Review Pregnancy of unknown location: an evidence-based approach to management

Authors Haritha Sagili / Kamel Mohamed

Key content:
• As women are presenting to early pregnancy assessment units at increasingly earlier gestations and are having earlier scans, the incidence of pregnancy of unknown location (PUL) is increasing.
• Although the vast majority will be failing PULs or intrauterine pregnancies, a small subset will be ectopic pregnancies; it is the detection of women in this group that poses the greatest challenge.
• Conservative management of PUL results in lower rates of unnecessary intervention, as the condition often resolves spontaneously; the difficulty is in determining which ones will not.

Learning objectives:
• To learn about the definition and clinical outcomes.
• To appreciate the role of biochemical tests and ultrasound in the assessment of women with PUL.
• To learn about conservative, medical and surgical management options.

Ethical issues:
• Is destroying a viable intrauterine pregnancy an acceptable cost for treating all ectopic pregnancies, given the limitations of diagnosis in PUL?

Keywords ectopic pregnancy / human chorionic gonadotrophin (hCG) / intrauterine pregnancy / progesterone

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Author details
Haritha Sagili MD MRCOG DFFSH MFSRH
Senior House Officer
Department of Obstetrics and Gynaecology, Nobles Hospital, The Strang, Braddan, Isle of Man IM4 4RJ, UK
Email: harithas@hotmail.com (corresponding author)

Kamel Mohamed MSc MRCOG DFFP MD
Consultant Obstetrician and Gynaecologist
Nobles Hospital, Isle of Man, UK

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Introduction

The term 'pregnancy of unknown location' (PUL) is used whenever there is no sign of either intra- or extraterine pregnancy or retained products of conception on transvaginal ultrasound, despite a positive pregnancy test. A pregnancy site will not be visualised in 8–31% of early pregnancy scans, although a lower incidence (8–10%) has been observed in specialised scanning units. The sonographer’s experience influences the prevalence of PUL.

Initial assessment

Whenever a woman presents with a positive pregnancy test but no evidence of pregnancy on transvaginal ultrasound, clinical assessment and serum beta human chorionic gonadotrophin (β-hCG) estimation should be carried out. Whilst it is very rare, a positive serum hCG does not always indicate pregnancy. Other causes include posterior cranial fossa germ cell tumours and placental trophoblastic tumours. Serum progesterone can be a useful adjunct in the management of women with PUL.

hCG and ultrasound

The concept of combining ultrasound with serum hCG using a discriminatory zone has been widely evaluated. It refers to a defined level of hCG above which the gestational sac of an intrauterine pregnancy should be visible on ultrasound with sensitivity approaching 100%. The current recommended value ranges from 1000–2400 iu/l.

In multiple pregnancies, hCG levels should be interpreted with caution as they are a little higher, requiring an extra 2 or 3 days for the sacs to become visible. The possibility of a heterotopic pregnancy should also be considered in the differential diagnosis.

In women with an hCG result above the discriminatory level but no intrauterine gestational sac on ultrasound, steps must be taken to determine whether the pregnancy is ectopic. The discriminatory zone predicts ectopic pregnancy with a positive predictive value of 18.2%. Transvaginal ultrasound must be performed meticulously because of potential pitfalls in image interpretation: considerable expertise is necessary. The diagnosis of ectopic pregnancy should be based on the identification of an extraterine sac and indirect signs such as a complex adnexal mass or echogenic fluid, rather than on a scan that fails to demonstrate an intrauterine pregnancy. A combination of the above transvaginal ultrasound findings has a positive predictive value of 93.5–100% for diagnosing ectopic pregnancy. Although the endometrial stripe has been reported to be thinner in women with ectopic compared with intrauterine pregnancy, there is significant overlap of endometrial stripe thickness values, which precludes its use as a single feature in the diagnosis of ectopic pregnancy. A trilaminar pattern, although specific (94%) for ectopic pregnancy, is associated with low sensitivity (38%). Transvaginal colour Doppler has not been shown to increase the detection rates of ectopic pregnancy when compared to 2D ultrasound but may be useful in showing enhanced trophoblastic flow.

Ideally, the discriminatory level for each test should be set by each institution based on that hospital’s success in correctly identifying ectopic pregnancy. This variation depends on three factors:

- hCG assay techniques in use
- quality of ultrasound equipment
- operator experience.

Setting a high discriminatory level minimises the risk of intervening inappropriately before an intrauterine pregnancy has become apparent but at the expense of delaying the diagnosis of ectopic pregnancy by a few days. A prospective observational study in 527 women found that the detection of ectopic pregnancy in a PUL population is not significantly improved by altering the discriminatory zone.

Progesterone

Serum progesterone levels are elevated, indicating the viability of the corpus luteum, and change little during the first 8–10 weeks of gestation, but decrease if the pregnancy fails. Several studies, including a metanalysis, have shown serum progesterone levels <25 nmol/l to be associated with nonviable pregnancy, although viable pregnancies (0.3%) have been reported with initial levels <15.9 nmol/l (<5 ng/ml). Serum progesterone <20 nmol/l predicts failing pregnancy with a positive predictive value of ≥95%, which compares favourably with complex multiparameter diagnostic models. The association of low progesterone with ectopic pregnancy when compared with intrauterine pregnancy has been reported since the late 1970s but there is no well-established cutoff to discriminate between the two. Serial determinations of progesterone have not been shown to increase its discriminatory power.

Levels >25 nmol/l are likely to indicate, and >60 nmol/l are strongly associated with, pregnancies subsequently shown to be intrauterine, although a small proportion of ectopic pregnancies (2.6%) have been reported with a serum progesterone concentration of >60 nmol/l (>20 ng/ml).
New markers for the detection of ectopic pregnancy

Serum CA125 and creatine kinase are not useful clinically because of poor ectopic pregnancy detection rates, although the CA125 ratio (at 48 and 0 hours) can distinguish failing PUL from intrauterine pregnancy. Vascular endothelial growth factor (VEGF), serum interleukin (IL-8 and IL-6) and tumour necrosis factor-alpha (TNF-alpha) are higher, while pregnancy-associated plasma protein A (PAPP-A), pregnancy-specific beta 1-glycoprotein (SP1), human placental lactogen (HPL), progesterone, glycolelin and leukaemia inhibitory factor (LIF) are decreased or unchanged in women with ectopic pregnancy when compared with intrauterine pregnancy. Serum inhibin and 17-OH progesterone concentrations are lower in ectopic pregnancy but there appears to be no difference in insulin-like growth factor binding protein (IGFBP) levels. Magnetic resonance imaging (MRI) appears to be 96% accurate for detecting ectopic pregnancy because of its high sensitivity to fresh haematoma. However, more studies are needed to clarify its role.

Conservative management of PUL

According to the Association of Early Pregnancy Units guidelines, if no intrauterine or ectopic pregnancy or retained products of conception are seen on transvaginal ultrasound and the woman is asymptomatic at initial assessment, she can be managed conservatively. This is irrespective of the hCG discriminatory zone and additional ultrasound findings, such as a suspicious adnexal mass <3 cm. Conservative management involves re-estimation of serum hCG levels at 48 hours to determine the pattern of hCG change from the initial assessment. Further follow-up with hCG and transvaginal ultrasound can be arranged or therapeutic intervention made.

hCG pattern after 48 hours

The pattern of rise or fall in hCG after 48 hours and the hCG ratio are useful in distinguishing between PULs that will develop into failing PULs from intrauterine and ectopic pregnancy. This is particularly the case whenever the hCG levels are lower than the discriminatory zone or when an ultrasound diagnosis cannot be made despite the hCG being above the discriminatory zone.

Rise or fall in hCG

The concept of the minimal rate of increase of hCG for an intrauterine pregnancy of 66% in 48 hours was first reported in 20 women using an 85% confidence interval. It predicts an intrauterine pregnancy with a positive predictive value of 96.5%. However, 12–21% of ectopic pregnancies have an hCG rise that mimics an intrauterine pregnancy. Although a doubling of hCG is often expected in 48 hours, this varies with gestation: as pregnancy progresses, doubling time lengthens. Intervention for an hCG rise of less than 66% over 2 days, a practice supported by previous data, would potentially result in the interruption of viable pregnancies. Recent studies have attempted to redefine the hCG values in an effort to reduce unnecessary intervention. Based on observations in 287 women, the minimum rise for a potentially viable pregnancy that presents with vaginal bleeding and/or pain is 53% at 2 days (99% confidence interval [CI]) but there was a lower cutoff (35% increase over 2 days) for intrauterine pregnancy (99.9% CI) in a cohort study of 1249 women.

If hCG levels fall by at least 15%, the most likely outcome is failing PUL, although 8% of ectopic pregnancies have a fall in hCG similar to spontaneous miscarriage and a higher cutoff value of 21–35% (90% CI) has been mentioned in another study.

When the rise or the fall in hCG is suboptimal, the most likely outcome is ectopic pregnancy. Approximately 71% of women with ectopic pregnancy have a rise in hCG that is slower than the minimal rise for a viable pregnancy or a decline that is slower than the minimal rate of fall in spontaneous miscarriage. A suboptimal rise in serum hCG predicts ectopic pregnancy with a positive predictive value of 43.5%. However, failing PULs and 15% of normal pregnancies will have an abnormal doubling time.

Further follow-up based on the patterns described above are summarised in an algorithm shown in Figure 1.

An ongoing randomised controlled trial that will provide guidance on the present management dilemmas in women with PULs with low and plateauing serum hCG concentrations is the METEX (methotrexate versus expectant management in women with ectopic pregnancy) study.

hCG ratio

Model using an hCG ratio (hCG at 48 hours: hCG at 0 hours), including a specific cutoff value of <0.87 in some studies, predicted failing PUL and intrauterine and ectopic pregnancy. Sensitivities were: 73.5–92.7%, 77.3–86.8% and 82.8–91.7%; positive predictive values were: 97–99%, 95.1–96.6% and 27.5–28.2%, respectively.

Expectant management of PUL has been shown to be safe and to reduce the need for unnecessary surgical intervention and is not associated with any serious adverse outcomes. Unfortunately, multiple visits to an early pregnancy assessment unit are necessary before a diagnosis can be made:
the median number of visits and days required to diagnose ectopic pregnancy is 3 (range 2–6) and 5 (range 2–25), respectively. A single visit strategy proposed to reduce the number of visits was shown to be unsafe as 67% of women with ectopic pregnancy were discharged without adequate follow-up. In women with PUL managed conservatively, 9–29% will require intervention because of a worsening clinical condition or nondeclining hCG. Ectopic pregnancy was detected 2.5 days earlier when compared with clinical diagnosis by altering cutoff values for minimum rise and fall in hCG. There was a failure to diagnose ectopic pregnancy in 12% of them because the curve of rise or fall of hCG mimicked that of a nonectopic gestation.

Clinical outcomes of PUL
The four possible outcomes of PUL are:

- failing PUL
- intrauterine pregnancy
- ectopic pregnancy
- persisting PUL

The most common outcome is failing PUL (44–69%), which resolves spontaneously\(^{27}\) and can be either intra- or extrauterine (never actually located on transvaginal ultrasound); serum progesterone at presentation will be <20 nmol/l and serial serum hCG levels will fall. Early intrauterine pregnancies too small to visualise on transvaginal ultrasound\(^{23,48}\) contribute to approximately 30–37% of PULs; 75% of these are viable intrauterine pregnancies on follow-up. The prevalence of early ectopic pregnancy in a PUL population is 8.1–42.8%\(^{3,23,49,50}\) and lower rates, of 8.1–14%, have been shown in specialised scanning units\(^{3,23}\) where the diagnosis of ectopic pregnancy was based on the visualisation of an adnexal mass rather than the absence of an intrauterine sac on transvaginal ultrasound. Approximately 87–93% of ectopic pregnancies are correctly identified by transvaginal ultrasound\(^{9,17,51}\) in specialised units, which means that only a few ectopic pregnancies will fall into the PUL category.

Persisting PULs are defined as those in which the serum hCG levels fail to decline, there is no evidence of trophoblastic disease and the location of pregnancy cannot be identified using transvaginal ultrasound or laparoscopy. Usually, the serum levels of hCG are low (<500 iu/l) and have reached a plateau\(^{24}\) (doubling time of 7 days or

Figure 1
Algorithm for management of PUL\(^{46}\)
more). This subset accounts for approximately 2% of the total number of PULs.\textsuperscript{46}

The vast majority of PULs will be at low risk of ectopic pregnancy and are made up of failing PULs and intrauterine pregnancies; only a small proportion in specialised scanning units are high-risk PULs representing ectopic pregnancies.\textsuperscript{46} Although the current criteria available in the prediction of intrauterine and failing intrauterine pregnancy are fairly accurate, they are still of poor value in predicting ectopic pregnancy, as hormone trends in women with early ectopic PULs are highly variable. At least 15% of ectopic pregnancies resolve spontaneously without any intervention and it is uncertain whether failing to diagnose them in this PUL population is a problem, as not all are dangerous. There is no method of predicting which ectopic pregnancies are likely to be self-limiting and which are likely to be dangerous. In practice, ruptured ectopic pregnancy can occur even with declining or very low levels (<10 iu/l).\textsuperscript{52} Rupture has even been reported with negative\textsuperscript{53} levels of serum hCG.

Management of women with ‘presumed’ complete miscarriage

In the Confidential Enquiry into Maternal and Child Health 2000–2002,\textsuperscript{14,15} 11 out of 17 deaths in the first trimester resulted from ruptured ectopic pregnancies and one potentially avoidable death was in a woman seen in a specialist centre with an empty uterus on ultrasound. This was interpreted as a complete miscarriage and death occurred 3 weeks later from a ruptured tubal pregnancy. Quantitative hCG testing would almost certainly have established the diagnosis. Thus, a history of passage of clots vaginally and ultrasound alone seems to be unreliable in making a diagnosis of complete miscarriage and it is recommended that these women be managed as PUL. This is because pregnancy has not been demonstrated at any time and it is possible that such women may have ectopic pregnancy, as evidenced by a study\textsuperscript{15} that showed that 9 out of 152 women (5.9%) with apparent complete miscarriage had an underlying ectopic pregnancy.

Medical management

There is limited data available regarding medical management of PUL. According to Condous et al.,\textsuperscript{46,47} methotrexate 50 mg/m\textsuperscript{2} has been used successfully in women with asymptomatic persisting PUL with subsequent resolution of serum hCG levels. A protocol for its administration is summarised in Table 1. Caution should be exercised prior to administering medical treatment for PUL until the site of pregnancy is identified. In medical treatment of ectopic pregnancy,\textsuperscript{46} methotrexate has been shown to be 90% effective. The clinician needs to be aware of the following points about administration of methotrexate:

- up to 75% of women experience abdominal pain between days 3–7
- hCG levels may rise in days 1–4
- the risk of tubal rupture is 7%
- the mean time to resolution is 35 days

A single injection of methotrexate is well tolerated and side-effects are minimal; pregnancy should be avoided for 3 months after administration. Alternatively, it can be given as a multiple dose regimen with alternate day administration of intramuscular methotrexate and folinic acid rescue.

One death reported by the 2003–05 report from the Confidential Enquiries into Maternal and Deaths in the UK\textsuperscript{58} resulted from substandard care following the administration of methotrexate for ectopic pregnancy. Medical treatment must be based on strict adherence to protocols and immediate access to inpatient facilities if complications occur.

Surgical management

Surgical management (laparoscopy/laparotomy) is indicated if the woman is symptomatic (either at presentation or during conservative management) or if an ectopic pregnancy is visualised. Some early ongoing and self-limiting ectopic pregnancies are too small to be seen, thus resulting in false negative laparoscopies. Laparoscopy has a false negative rate of 3–4% (if done too early) and a false positive rate of 5% (because of retrograde uterine bleeding). Uterine curettage is not usual in UK practice, although common in the USA. There is no strong clinical evidence to suggest any necessity for a change in practice. A recent study\textsuperscript{59} showed that inadvertent termination of pregnancy may result in 0.5–12.3% of cases, whilst more than half the women undergo unnecessary surgical intervention if uterine curettage is performed based on biochemical criteria. This emphasises the fact that it has no, or at most a very limited role in the management of PUL.

One potentially avoidable death reported by the 2003–05 report from the Confidential Enquiries into Maternal Deaths in the UK\textsuperscript{58} occurred in a woman who was awaiting a repeat hCG assay. This
was carried out despite a modestly raised hCG level, no evidence of an intrauterine pregnancy and a pelvic mass on ultrasound compatible with ectopic pregnancy. Hence, laparoscopy/laparotomy should be undertaken without delay if there are clinical signs suggestive of tubal rupture.

Conclusion

Asymptomatic PUL should be managed conservatively as none of the methods to predict the clinical outcome of PUL is 100% accurate. It is advisable to follow up with hCG and transvaginal ultrasound assessments until the pregnancy is located accurately or intervention becomes necessary. Identified ectopic pregnancy should be managed according to local guidelines. Women with ‘presumed’ complete miscarriage should also be managed as though they have a PUL. Medical management is reserved for women with asymptomatic persisting PUL. Surgery is indicated if the woman is symptomatic at presentation or during subsequent expectant management. Early pregnancy assessment units should develop and use diagnostic and therapeutic algorithms of care.

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References