAU Or If a viable intrauterine pregnancy **is not** confirmed, obtain immediate clinical review by a middle grade doctor or higher		**PLAN**: If asymptomatic or has only mild symptoms arrange for a third serum βHCG level 48 hours after the second level and review in EPGAU. Discuss management options which include **expectant management** with weekly βHCG levels until negative, **methotrexate**, or **laparoscopy +/- ERPC**. This is dependent on the patient's symptoms, βHCG levels, ultrasound findings and preferences. Consider a repeat ultrasound. ßhCG secreting tumour??	In relation to the day 14 ßhCG: • **if negative** the patient can be discharged. • **If positive** repeat TVUS, serial clinical review within 24 hrs o Level plateau consider MTX o Level low consider MTX or further ßhCG once weekly until the ßhCG is 'negative' (less than 10 U/l). If

Name/DOB/Hosp ID

Patient ßhCG Summary Sheet and Plan of Care

Date	ßhCG level	% change	TAS or TVS	Scan Result	Plan	Name/Sign

Flowchart on the Management of Pregnancy of Unknown Location (PUL)



Methotrexate (MTX) treatment for Ectopic Pregnancy / PUL

Addressograph

Patient contact nº
Consultant
Diagnosis

Inclusion criteria	TICK	Exclusion criteria	TICK
No significant pain		Clinical or TVS features of intra-peritoneal haemorrhage	
No intrauterine pregnancy		Adnexal mass ≥35mm diameter	
TVS confirmed unruptured ectopic with adnexal mass <35mm and no FH seen		The presence of FH activity (live ectopic)	
Haemodynamically stable		Haemodynamically unstable	
Normal FBC, U&E, LFT		Hepatic dysfunction, **severe renal impairment**, thrombocytopaenia (platelets <100), blood dyscrasia (WCC <2.0), severe anaemia, **photosensitivity eg) psoriasis**	
Failed or incomplete surgical management		Active pulmonary disease	
BhCG levels not falling by at least 50%		Peptic ulcer or ulcerative colitis	
Patient able to commit to lengthy follow-up process		Patient **not** able to commit to lengthy follow-up process	
BhCG values <1500 IU/Litre – offer MTX as first line treatment (NB: If BhCG value <1000 IU/Litre consider conservative management and repeat serum BhCG in 48 hours if patient remains stable)		Clinical issues: • Active infection or immune-supressed • Steroid use • Alcoholism • Anti-coagulant use	
BhCG level 1500-5000 IU/Litre – ensure surgery has been discussed as alternative		If BhCG levels are rising, one must exclude intrauterine pregnancy before starting treatment	

Checklist	TICK
G&S taken	
At least 2 BhCG taken	
Consultant informed	
Patient information leaflet provided	
Worsening advice given re: symptoms to look out for	
Contact details of EPAU and where to go in emergency provided	
Patient agrees to contraception for minimum 3 months following treatment	
Written consent form completed and signed	

DAY	DATE	BLOOD TESTS AND SCAN	RESULTS	ACTION	SIGNATURE
1		Hb			
		Platelets			
		WCC			
		Urea			
		Creatinine			
		ALT			
		Bilirubin			
		BhCG (incl %change)			
4		**BhCG (incl %change)**			
7		Hb			
		Platelets			
		WCC			
		Urea			
		Creatinine			
		ALT			
		Bilirubin			

		BhCG (incl %change)			
14		**BhCG (incl %change)**			
21		**BhCG (incl %change)**			
28		**BhCG (incl %change)**			
35		**BhCG (incl %change)**			