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Review

The role of ultrasonography in the diagnosis and management of early pregnancy complications

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Key content

- The diagnosis of miscarriage and management of pregnancy of uncertain viability.
- Ultrasound features that increase the suspicion of pregnancy failure.
- Ultrasound features of both tubal and non-tubal ectopic pregnancy.
- Pregnancy of unknown location: how to stratify risk using serum biochemistry and prediction models.

Learning objectives

- To understand the role of ultrasonography as a diagnostic tool in early pregnancy and what should be expected of it.
- To highlight the importance of safety and caution when using ultrasound in early pregnancy.
- To understand the management options for a pregnancy of unknown location.
- To clearly understand the criteria that must apply before a diagnosis of miscarriage can be made.
- To know the ultrasound features of ectopic pregnancy and be aware of the risks of methotrexate treatment in the event of misdiagnosis.

Ethical issues

- Misdiagnosis of miscarriage.
- Inappropriate use of methotrexate for treatment of presumed ectopic pregnancy.
- Maintaining patient choice in relation to the management of miscarriage and ectopic pregnancy.

Keywords: early pregnancy / ectopic pregnancy / methotrexate / miscarriage / pregnancy of unknown location / pregnancy of unknown viability / ultrasound

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Introduction

Early pregnancy complications are among the most common reasons women seek medical care.[1] These events peak between 8 and 11 weeks of gestation. Ultrasonography is integral to assessing such women, and the transvaginal approach is now standard. While the majority of transvaginal ultrasound scans will provide a diagnosis, a proportion will remain non-diagnostic. In these cases, if an intrauterine gestation sac has been identified, this is classified as a pregnancy of uncertain viability. If a pregnancy has not been visualised either inside or outside the uterus, it is described as a pregnancy of unknown location. Neither of these terms is a diagnosis; they simply describe the diagnostic position at a moment in time.

It is important to remember that the potential for damage from inappropriate intervention following an incorrect ultrasound assessment in early pregnancy may have serious consequences. Errors have resulted in public inquiries in the UK and Ireland, and are highlighted in the Confidential Enquiries into Maternal Deaths reports. As so many women undergo early ultrasound examinations, even if the rate of misdiagnosis is probably low, the absolute number of errors is potentially extremely important.[2] Seeking a second opinion and repeating scans before making a diagnosis of miscarriage should be embedded in clinical practice, and great care should be taken before treating an ectopic pregnancy with methotrexate in order to avoid inadvertent damage to an intrauterine pregnancy. The use of ultrasound, along with

serum biochemical markers (progesterone and human chorionic gonadotrophin [hCG]) has transformed the management of early pregnancy; however, the misuse and misinterpretation of these investigations can cause significant damage. It should be remembered that for women who are haemodynamically stable, waiting until a diagnosis is definitive is unlikely to be harmful.

In this article the authors review the pivotal role ultrasound plays in the diagnosis and management of early pregnancy complications.

Intrauterine pregnancy

Measurements

The key measurements in early pregnancy are the crown–rump length of the embryo (CRL) and the mean gestation sac diameter (MSD). The MSD is measured in three orthogonal planes from the inner borders of the sac. This usually appears as a round hypoechoic structure with an echogenic rim, eccentrically situated within the decidua, usually at or near the uterine fundus from as early as day 28–31 (postmenstrual age). The embryonic pole is first visualised from around day 35 as a linear echogenic structure adjacent to the yolk sac. Initially, the embryonic pole is linear and so is measured as the greatest length; however, once the CRL measures more than 5 mm the cranial and caudal ends may be easier to distinguish. The embryo at this stage is flexed and so the neck–rump length is usually measured. Once the CRL is more than 18 mm, from the time limb buds develop, the true CRL may be measured. The cranial end should be in a neutral position and measurements taken in the sagittal plane. CRL measurements are less reliable after 14 weeks of gestation.

The importance of accurately measuring the CRL lies in its use for both diagnosing miscarriage and pregnancy dating. Measurements of MSD are also used in the context of diagnosing miscarriage. Caution must be exercised when diagnosing miscarriage based on either CRL or MSD measurements, as there is clinically significant inter-observer variation, particularly for MSD.[3]

Viable intrauterine pregnancy

A viable intrauterine pregnancy may be defined as when an intrauterine gestational sac containing an embryo with a heartbeat has been visualised. Features of the pregnancy on ultrasound may give the examiner an indication of the likelihood of miscarriage, although they play no role in making a diagnosis. A prospective observational case–control study described a scoring system to predict an individual's risk of subsequent miscarriage in the first trimester.[4] The study found that a combination of factors, such as maternal age, gestational age, bleeding score, mean gestation and yolk sac sizes, and the presence of embryonic cardiac activity, provides an accurate prediction of viability.[4] These have been used to produce a simple scoring system for viability that can be usefully employed in practice.[5] Although such a prediction will not alter the outcome of a pregnancy, information about likely outcome may be useful when counselling women about their expectations and probable findings on a repeat scan, as well as for triaging women for further ultrasound surveillance.

Pregnancy of unknown viability

Whether it is possible to make a definitive diagnosis of viability is largely determined by the gestational age at the time of the scan (Figure 1).[5] If an ultrasound scan shows a pregnancy of unknown viability, this may be an early viable pregnancy, or a slow growing pregnancy that is destined to miscarry. A pregnancy should be classified as being of 'unknown viability' when transvaginal ultrasonography has shown the following, irrespective of the date of a woman's last menstrual period:[6]

- an intrauterine gestational sac seen with an MSD of less than 25 mm without a visible yolk sac or embryonic pole
- an intrauterine gestational sac with MSD of less than 25 mm with a yolk sac seen without a visible embryonic pole
- an intrauterine gestational sac with an embryo with a CRL measuring less than 7 mm with no visible heartbeat.

In these circumstances, a woman should be offered a repeat ultrasound scan at an interval in order to confirm viability. There are few data to indicate the optimal time interval between scans; however, a consensus would suggest between 10 and 14 days. Data from a multicentre observational study by Abdallah et al.[7] suggest an absence of growth in MSD may not be diagnostic of miscarriage. Their study showed that, in the event of an empty gestation sac, the absence of the appearance of embryonic structures or the failure to visualise a heartbeat in an embryo on a repeat scan were always diagnostic of miscarriage.[7]

A common sense approach to the diagnosis of miscarriage was proposed following a consensus conference of the US Society for Radiologists in Ultrasound in 2012. The authors proposed that on a follow-up transvaginal ultrasound scan a diagnosis of pregnancy failure may be made on the basis of the following findings:[6]

- embryo with a CRL of more than 7 mm with no heartbeat
- mean gestational sac diameter of more than 25 mm with no embryo
- an absence of an embryo with a heartbeat if more than two weeks has elapsed following a scan that showed a gestational sac without a yolk sac
- an absence of an embryo with a heartbeat more than 11 days after a scan that showed a gestational sac and yolk sac.

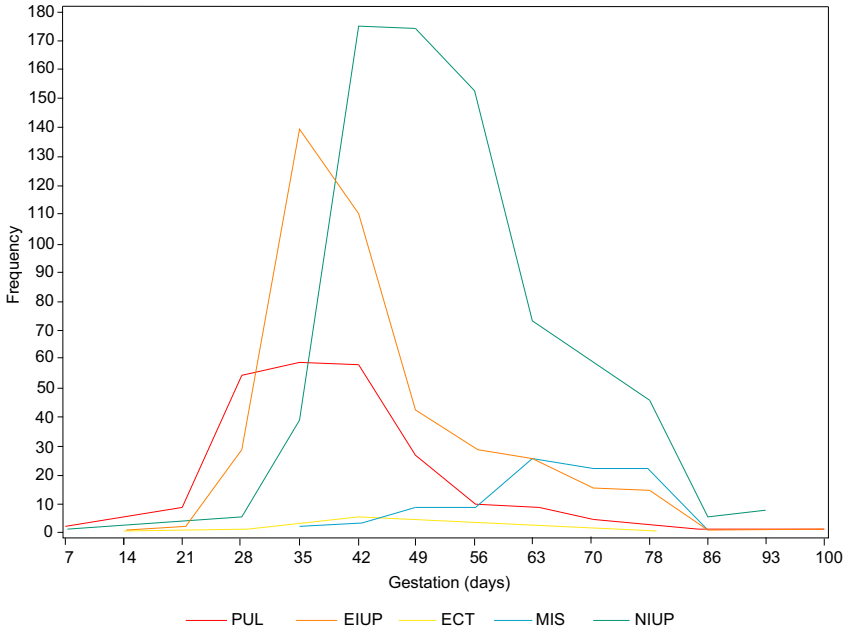


Figure 1. Likely findings on ultrasound scan dependent on gestation showing that a pregnancy is likely to be classified as a pregnancy of unknown location or unknown viability at early gestations. The optimal timing for an ultrasound scan for viability is 49 days. The frequency illustrates the number of times each diagnosis is made depending on gestation.
ECT = ectopic pregnancy; EIUP = early intrauterine pregnancy or pregnancy of unknown viability; MIS = miscarriage; NIUP = normal intrauterine pregnancy; PUL = pregnancy of unknown location.
Reproduced from Bottomley C et al. The optimal timing of an ultrasound scan to assess the location and viability of an early pregnancy. *Hum Reprod* 2009;24:1811–7, with permission from Oxford University Press.

Diagnostic criteria for miscarriage using ultrasonography

When diagnosing miscarriage, it is axiomatic that a false-positive diagnosis (erroneously diagnosing miscarriage) is a critical error. It will not be possible to have a clear diagnosis on the basis of one examination in a number of women, particularly when findings are around the decision boundaries that are used for diagnosis.[6] There are ultrasound features that increase the suspicion of likely pregnancy failure, for example, subchorionic haematoma, a small gestational sac for gestation[8] or an enlarged yolk sac.[9] While these features may give an indication of the prognosis of a pregnancy,[4] they play no part in establishing a definitive diagnosis of miscarriage.

Previous guidance on using ultrasound to diagnose miscarriage in the UK used cut-off values for the MSD of an empty gestation sac of 20 mm or more, and for the CRL of an embryo without a heartbeat of 6 mm or more. This changed when a series of papers published in 2011 led to guidance being modified within days and subsequent changes to protocols being made internationally.[10] In a systematic review of the evidence on which previous diagnostic criteria were based, Jeve et al.[11] concluded that guidelines were founded on a small number of old poor quality studies. Furthermore, Pexsters et al.[3] showed that there is sufficient inter-observer variation in measurements of MSD and CRL to be clinically significant and potentially lead to misdiagnosis. The implication therefore is that any cut-off values used to diagnose miscarriage must take such variation into account.

A multicentre observational study carried out by Abdallah et al.[10] showed that cut-off values for CRL and MSD used in previous guidance were associated with a significant false-positive diagnosis rate for miscarriage. These data suggested that an empty gestational sac of MSD 25 mm or more, or an embryo with a CRL measurement of 7 mm or more without an embryonic heartbeat would be safer criteria on which to base a diagnosis of miscarriage with a minimal risk of error.[10] In the event of any doubt or when measurements are around these decision boundaries, an ultrasound scan should be repeated at an interval and the ultrasound findings checked by a colleague.[12] Care must also be taken in the presence of uterine fibroids or an axial uterus, both of which make examination of the uterus more difficult.

It must be emphasised that the cut-off values referred to relate to the use of transvaginal ultrasonography. While a transabdominal scan may be used to show a pregnancy is viable, this approach should not be used to make a diagnosis of miscarriage, to classify a pregnancy as a pregnancy of

unknown location or to assess for the presence of an ectopic pregnancy. While common sense would suggest that MSD and CRL measurements should be looked at in the context of the woman's last menstrual period, there are currently no data to support this and therefore gestational age must not be used as a consideration when applying ultrasound criteria for miscarriage. Even women who are certain of their dates have very significant differences in the ovulation–implantation interval that may lead to misinterpretation of gestation sac or embryo size.[13]

The new cut-off levels for MSD and CRL proposed by Abdallah et al.[10] were adopted by the Royal College of Obstetricians and Gynaecologists in a revision of its Green-top guidance,[14] and in the 2012 National Institute for Health and Care Excellence (NICE) guidance on diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage.[15] The NICE guidance also advises that once a diagnosis of miscarriage has been made, all women should be given a trial of expectant management. However, clinicians may wish to counsel women regarding all suitable options including medical and surgical management, rather than restrict patient choice.[16]

Complete and incomplete miscarriage

A diagnosis of complete miscarriage should not be made on the basis of a single ultrasound scan. By definition, if a pregnancy has not been visualised in the uterus on the current scan and there is no previous scan to confirm an intrauterine pregnancy, the pregnancy should be classified as a pregnancy of unknown location. Serial hCG levels should be taken to confirm a failing pregnancy because it has been reported that up to 6% of such cases will subsequently be found to be an ectopic pregnancy.[17]

Previous studies have suggested that measurements of endometrial thickness may be used to diagnose incomplete miscarriage.[18,19] These are now not thought to be helpful.[20] Using ultrasonography, an incomplete miscarriage may be defined as the finding of irregular heterogeneous echoes within the endometrial cavity and the diagnosis is based on the subjective impression of the examiner and the clinical findings. Power Doppler may have value in these circumstances by showing significant vascularity in the event of retained tissue being present as opposed to a blood clot.[21]

Ectopic pregnancy

An ectopic pregnancy is defined as the implantation of a fertilised ovum outside the endometrial cavity and is potentially life threatening. In the UK, 11 maternal deaths were attributed to ectopic pregnancy in the last triennial Centre for Maternal and Child Enquiries report.[22] Although there are a number of recognised risk factors – smoking, pelvic inflammatory disease, previous ectopic pregnancy, assisted reproductive treatment and previous tubal surgery – in over 50% of women, there are no identifiable risk factors.[23]

Tubal pregnancy

Tubal ectopic pregnancies account for over 90% of ectopic pregnancies.[24] The ultrasound features include:

- an extrauterine gestational sac with a yolk sac and embryonic pole with cardiac activity (viable)
- an extrauterine gestational sac with a yolk sac and embryonic pole without cardiac activity (nonviable)
- an adnexal mass with a hyperechoic ring around the gestational sac (bagel sign)
- a homogenous mass seen separate to the ovary (blob sign).

Transvaginal ultrasonography is now the gold standard technique for the diagnosis of ectopic pregnancy.[24,25] Using this approach over 70% of ectopic pregnancies may be diagnosed at the time of presentation and over 90% may be visualised once follow-up scans have been performed.[25] Ectopic pregnancies not visualised initially will be classified as a pregnancy of unknown location,[26] often because the ectopic pregnancy is simply smaller and earlier in its disease course.[27]

The majority of ectopic pregnancies are visualised as a homogenous mass (Figure 2).[24,28] This is important when considering treatment options. Careful consideration should be given to the quality of ultrasound scanning in this context, because while in expert hands the specificity of ultrasound has been reported to be over 99%,[25,26] in older studies specificities of as low as 84% have been described.[29] The 2012 NICE guidance recommended the use of methotrexate as

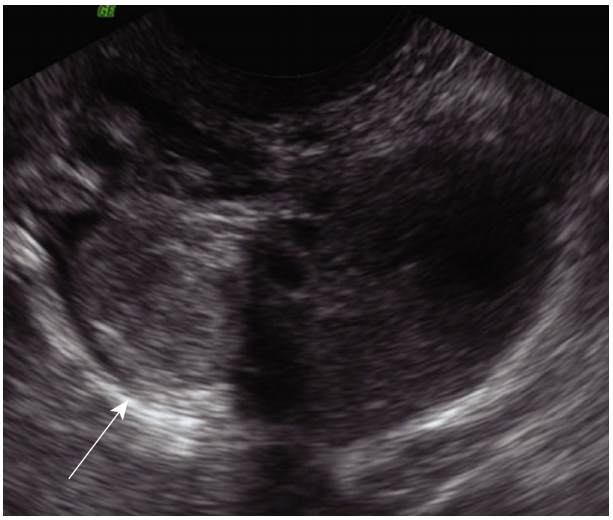


Figure 2. Transvaginal ultrasound showing a tubal ectopic pregnancy (white arrow). The majority of tubal ectopic pregnancies are visualised as homogenous masses or 'blobs'.

first-line treatment of ectopic pregnancy.[15] However, prior to such treatment, it is vital to ensure that there is no possibility of there being a false-positive test result in the presence of an early intrauterine pregnancy. The NICE guidance also omits to address diagnostic criteria on which to base a diagnosis of ectopic pregnancy.[15] This is unfortunate because errors with methotrexate use have become a significant issue in the USA and are associated with major congenital abnormalities if the embryo survives.[30]

A woman being considered for methotrexate treatment should be stable and compliant. Waiting 48 hours to assess the serum hCG ratio in order to exclude the possibility of a viable intrauterine pregnancy and/or repeat the scan is a safe approach. Knowledge of the hCG ratio may also be used to select women rationally for expectant or medical management.[31] A further limitation of the NICE guidance is that it has omitted to consider the option of expectant (watch and wait with no medical therapy) management.[16] Mavrelos et al.[32] have shown that in appropriately selected, clinically stable women (ectopic mass measuring less than 30 mm in mean diameter, no embryonic cardiac activity and serum hCG level below 1500 IU/l) one-third of women diagnosed with an ectopic pregnancy may be successfully managed expectantly.

Non-tubal pregnancy

Non-tubal ectopic pregnancies represent a minority of ectopic pregnancies; however, they are important because they are responsible for a disproportionate level of morbidity. They often present relatively late and may be difficult to diagnose. This section will focus briefly on interstitial, cervical, caesarean section scar and heterotopic pregnancies. Other non-tubal ectopic pregnancies are found in the non-communicating horn of a congenitally abnormal uterus (cornual), the ovary and abdomen.

Interstitial ectopic pregnancy

Interstitial ectopic pregnancy is when implantation occurs in the interstitial portion of the fallopian tube and occurs in 1–6% of ectopic pregnancies.[33] The 'interstitial line sign' involves visualising the thin echogenic line of the endometrial cavity and following this along to the periphery of the interstitial sac.[34] This sign has been shown to have a sensitivity of 80% and a specificity of 98%.[34] Anecdotally, interstitial pregnancies often present at later gestations and with higher initial serum hCG levels. Three-dimensional ultrasonography offers a unique coronal view of the uterus that is ideally suited to visualising the interstitial segment of the tube (Figure 3).[33] Using three-dimensional ultrasound invariably allows a connection to be seen between the endometrial cavity and the gestation sac. This is in contrast to previous criteria that suggested a mantle of myometrium should always be visible between the two.

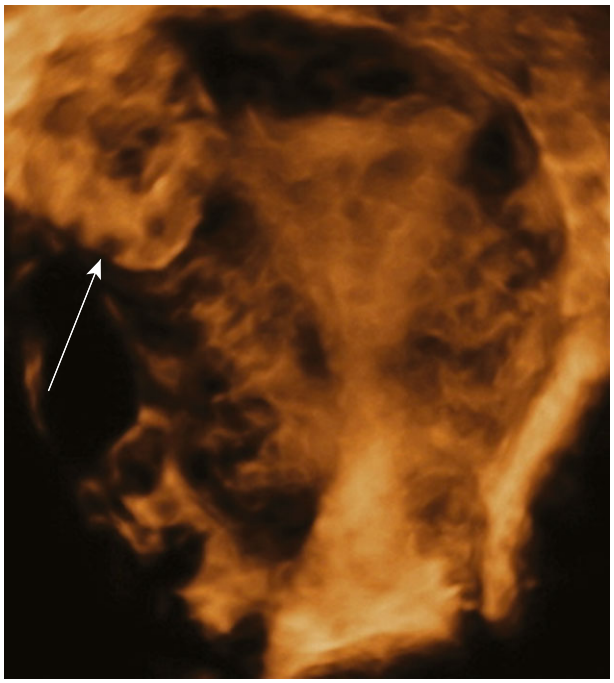


Figure 3. Three-dimensional image showing the coronal view of the uterus with a right-sided interstitial ectopic pregnancy (white arrow). The ectopic pregnancy was successfully treated with a single dose of intramuscular methotrexate.

Cervical pregnancy

Ultrasound criteria currently used to make a diagnosis of cervical pregnancy are:[35]

- an empty uterus
- a barrel-shaped cervix
- a gestational sac or trophoblastic mass below the level of the internal cervical os
- a negative 'sliding sign'
- evidence of sustained peri-trophoblastic circulation on colour Doppler examination.

Caesarean section scar pregnancy

A national registry for uncommon events in early pregnancy has been started: the UK Early Pregnancy Surveillance Service (UKEPSS). The first project for the UKEPSS aims to understand more about the risk factors, diagnostic criteria and management for caesarean scar pregnancy. All readers are encouraged to submit cases to the registry, which can be accessed online.[36] The criteria used in the UKEPSS study to diagnose caesarean scar pregnancy are as follows:[37]

- location outside the uterine cavity
- implantation of the pregnancy into a deficient scar with the gestational sac partially or completely located within the myometrial mantle
- evidence of sustained peri-trophoblastic flow on colour Doppler examination.

Both cervical and caesarean scar pregnancy may pose a diagnostic challenge, as they must be differentiated from a miscarriage where the sac is low within the cavity. The sliding sign in these circumstances may be useful: when pressure is applied to the cervix using the vaginal ultrasound probe, in a miscarriage the gestational sac slides against the endocervical canal but it does not in an implanted cervical or scar pregnancy. It should be remembered that the performance of the above diagnostic criteria for caesarean scar pregnancy has not been tested and there is an argument that these cases should be reviewed and managed at specialist centres. It is hoped that the UKEPSS initiative will lead to more definitive guidance about the optimal approach to diagnosing and managing these pregnancies.

Heterotopic pregnancy

A heterotopic pregnancy is a combination of both an intrauterine and an ectopic pregnancy. This is associated with assisted reproduction techniques. The majority are initially diagnosed as intrauterine singleton or twin pregnancies. This may be explained by examiners being falsely reassured after confirming the presence of an intrauterine pregnancy. The key clinical point here is to be aware that when a woman has undergone fertility treatment, visualisation of an intrauterine pregnancy does not exclude an ectopic pregnancy.

Pregnancy of unknown location

Pregnancy of unknown location is not a diagnosis but a temporary classification assigned to a woman until a definitive diagnosis is made. The number of ectopic pregnancies in women classified as having a pregnancy of unknown location varies and rates ranging from 7% to over 30% have been reported.[25,38] This ectopic pregnancy rate reflects the quality of ultrasonography and patient population in a department.

Management of pregnancy of unknown location is now centred on assigning risk: low (failing pregnancy of unknown location – location unknown, or viable intrauterine pregnancy) or high (ectopic pregnancy). Expectant management with hCG follow-up has been shown to be safe.[38] Low-risk pregnancies of unknown location require minimal follow-up (for example, a urinary pregnancy test in two weeks or repeat ultrasound in 1 week), while high-risk pregnancies of unknown location may require further ultrasound scans and measurements of serum hCG. Risk is evaluated using serum biochemistry.

Serum progesterone can select women with failing pregnancy of unknown location as low risk.[39] A systematic review and meta-analysis (five studies with 1998 participants and cut-off values from 3.2 to 6 ng/ml) concluded that a single progesterone measurement predicts nonviability with a pooled sensitivity of 74.6% (95% CI 50.6–89.4%) and specificity of 98.4% (95% CI 90.9–99.7%).[40] Cordina et al.[39] have also demonstrated in a single centre, how follow-up arrangements for pregnancy of unknown location can be rationalised using serum progesterone measurements. The limitation of using progesterone for triage is that it allocates most viable intrauterine pregnancies into the high-risk category and misclassifies more ectopic pregnancies as low risk compared with serum hCG-based triage.

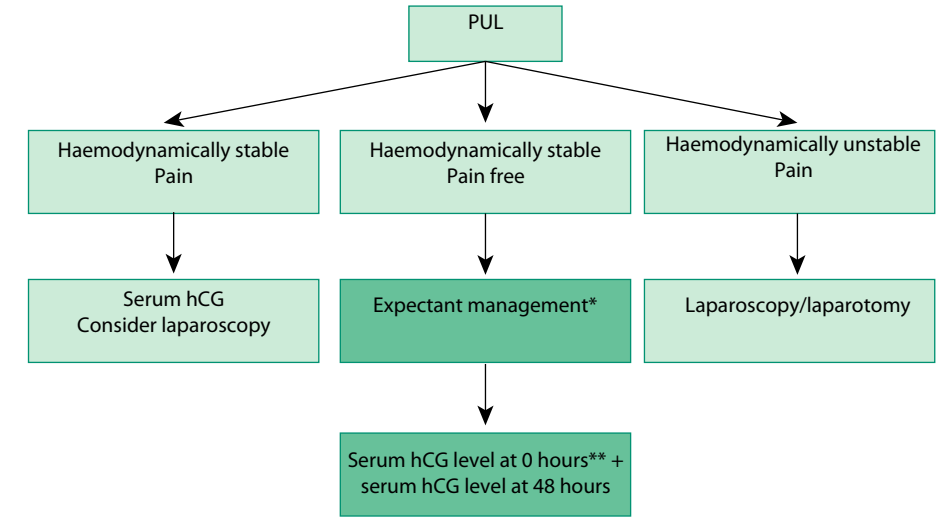
A multinomial logistic regression model (M4) based on serum hCG levels at presentation and the hCG ratio (hCG 48 hours/hCG 0 hours) has been developed that has been both internally and externally validated in over 1900 pregnancies of unknown location. In a further study on 1271 pregnancies of unknown location, triage based on serum progesterone, the hCG ratio and the M4 model were compared. These data showed that the M4 model performs significantly better than the hCG ratio, which in turn performs better than serum progesterone.[41,42] The M4 model can be downloaded online.[43] Two possible strategies that may be used to triage and follow-up pregnancies of unknown location are shown in Figure 4.

Molar pregnancy

Gestational trophoblastic disease can present in a very similar way to miscarriage, with vaginal bleeding being the most common symptom. The gold standard for diagnosis remains histopathological examination of retained products of conception obtained during surgical evacuation of the uterus. The classically described 'snowstorm' appearance is more common with complete molar pregnancy than with a partial mole, but is still rarely seen. More commonly with complete molar pregnancy, an ultrasound scan will show a complex, intrauterine echogenic mass with cystic spaces. Partial molar pregnancies are more commonly diagnosed as missed miscarriages. The positive predictive value of ultrasound in for the diagnosis of molar pregnancy has been shown to be approximately 48%, with a sensitivity of 44%.[44] Difficulties arise when trying to differentiate between hydropic changes in a miscarriage and molar change.

Conclusion

Transvaginal ultrasonography is the cornerstone of the management of women with early pregnancy complications. Furthermore, a clear understanding of the behaviour of serum hCG and progesterone is a requirement for those working in the field of early pregnancy care. It is also important to remember that we treat women and not ultrasound scans, therefore the clinical status of the women is paramount.



Triage with model M4

The model will assign a PUL as low risk (urinary pregnancy test in 2 weeks) or high risk (repeat hCG and/or TVS in 48 hours)

Change in hCG (hCG ratio: hCG 48 hours/ hCG 0 hours)	Likely diagnosis	Follow-up
>13% decrease (<0.87)	Failed PUL	Urinary pregnancy test in 2 weeks. Repeat serum hCG if +ve
>66% increase (>1.66)	Normal intrauterine pregnancy	Repeat TVS on day 7
<66% increase (1.00-1.65)	Probable ectopic pregnancy	Repeat TVS on day 7 or when hCG expected to be >1000 IU/l
<13% decrease (0.87-1.00)	Failed PUL or possible ectopic pregnancy	Repeat serum hCG on day 7

Figure 4. Two possible strategies to triage and follow-up pregnancies of unknown location. One uses the conventional change seen over time in the serum hCG level (the hCG ratio) and the other uses the M4 prediction model.
*Women must be given information and advice, and be considered compliant with follow-up and have no significant language or other communication barrier. Women should be advised to return for review before the scheduled follow-up visit if they have any severe pain or concerns. **If hCG >1000 IU/l at 0 hours and history not suggestive of complete miscarriage, then repeat TVS as soon as possible.
hCG = human chorionic gonadotrophin; PUL = pregnancy of unknown location; TVS = transvaginal ultrasonography.
Reproduced from Kirk E, Bottomley C, Bourne T. Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location. *Hum Reprod Update* 2014;20:250–61, with permission from Oxford University Press.

Recent changes in the criteria used to diagnose miscarriage have focused attention on the care that must be taken when using ultrasonography to make such critical clinical decisions. Most ectopic pregnancies should be visualised directly prior to treatment. Many of these may be managed successfully without any intervention and if methotrexate is considered it is essential that the possibility of a false-positive diagnosis is considered and an intrauterine pregnancy excluded. Pregnancy of unknown location is a classification not a diagnosis and should be managed on the basis of risk that in turn can be used to rationalise sensible follow-up arrangements.

Irrespective of whatever cut-off values or guidelines are used, the key issue is the capability of the ultrasound examiner. Significant experience is required to be competent in the safe use of ultrasound in gynaecology and early pregnancy. This only comes with appropriate training and supervision. It is important to remember the fundamental nature of decisions made in early pregnancy diagnostics. Misdiagnosis of miscarriage should be a 'never' event. It is worth quoting one of the conclusions from the report on the misdiagnosis of miscarriage by Campbell and colleagues:[45] 'The death of an embryo should be regarded as of equal significance to that occurring at a later stage'. In the authors'

view this should be the starting point when considering the care of women with complications in early pregnancy.

Contribution to authorship

MAM and TB drafted the manuscript. All authors revised and commented on subsequent drafts and approved the final version for submission.

Disclosure of interests

The authors declare no conflicts of interest.

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