Our Vision
The best care for every patient

NHS
Norfolk and Norwich University Hospitals
NHS Foundation Trust

Guidelines on the Diagnosis and Management of Ectopic Pregnancy and Pregnancy of Unknown Location (PUL)

A clinical guideline recommended

For use in:	Gynaecology, Early Pregnancy Assessment Unit
By:	Doctors, Registered Nurses
For:	The management of ectopic pregnancy and Pregnancy of Unknown location (PUL)
Division responsible for document:	Division 3
Key words:	Ectopic pregnancy, diagnosis, management, pregnancy of unknown location (PUL)
Name of document author:	Gautam Raje
Job title of document author:	Consultant Obstetrician and Gynaecologist
Name of document author's Line Manager:	Jo Nieto
Job title of document author's Line Manager:	Chief of Service, Gynaecology
Supported by:	Gynaecology Guidelines Committee
Assessed and approved by the:	Gynaecology Guidelines Committee
Date of approval:	01 April 2022
Ratified by or reported as approved to (if applicable)**:**	Clinical Safety and Effectiveness Sub-Board
To be reviewed before: This document remains current after this date but will be under review	01 April 2025
To be reviewed by:	Gautam Raje
Reference and / or Trustdocs ID No:	G3 – ID No: 761
Version no:	5
Compliance links: *(is there any NICE related to guidance)*	NICE clinical guideline 126: Ectopic pregnancy and miscarriage: Diagnosis and initial management. April 2019.
If Yes – does the strategy/policy deviate from the recommendations of NICE? If so, why?	No

Guidelines on the Diagnosis and Management of Ectopic Pregnancy and Pregnancy of Unknown Location (PUL)

Version and Document Control:

Version Number	Date of Update	Change Description	Author
5	01/04/2022	Reviewed and amended to be in line with NG126.	Gautam Raje

This is a Controlled Document

Printed copies of this document may not be up to date. Please check the hospital intranet for the latest version and destroy all previous versions.

Background

The rate of ectopic pregnancy is 11 per 1000 pregnancies, with a maternal mortality of 2 per 10000 estimated ectopic pregnancies. Early diagnosis is the key to minimise mortality and morbidity.

Risk Factors

- Previous pelvic inflammatory disease
- Tubal surgery/tubal ligation
- Previous ectopic pregnancy
- Infertility
- Assisted reproductive techniques
- Smoking
- Maternal age > 40 years
- Pregnancy while on intrauterine contraceptive device
- Previous caesarean section

The possibility of ectopic pregnancy needs to be excluded, even in the absence of risk factors, because about a third of women with an ectopic pregnancy will have no known risk factors.

Diagnosis

The aim is early diagnosis of ectopic pregnancy, to reduce the risk of tubal rupture and associated life-threatening haemorrhage. A diagnosis can be made by a combination of history and examination, transvaginal ultrasound and quantitative βHCG assessment.

Clinical features

Ectopic pregnancy presents with a variety of clinical features. Atypical presentation for ectopic pregnancy is common.

Symptoms of ectopic pregnancy include:

- Common Symptoms:

  Abdominal Or Pelvic Pain

  Amenorrhoea Or Missed Period

  Vaginal Bleeding (Can Vary From Spotting To Heavy Bleeding With Clots)

- Other Reported Symptoms:

  Breast Tenderness

  Gastrointestinal Symptoms Like Diarrhoea And Vomiting

  Dizziness, Fainting Or Syncope

  Shoulder Tip Pain

  Urinary Symptoms

  Passage Of Tissue

  Rectal Pressure or pain on defecation.

Ectopic pregnancy can present with a variety of signs on examination by a healthcare professional.
Signs of ectopic pregnancy include:

- More Common Signs:

  Pelvic Tenderness

  Adnexal Tenderness

  Abdominal Tenderness

- Other Reported Signs:

  Cervical Motion Tenderness

  Rebound Tenderness Or Peritoneal Signs

  Pallor

  Abdominal Distension

  Enlarged Uterus

  Tachycardia (More Than 100 Beats Per Minute) Or Hypotension (Less Than 100/60 Mmhg)

  Shock Or Collapse

  Orthostatic Hypotension.

Ruptured ectopic pregnancy can present with severe abdominal pain with features of haemodynamic instability or shock.

Vaginal examination should be offered with clear documentation if declined by the patient.

Investigations

For women suspected to have ectopic pregnancy Transvaginal Ultrasound Scan (TVS) by a trained operator is the diagnostic tool of choice. TVS has a sensitivity of 87 - 99% and a specificity of 94 – 99.9% for the diagnosis of ectopic pregnancy. The initial TVS is non diagnostic in 8-30%.

When ultrasound scan facility is not available out of hours the management should depend on the clinical features. Clinically stable minimally symptomatic women should be offered the next available appointment in Early pregnancy Assessment Unit (EPAU).

Serum βHCG or progesterone should not be used for the initial assessment.

Transvaginal Ultrasound

The ultrasound appearances suggestive of ectopic pregnancy are variable.
The ultrasound features include an empty uterine cavity with

- Complex, inhomogeneous adnexal mass, moving separate to the ovary
- An adnexal mass, moving separately to the ovary, with an empty gestational sac (sometimes described as a 'tubal ring' or 'bagel sign')
- an adnexal mass, moving separate to the ovary, comprising a gestational sac containing a yolk sac or comprising a gestational sac and fetal pole (with or without fetal heartbeat)
- Moderate to large amount of free fluid in the peritoneal cavity or Pouch of Douglas, which might represent haemoperitoneum
- Intrauterine pseudosac – collection of fluid within the uterine cavity (in up to 20% of ectopics)

Identifying an intrauterine gestation sac will largely exclude ectopic pregnancy but will not rule it out completely The possibility of a heterotopic pregnancy should be kept in mind (1 in 3000 – 4000 of spontaneous conceptions and 1% - 3% of assisted conceptions). Confusion can occur when a pseudosac is seen in the uterus.

Please note that a complete miscarriage cannot be assumed with just an empty uterus on ultrasound scan unless the patient had a previous scan that confirmed an intrauterine gestation or there is a histology report confirming products of conception. Relying on the macroscopic appearance of tissues can be misleading. If tissue is obtained it needs to be sent for urgent histology for confirmation of pregnancy tissue. If the histology does not confirm trophoblastic tissue or if no tissue has been obtained, then these patients should be managed as Pregnancy of Unknown Location (PUL).

Treatment of ectopic pregnancy

Management depends on the clinical presentation, ultrasound findings, HCG level and woman’s preference.
Management options include medical, surgical and expectant methods.

Medical management with methotrexate as first line

Methotrexate is an antimetabolite which prevents the growth of rapidly dividing cells by interfering with DNA synthesis. Its success rate is over 90% in selected cases; the tube is conserved and there is an 80% chance of tubal patency.
Offer systemic methotrexate as a first-line treatment to women who are able to return for follow-up and who have all of the following:

- No significant pain
- An unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat
- A serum βHCG level less than 1500 IU/litre
- No intrauterine pregnancy (as confirmed on an ultrasound scan)

Methotrexate should only be offered on a first visit when there is a definitive diagnosis of an ectopic pregnancy, and a viable intrauterine pregnancy has been excluded. Offer surgery where treatment with methotrexate is not acceptable to the woman. Refer to guideline **G27 'Methotrexate for ectopic pregnancy'** for further information.

Surgical Management as first line

Offer surgery as a first-line treatment to women who are unable to return for follow-up after methotrexate treatment or who have any of the following:

- Ruptured ectopic pregnancy with collapse and / or significant free fluid in the abdomen (haemoperitoneum)
- An ectopic pregnancy and significant pain
- An ectopic pregnancy with an adnexal mass of 35 mm or larger
- An ectopic pregnancy with a fetal heartbeat visible on an ultrasound scan
- An ectopic pregnancy and a serum βHCG level of 5000 IU/litre or more

In the presence of a haemodynamically unstable patient the quickest route for achieving haemostasis should be considered (either a laparoscopy or laparotomy).

A laparoscopic approach to the surgical management of tubal pregnancy, in the haemodynamically stable patient, is preferable to an open approach. In the presence of a healthy contralateral tube, salpingectomy should be performed in preference to salpingotomy. In women with a history of fertility-reducing factors (previous ectopic

pregnancy, contralateral tubal damage, previous abdominal surgery, previous pelvic inflammatory disease), salpingotomy should be considered. Suturing the salpingotomy incision provides no benefit.

If a salpingotomy is performed, women should be informed about the risk of persistent trophoblast (3.9 – 11%) with the need for serum hCG level follow-up. Serum hCG measurement should be arranged on day 7 followed by weekly hCG measurements until negative result is obtained (hCG less than 20). Women should also be counselled that there is a twenty percent risk (1 in 5) that they may need further treatment in the form of systemic methotrexate or salpingectomy.

Advise women who have had a salpingectomy that they should take a urine pregnancy test after 3 weeks. Advise women to return for further assessment if the test is positive.

Choice of either medical or surgical management

Offer the choice of either methotrexate or surgical management to women with an ectopic pregnancy who have a serum βHCG level of at least 1500 IU/litre and less than 5000 IU/litre, who are able to return for follow-up and who meet all of the following criteria:

- No significant pain
- An unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat
- No intrauterine pregnancy (as confirmed on an ultrasound scan)

Advise women who choose methotrexate that their chance of needing further intervention is increased and they may need to be urgently admitted if their condition deteriorates.

Expectant management

Expectant management is a reasonable option for appropriately selected and counselled women. They must be willing and able to attend for follow-up, have minimal pain, and have low or declining serum b-hCG levels. Reported success rates range from 57–100% and are very dependent on case selection.

Success rates are inversely proportional to serum b-hCG levels, with lower success rates associated with higher initial serum b-hCG levels. One study reported success rates of 96% with serum b-hCG levels of less than 175 iu/l and 66% if serum b-hCG levels were 175–1500 iu/l. Other studies have reported success rates of 80–90% if the serum b-hCG levels are less than 1000 iu/l and 60–67% if b-hCG levels are less than 2000 iu/l.

Criteria for expectant management based on NICE recommendations (NG 126) are as follows

Offer expectant management as an option to women who:

- Are clinically stable and pain free and

- Have a tubal ectopic pregnancy measuring less than 35 mm with no visible heartbeat on transvaginal ultrasound scan with no haemoperitoneum and
- Have serum Hcg levels of 1,000 iu/l or less and
- Are able to return for follow-up and understand the importance of compliance

Consider expectant management as an option for women who:

- Are clinically stable and pain free and
- Have a tubal ectopic pregnancy measuring less than 35 mm with no visible heartbeat on transvaginal ultrasound scan with no haemoperitoneum and
- Have serum Hcg levels above 1,000 iu/l and below 1,500 iu/l and
- Are able to return for follow-up and understand the importance of compliance

For women with a tubal ectopic pregnancy being managed expectantly, repeat hcg levels on days 2, 4 and 7 after the original test and:

- 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 (less than 20 iu/l) is obtained or
- If Hcg levels do not fall by 15%, stay the same or rise from the previous value, review the woman's clinical condition, repeat transvaginal scan and seek senior advice to help decide further management.
- Methotrexate should be considered if the βhcg is plateauing or rising.
- Surgery should be considered if the patient becomes symptomatic or there is increasing free fluid in the pelvis.
- **A consultant or senior resident should be involved in the decision for expectant management.**

Advise women that, 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
- The need for additional treatment, but that they might need to be admitted urgently if their condition deteriorates
- Health status, depression or anxiety scores

Advise women 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.

Ectopic in the rare sites

An ectopic in any site other than the fallopian tube should prompt involvement of a consultant opinion for decision regarding further management. Cervical, interstitial and caesarean scar pregnancies are examples.

Anti- D

Anti-D Ig 250 iu **should** be given to all non-sensitised rhesus negative women who have a surgical procedure to manage an ectopic pregnancy.

Do not offer anti-D rhesus prophylaxis to women who receive solely medical management or expectant management for an ectopic pregnancy

Chlamydia testing

All women with a diagnosis of ectopic pregnancy should be offered testing for Chlamydia with documentation if declined.

Pregnancy of unknown location (PUL)

A descriptive term used to classify a pregnancy when a woman has a positive pregnancy test but no pregnancy can be seen on an ultrasound scan.

Management of PUL

The management is based on serial βHCG measurements and repeat ultrasound scan findings.
Be aware that women with a pregnancy of unknown location could 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.

1. Use serum βHCG measurements only for assessing trophoblastic proliferation to help to determine subsequent management.

2. 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).

3. 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.

4. 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 gynaecologist.

5. 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 14 days after the second serum βHCG test, 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.

6. For a woman with a change in serum βHCG concentration between a 50% decline and 63% rise inclusive, please refer to the diagnostic algorithm.

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%.
- A single measurement of serum progesterone as an adjunct to serum βHCG will not help with the diagnosis of viable intrauterine pregnancy or ectopic pregnancy. However, a very low level is highly specific of a nonviable pregnancy (less than 20 nmol/l) and should be performed to aid decision making. It is hoped that it will help to reduce the number of unnecessary βHCG and hospital visits. However a low serum progesterone level does not exclude an ectopic pregnancy.
- 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.

Caution:

- 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.

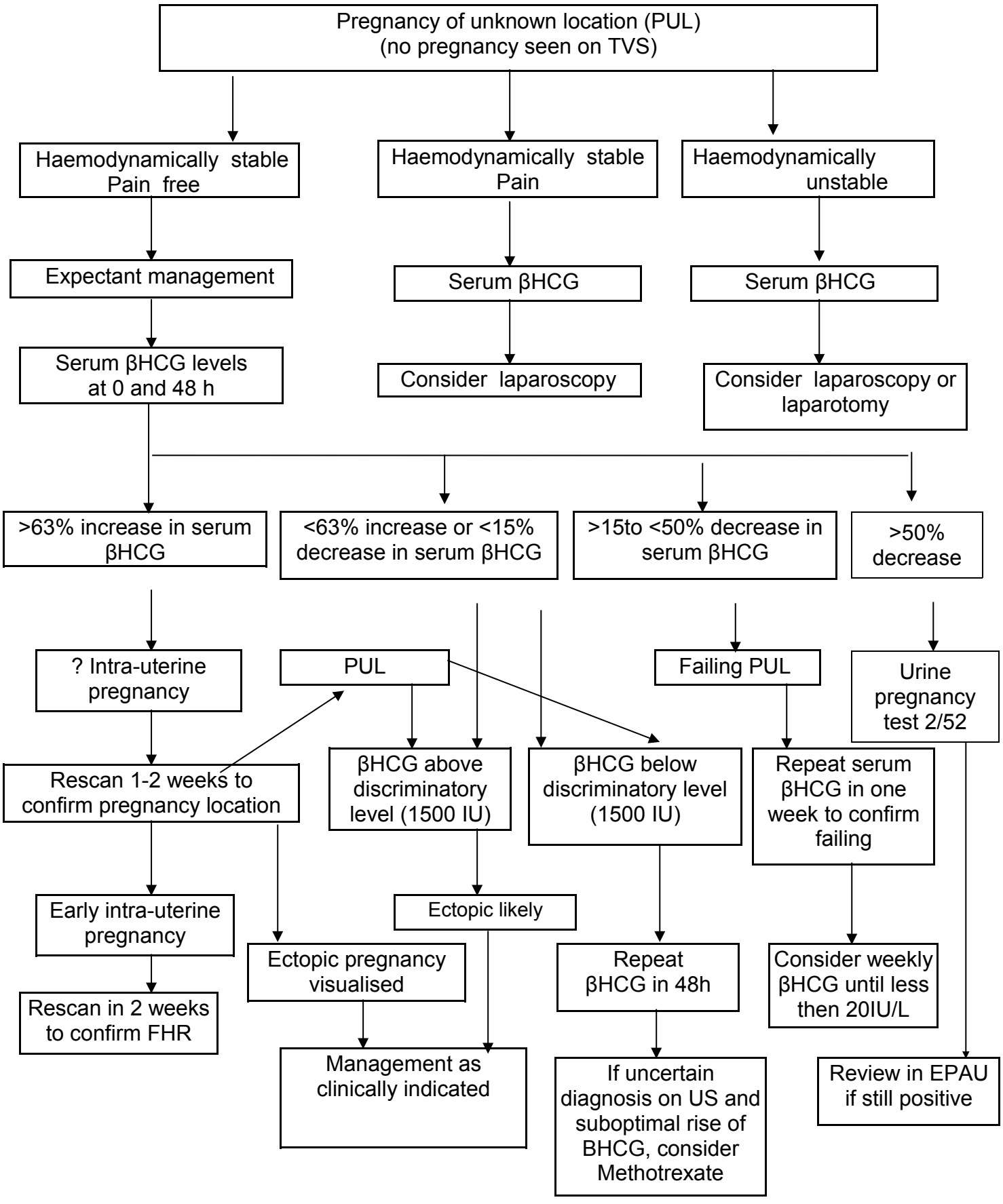
After two serial HCG measurements, a senior opinion (consultant or senior registrar) should be sought if the diagnosis is still not established.

Senior doctors should NOT be asked for opinions on patients other consultants have seen without the notes (unless not in the hospital). Serial opinions by different doctors on an individual patient are suboptimal and should be avoided if practicable.

Suggested Core Standards for the B-HCG review:

1. All βHCG results requested in EPAU during the morning session will be reviewed by the same doctor or EPAU nurse who requested them. It is the responsibility of this doctor or nurse to do this before 17.00 hours the same day.
2. The βHCG results requested in the EPAU during the afternoon session will be reviewed the next day by the doctor or nurse for EPAU at the beginning of the morning clinic.
3. All βHCG results from Cley available between 09.00hours and 17.00hours on weekdays must be reviewed by the on call Gynaecology Registrar at the end of each of their on–call duty at 17.00 hours. The on call gynaecology registrar should discuss any complicated patients with the on call senior registrar/consultant before finishing the shift.
4. All βHCG results from Cley available between 17.00hours and 09.00 hours during the week days will be reviewed the next day by the doctor or nurse for EPAU at the beginning of the morning clinic. The only exceptions are the patients who are clinically unwell. For these cases the results must be seen ASAP by the most senior doctor on-call (SpR/Consultant).
5. The βHCG results from cley over the weekend should be reviewed by the registrar on call on Saturday and Sunday on a daily basis, whenever the results are available. The on call registrar should discuss any complicated patients with the on call senior registrar/consultant.
6. All βHCG results have to be written down on the proforma sheet (see attachment) with a date, clear management plan, signature and printed name.

Algorithm for Management of Pregnancy of Unknown Location



References:

1. NICE guideline 126. Ectopic pregnancy and miscarriage: diagnosis and initial management. April 2019. Last updated 24 November 2021
2. RCOG/AEPU Joint Green-top Guideline No. 21. Diagnosis and management of ectopic pregnancy. November 2016.
3. Elson J,Tailor A,Baerjee S,Salim R,Hilaby K,Jurkovic D.Expectant management of Tubal pregnancy:Prediction of successful outcome using decision tree ananlysis.Ultrasound Obstet Gynecol.2004 Jun ;(6):552-6
4. Martin C Sowter,Cindy M Farquhar,Keith J Petrie,Guy Gudex.A randomised trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured tubal pregnancy.British Journal of Obstetrics and Gynaecology.February 2001,Vol.108,pp.192-203.
5. Condous G,Lu C,Van Huffel SV,Timmerman D,Bourne T.Human chorionic gonadotrophins and progesterone levels in pregnancies of unknown location.In J Gynaecol Obstet.2004 Sep;86(3):351-7.
6. Dart R, Ramanujam P, Dart L.Progesterone as a predictor of ectopic pregnancy when the ultrasound is indeterminate: Am J Emergency Med.2002 Nov; 20(7):575-9.
7. McCord ML,Muram D,Buster JE,Arheart KL,Stoval TG,Carson SA.Single serum progesterone as a screen for ectopic pregnancy:exchanging specificity and sensitivity to obtain optimal test performance.Fertil Steril.1996 Oct;66(4):513-6.
8. Rajesh Varma and Lawrence Mascarenhas.Evidence-based management of ectopic pregnancy.Current Obstetrics & Gynaecology (2002)12.191-199
9. Guidelines of the Association of Early Pregnancy Units (AEPU) (2007)
10. NICE clinical guideline 154. Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. December 2012.
11. Saving Lives, Improving Mothers' care. Surveillance of maternal deaths in the UK 2011-13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and 2009 – 13 (MBBRACE-UK).
12. Ankum WM, Mol BW, Van der Veen F, Bossuyt PM. Risk factors for ectopic pregnancy: a meta-analysis. Fertil Steril 1996;65:1093-9.
13. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol 2003;157:185-94.
14. Cacciatore B, Stenman UH, Ylostalo P. Comparison of abdominal and vaginal sonography in suspected ectopic pregnancy. Obstet Gynecol 1989;73:770-4.
15. Kirk E, Papageorghiou AT, Condous G, Tan L, Bora S, Bourne T. The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. Hum Reprod 2007;22:2824-8.
16. ACOG Practice Bulletin no. 94: Medical management of ectopic pregnancy. Obstet Gynecol 2008;111:1479-85.

17. 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.**
18. Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison. Hum Reprod2013 Jan;28(1):60-7.
19. Van Mello NM, Mol F, Hajenius PJ, et al. Randomized comparison of health-related quality of life in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management. Eur J Obstet Gynecol Reprod Biol 2015; 192:1.
20. Craig LB, Khan S. Expectant management of ectopic pregnancy. Clin Obstet Gynecol 2012;55:461–70.
21. Elson J, Tailor A, Banerjee S, Salim R, Hillaby K, Jurkovic D. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. Ultrasound Obstet Gynecol 2004;23:552–6.
22. Shalev E, Peleg D, Tsabari A, Romano S, Bustan M. Spontaneous resolution of ectopic tubal pregnancy: natural history. Fertil Steril 1995;63:15–9.
23. Cohen MA, Sauer MV. Expectant management of ectopic pregnancy. Clin Obstet Gynecol 1999;42:48–54

Audit topics:

1. Success rate of the different types of management of ectopic pregnancy
2. Compliance with the diagnostic algorithm for management of PUL.
3. Compliance with the core standards for βHCG review.

Management Plan for βHCG/Review *(Use dd/mm/yyyy and 24hr clock)*					Patient indentifer label
TelephoneNumber(s)					
Date		Nursing Consultation:			
Time					
BHCG		Progesterone		Diagnosis	
Senior Doctor / Consultant Review / Management Plan:					
Nurses Action:					
Print Name		Signature		Designation	

Management Plan for βHCG/Review					Patient indentifer label
Management Plan for					Patient indentifer label
Management Plan for βHCG/Review *(Use dd/mm/yyyy and 24hr clock)*					Patient indentifer label
TelephoneNumber(s)		Consultation:			
		Nursing			
Date		Nursing Consultation:		Diagnosis	
Time					
BHCG		Progesterone		Diagnosis	
Senior Doctor / Consultant Review / Management Plan:					
Nurses Action:		Signature		Designation	
Print Name		Signature		Designation	