



Editor's choice  
Scan to access more  
free content

# A missed opportunity for excellence: the NICE guideline on the diagnosis and initial management of ectopic pregnancy and miscarriage

Tom Bourne

Adjunct Professor and Consultant Gynaecologist, Queen Charlotte's & Chelsea Hospital, Imperial College, London, UK and Visiting Professor, Department of Development and Regeneration, KU Leuven, Belgium

## Correspondence to

Professor Tom Bourne, Early Pregnancy and Acute Gynaecology Unit, Queen Charlotte's & Chelsea Hospital, Du Cane Road, London W12 0HS, UK; [tbourne@imperial.ac.uk](mailto:tbourne@imperial.ac.uk)

Received 9 July 2014  
Revised 6 November 2014  
Accepted 7 November 2014

## INTRODUCTION

Early pregnancy problems are thought to lead to over 500 000 visits and about 50 000 admissions to UK hospitals annually. The emotional cost to women and their partners is considerable, and both miscarriage and ectopic pregnancy (EP) are associated with significant morbidity and even mortality.

In 2013, a National Institute for Health and Care Excellence (NICE) guideline was produced on the diagnosis and initial management in early pregnancy of EP and miscarriage.<sup>1</sup> The attention given by NICE to this clinical area is welcome and is to be applauded. Understandably in many places it is not evidence based, but represents the opinion of members of the guideline development group that produced the document. This is problematic as it means that the initial draft guidance reflected the views of a very small number of people with clinical experience of the conditions under review. A similar point was also made recently in relation to the NICE draft guidance on intra-partum care.<sup>2</sup> Furthermore the content of NICE guidance is not subject to formal peer review as would be expected with any other publication. Whilst feedback is invited, there is no requirement for NICE to incorporate such feedback in a way that requires aspects of the guidance to be acceptable to stakeholders. As a result the inclusion criteria, data synthesis and conclusions drawn when developing such guidance are not rigorously tested. This is a weakness in the process.

Whilst NICE does have a stated way of assessing tests (QUADAS-2), difficulties may arise if evidence is considered to be of poor quality as this leads to the

opinions of NICE panels being perhaps too influential in what is or is not included in final guidance. The quality indicators used by NICE are however a concern. As high-quality evidence is only deemed to relate to randomised trials or systematic reviews, virtually any diagnostic test study where performance is compared to the presence or absence of a pathology in a population is described as being of poor quality. This approach to the evaluation of studies relating to diagnostic tests is a wider problem, but perhaps NICE could take a lead on this. The result of these and other issues is that there are problems with the guidance. I will approach these under clinical headings. It is not possible within the space constraints of this article to forensically dissect the entire document, so this article does represent a selective approach.

## ACCESS TO EARLY PREGNANCY UNITS

Which women should be referred to an early pregnancy unit (EPU) because they are at risk of EP is unclear. There seems to be the belief that women with vaginal bleeding and no pain are not at risk of EP. NICE advises that such women be told to carry out a urinary pregnancy test in 10 days and "come back if it is positive". This is inappropriate as it is not possible on the basis of symptoms alone to select women in early pregnancy that have an EP, miscarriage or viable intra-uterine pregnancy (IUP). In an unpublished study of 596 women attending our EPU, vaginal bleeding in isolation was a significant risk factor for the presence of an EP particularly if it lasted for more than 3 days. Concerns about EP may also exist whether the gestational age of the pregnancy is greater than or less than



CrossMark

To cite: Bourne T. *J Fam Plann Reprod Health Care* 2015;41:13–19.

6 weeks. The guidance suggests that there is a specific cut-off in gestational age below which an EP is not dangerous, as they advise referral in many cases only when the gestation is over 6 weeks. Again this will lead to EPs being missed – often when they are small and perhaps most easily treatable. In the event of a patient being asymptomatic and undergoing an ultrasound scan to check gestation or for reassurance, in these circumstances rationalising access according to gestation is not unreasonable, with the optimal gestational age probably being 49 days.<sup>3</sup>

The recommendation by NICE that transvaginal ultrasonography (TVS) should be available out of hours is laudable but represents a risk to patients given current constraints on training. A key factor in maternal deaths from EP described in the recent Confidential Enquiry report relates to poor quality ultrasonography.<sup>4</sup> In the Irish Health Service Executive report into misdiagnosis of miscarriage, lack of training was identified as a key contributing factor.<sup>5</sup> Providing access to scanning out of hours should only occur when there is availability of suitably trained clinicians. Ultrasonography in trained hands is tremendously valuable; but in inadequately trained hands it is dangerous. By making provision of out of hours ultrasound a key priority for implementation, NICE risks that such services will be introduced to ‘tick boxes’, but with limited or no appropriate oversight. This would seem likely to do more harm than good.

## MISCARRIAGE

### Diagnosis

The NICE guidance follows the advice given by the Royal College of Obstetricians and Gynaecologists (RCOG) in their amended Green-top Guideline for the diagnosis of miscarriage.<sup>6</sup> This amended guideline was produced following the publication of a systematic review by Jevé *et al.*<sup>7</sup> and two new papers by Abdallah *et al.* in 2011.<sup>8,9</sup> These showed that previous cut-off values for measurements of embryo size [expressed as the crown–rump length (CRL)] or mean gestation sac diameter (MSD) that may be used to define miscarriage when using TVS were potentially unsafe. Accordingly MSD values of  $\geq 25$  mm and CRL values of  $\geq 7$  mm are now used. Where guidance is unclear is on the time interval required between ultrasound examinations when a scan is inconclusive (pregnancy of uncertain viability), and there is nothing in the guidance to indicate what should be found on a repeat ultrasound scan to definitively define viability. This is concerning, given that the diagnosis of miscarriage in the guidance is almost entirely based on the findings on repeat scans after an interval.

There are data that suggest that a *viable* pregnancy may be associated with little or no growth in MSD over 7–10 days,<sup>9</sup> so gestation sac growth is probably not a safe variable to use. More reliable markers of

miscarriage are the absence of embryonic structures after an interval of 14 days in a previously empty gestation sac, or absence of a visible heartbeat in a previously visualised embryo of any size after at least 7 days. Clinicians should also be aware that the appearance of a new feature such as a yolk sac in a previously empty gestation sac is an indication of possible viability and that a further scan should be arranged; however, the data to confirm this are not conclusive.<sup>8</sup>

Where NICE is clear is that great care must be taken when making a diagnosis of miscarriage, with an emphasis on repeating scans and asking for review by a second operator before making a definitive diagnosis. This is sensible around the decision boundaries of 25 mm (MSD) and 7 mm (CRL) referred to above, but many would argue that repeating scans for large empty gestation sacs and large embryos with an absent heartbeat is both unnecessary and unreasonable for patients. A common-sense approach to this issue was published recently in the *New England Journal of Medicine* by Doubilet *et al.*<sup>10</sup> The criteria to define pregnancy failure, or findings that are concerning regarding the possibility of miscarriage, are listed in Box 1. A further concern is that the guidance suggests that a complete miscarriage can be diagnosed using ultrasound. Clearly this is true if there has been a previous ultrasound scan confirming an IUP, but on a *single* scan, if a pregnancy cannot be seen, miscarriage of an IUP cannot be assumed and the pregnancy should be managed as a pregnancy of unknown location (PUL).<sup>11</sup>

### Treatment

Much of the guidance in relation to miscarriage treatment is taken from the MIST trial of the management of miscarriage.<sup>12</sup> However, although this trial was randomised, drawing conclusions from it is difficult. Of 3905 women attending EPUs, 1621 refused trial entry and 1085 were not eligible. The result is that only 1200/3905 (31%) women were randomised and the trial had to be extended by 33 months to overcome recruitment problems. It is clear that the subjects included represented a highly selected population. Accordingly, making policy on the basis of the outcome of these 1200 women is flawed. This is particularly so for psychological outcomes as the women who consented to take part in the trial may have been more likely to be motivated and so potentially less likely to show psychological morbidity, whichever management option was taken.

From a practical viewpoint, the NICE guidance does not consider the gestational age of a pregnancy as a factor when counselling women regarding treatment options. However, units often rely on protocols that use ultrasound criteria to decide if medical management is appropriate based on gestation sac and embryo size as well as whether or not the pregnancy is multiple. The experience of a miscarriage may be very different for a pregnancy at 11 weeks' gestation

### Box 1 Guidelines for transvaginal ultrasound diagnosis of pregnancy failure in a woman with an intrauterine pregnancy of uncertain viability\*

#### Findings diagnostic of pregnancy failure

- ▶ CRL  $\geq 7$  mm and no heartbeat, MSD  $\geq 25$  mm and no embryo
- ▶ Absence of embryo with heartbeat  $\geq 2$  weeks after a scan that showed a gestational sac without a yolk sac
- ▶ Absence of embryo with heartbeat  $\geq 11$  days after a scan that showed a gestational sac with a yolk sac

#### Findings suspicious for, but not diagnostic of, pregnancy failure†

- ▶ CRL  $< 7$  mm and no heartbeat
- ▶ MSD 16–24 mm and no embryo
- ▶ Absence of embryo with heartbeat 7–13 days after a scan that showed a gestational sac without a yolk sac
- ▶ Absence of embryo with heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac
- ▶ Absence of embryo  $\geq 6$  weeks after LMP
- ▶ Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo)
- ▶ Enlarged yolk sac ( $> 7$  mm)
- ▶ Small gestational sac size in relation to the embryo (MSD-CRL difference  $< 5$  mm)

\*Adapted from Doubilet *et al.*<sup>10</sup>

†When there are findings suspicious for pregnancy failure, follow-up ultrasonography in 7–10 days to assess the pregnancy for viability is generally appropriate.

CRL, crown–rump length; LMP, last menstrual period; MSD, mean sac diameter.

that failed at 6 weeks compared to an 11-week twin pregnancy that has only just failed. Yes, there are no useful data on this, but this does not mean that common sense should not be applied.

NICE recommends that all women with miscarriage should be given a trial of expectant management (watch and wait for resolution). This guidance seems to be based purely on an economic argument and uses the MIST trial to suggest that there is 'equipoise' between the different management options, and so argues that economics should be the main driver. This advice removes patient choice and has therefore been a significant concern to patient groups.<sup>13</sup> Furthermore, the assumption that the outcomes of the management options for miscarriage are similar fails to consider the fact that 69% of women who could have entered the MIST trial either exercised their choice to undergo surgery or were not eligible for the trial.<sup>12</sup> That it was so hard to recruit women into this trial should perhaps give pause for thought about what patients want. Many do not want expectant management for a variety of reasons. What MIST does suggest is that there is no advantage to be gained from medical management of incomplete miscarriage, where the gestation sac has been passed but some

products of conception still remain in the endometrial cavity. This is consistent with the first trials on this subject by Nielsen *et al.*<sup>14</sup> So although NICE appears to recommend it, medical management for incomplete miscarriage is unlikely to offer any advantage over a simple expectant approach, as most of these women will resolve their miscarriage without any need for intervention.

#### PREGNANCIES OF UNKNOWN LOCATION

The guidance defines a PUL as: "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". This is not entirely correct. Current publications on the subject of PUL relate to a failure to locate a pregnancy with TVS. Thus in the event of a pregnancy being classified as a PUL using the transabdominal approach, the correct next step is to carry out a TVS.

The guidance in relation to the management of PUL does not focus on identifying the location of the pregnancy. This reflects current practice, as the aim now is to evaluate risk, as for many PUL the location of the pregnancy is never known. Whether serial serum measurement of human chorionic gonadotrophin (hCG) can predict an EP and/or an IUP rather misses the point. Serial hCG levels, expressed for example as the hCG ratio (the serum hCG after 48 hours/serum hCG at presentation), are not used to diagnose EP. A PUL is either low risk (failing PUL or IUP) or high risk (probable EP). Accordingly serum hCG levels may be used to predict a failing pregnancy (low risk), and in such cases a urinary pregnancy test in 2 weeks is appropriate follow-up. If a viable IUP (low risk) is predicted, an ultrasound scan 1–2 weeks later may be carried out.

Identifying low- or high-risk PUL can be carried out effectively using published, easily used prediction models.<sup>15</sup> Measurements of serum progesterone to triage PUL may also be used in this context, as this is effective at predicting early pregnancy failure.<sup>16</sup> Although measuring serum progesterone is not recommended by NICE, it does offer the advantage of triaging women on the basis of one visit and one blood test, and Cordina *et al.* have shown that a significant number of women can be triaged using this approach at presentation.<sup>17</sup> The use of prediction models is also not considered in the guidance, and although published after the guideline was developed, Guha *et al.*<sup>18</sup> have shown the prediction model M4 outperforms both the hCG ratio and progesterone for effective triage of women with a PUL.

#### TUBAL ECTOPIC PREGNANCY

The NICE guidance limits its scope to tubal EP, which is unfortunate as guidance particularly in relation to interstitial EP and caesarean section scar pregnancies would have been helpful. Diagnostic accuracy studies for tubal EP considered in the guidance are largely

historical and so tell us very little that is new. TVS is a reasonably sensitive test for the detection of an EP, but it is not perfect. Most studies report ultrasound findings immediately prior to surgery. Kirk *et al.*<sup>19</sup> perhaps give a more realistic picture and showed that 74% of EPs can be visualised on an initial TVS, although 98% were seen prior to surgery. Criticism of this study could be that it was carried out in a specialist referral unit for gynaecological ultrasound, so the results may be over-optimistic. However despite this, 3/91 cases of EP diagnosed on an initial scan were false-positive test results. This may be because most EPs are visualised on ultrasound as a homogenous mass or 'blob'.<sup>19–21</sup> To avoid false-positive results in these circumstances it has been proposed that such ultrasound findings are evidence of a probable, rather than a definite, EP. Some EPs may be relatively difficult to visualise and some are not seen on an initial scan simply because they are too small and early in their natural history.<sup>22</sup> The ultrasound criteria to make a diagnosis of EP are not discussed in the NICE guidance, which would seem to be a significant omission given the reliance given to this when considering treatment.

#### Conservative treatment of EP

Some authors consider that a definitive diagnosis of tubal EP can only be made when an extrauterine gestation sac containing a yolk sac or embryonic pole is visualised. A recent consensus publication on nomenclature proposed that 'definite EP' is used if an extrauterine gestation sac with a yolk sac and/or embryo (with or without cardiac activity) is seen.<sup>23</sup> As alluded to above, a 'probable EP' is suggested if only a homogenous mass (blob sign) or an extrauterine sac-like structure is visualised. Using this classification, the specificity of ultrasound to detect EP is very high, but at the cost of lowering the sensitivity. Limiting the definitive diagnosis of EP to when embryonic structures are visible is an attempt to reduce false-positive diagnoses which, though rare, do occur due to amongst others the presence of pedunculated or broad ligament fibroids, pelvic inflammation or highly exophytic ovarian cysts.

This stringent approach reflects the very high level of diagnostic certainty required in the event that methotrexate treatment is considered. Even in the context of clinical trials, false-positive diagnoses of EP can occur.<sup>24</sup> This may lead to inappropriate use of methotrexate leading to termination of an undetected viable IUP, or to severe abnormalities in surviving pregnancies.<sup>25</sup> The American College of Obstetricians and Gynecologists (ACOG) recommends that methotrexate should only be administered for a 'probable EP' (i.e. a homogenous mass with no embryonic features) in cases where serial measurements of serum hCG confirm that the increase is incompatible with an ongoing early IUP. The difficult issue, however, is how

to define 'incompatible'. The ACOG defines this as there being a less than 53% rise in hCG over a 48-hour period.<sup>26</sup> This definition of non-viability is controversial. In a paper addressing the safety of curettage for the management of PUL, Condous *et al.*<sup>27</sup> showed that a viable IUP may be associated with an hCG rise of significantly less than 50%. Great care must be taken in these circumstances. In the event that the finding of an inhomogeneous mass is a false-positive finding, giving methotrexate with an hCG rise of less than 53% could lead to termination of a wanted pregnancy. An hCG rise of less than 35% is now considered a safer definition of non-viability in women with probable EP when methotrexate is being considered for management.<sup>28</sup> The key issue here is the quality of ultrasonography. When considering methotrexate treatment it is essential that the ultrasound findings have been reviewed by an experienced examiner and that there is certainty about the diagnosis.

Against this background the NICE guideline is concerning. It does not consider expectant management for EP, yet in a recent study of 333 women diagnosed with EP, 146 commenced expectant management and 104 successfully resolved their EP without further intervention (31.2%, 95% confidence interval 26.2–36.2),<sup>29</sup> although it should be noted that this protocol has not been externally validated. So, whilst one might expect there to be discussion in the guidance about selection criteria, follow-up and economic impact, for expectant management to be omitted entirely is a serious oversight. Unless clinicians choose to disregard the NICE guidance they may be giving methotrexate to women whom they know do not require treatment in perhaps one-third of cases. This raises difficult ethical issues, especially as methotrexate does not have a licence for this indication in the UK.

So we are left with the guidance recommending the use of methotrexate as the first-line treatment for EP, whilst not considering either how to diagnose EP safely, or to definitively exclude the possibility of a viable IUP. The presumption appears to be that a false-positive misdiagnosis of EP is not possible. If followed, this guidance is likely to lead inevitably in some cases to viable IUPs being terminated due to medical error, whilst in others to women being subjected to potentially hazardous drug treatment that they do not need.<sup>30</sup>

#### NON-TUBAL ECTOPIC PREGNANCY

Although the guidance has been given the title 'Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage', all forms of non-tubal EP are excluded. This is regrettable as these forms of EP cause disproportionate morbidity and also management difficulties for everyone involved in early pregnancy care. The evidence base for the treatment of these conditions is poor; however, some

guidance would have been helpful, particularly for the diagnosis and management of caesarean scar pregnancies and interstitial EP. It would have been particularly beneficial if the diagnostic criteria and management of caesarean scar pregnancies had been cited by NICE as a research priority, as well as perhaps advising that such pregnancies be treated in regional centres. The importance of this condition has recently been recognised in the UK with the setting up of the UK Early Pregnancy Surveillance Service for uncommon disorders of early pregnancy and acute gynaecology (UKEPSS), which has set caesarean scar pregnancy as its first research priority.<sup>31</sup>

### PSYCHOLOGICAL SUPPORT

The guidelines propose medical management of EP and expectant management of miscarriage as the first treatment of choice for all women; however, the psychological impact of these procedures has not yet been evaluated. In the absence of any such evidence, it is likely that an informed choice of treatment method would be more beneficial for the women's psychological wellbeing. Women's experiences of early pregnancy loss vary a great deal, with some reporting disabling post-traumatic stress disorder, depression and/or anxiety for a considerable time afterwards and others being able to resume daily life as soon as their physical symptoms allow, with little or no psychological impact. At present there is no way of predicting who will suffer psychological morbidity after their pregnancy loss and who will not, and similarly no clear referral pathways exist for accessing psychological support services. Local referral pathways should be drawn up to identify and offer specialist treatment to those women who suffer from mental health problems as a result of their early pregnancy loss.

### QUALITY STANDARDS

At the time of writing, the quality standards proposed by NICE state that the quality of early pregnancy care should be judged on whether women with a possible miscarriage or EP are seen within 24 hours, whether they are offered a TVS, whether women with a possible miscarriage are offered a repeat TVS to confirm the diagnosis, and whether women with suspected EP or miscarriage are offered evidence-based information. What are we to make of these?

I think that there is not an absolute requirement in a stable woman that she be seen within 24 hours of onset of symptoms of a possible miscarriage or EP. This also rather contradicts the guidance where bleeding in isolation is not considered a reason for referral to an EPU. Clearly it is preferable that such women are seen within 24 hours; however, in many cases waiting, for example from Saturday evening to Monday morning, whilst not ideal, may result in a better outcome. What is important is that when she is

seen the quality of ultrasound scanning is optimal in order to avoid false-positive and false-negative diagnoses.

The quality standard that requires that all women be offered a TVS is possibly unethical. Why is it necessary to carry out a TVS on a woman with a 9-week pregnancy to confirm viability? Using modern transabdominal probes this diagnosis should be straightforward, with TVS being reserved in the event that there is uncertainty. Should all women with a diagnosis of miscarriage be offered a repeat scan to confirm the diagnosis? This is of course absolutely the case around the decision boundaries. But if an embryo with a CRL of 25 mm and no visible fetal heartbeat or a 45 mm diameter empty gestation sac are seen, is it really appropriate to offer the patient a repeat scan in 2 weeks? The implication is that somehow the diagnosis might not be reliable and there is hope that the pregnancy will be viable on the repeat scan. The only reason for such a policy is if it is thought that the first scan was carried out incompetently. The answer to this would seem to be to ensure adequate audit standards, appropriate training and supervision, not dragging women back for repeat intrusive examinations whilst prolonging the uncertainty about whether they have miscarried.

### CONCLUSIONS

For those of us who have worked for years in early pregnancy care both clinically and academically, the news that NICE was planning to provide guidance for miscarriage and EP was greeted with real enthusiasm. Unfortunately in many aspects the outcome is a missed opportunity. In my opinion the guidance ducks the issue in relation to difficult management problems in early pregnancy such as non-tubal EP. Issues such as criteria for diagnosis of EP, excluding the possible presence of a viable IUP when using methotrexate, and follow-up findings in the event of possible miscarriage on a first ultrasound scan, are inadequately addressed. The guidance that all women with a miscarriage should have expectant management is likely to become a millstone if adopted as a quality standard. The basis of this advice, relying largely on the MIST trial,<sup>11</sup> is flawed in any event. It certainly represents an erosion of patient choice. The suggestion that methotrexate is used as first-line treatment for EP, if taken up clinically, will condemn many women to drug treatment unnecessarily and, with the lack of attention given to diagnostic criteria for EP, will probably lead to inadvertent termination of wanted pregnancies. It is unfortunate that if quality of care is based on adherence to many aspects of the guidance, the care for women with early pregnancy problems is likely to be made worse rather than improved.

The NICE guidance makes sensible suggestions in relation to the organisation of services, but this is not novel and reflects the established system of early

pregnancy care in many areas of the UK. What would have been useful would have been meaningful suggestions in relation to quality standards, training and supervision. In practical terms NICE could have advised that all EPUs have appropriate reporting databases to enable hard-pressed staff to produce standardised reports, archive images, and simplify audit. Suggestions for auditable quality standards would have been useful; an example might be the PUL rate (the number of new patients classified as a PUL) as an indicator of ultrasound quality. It is to be hoped that NICE will recognise the limitations of the guidance they have produced on this subject by updating and carefully reviewing the clinical interpretation of the evidence that is available.

**Acknowledgements** The author is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

**Competing interests** None.

**Provenance and peer review** Commissioned; externally peer reviewed.

## REFERENCES

- National Institute for Health and Clinical Excellence. *Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management in Early Pregnancy of Ectopic Pregnancy and Miscarriage (Clinical Guideline 154)*. 2012. <http://www.nice.org.uk/CG154> [accessed 3 July 2014].
- Rajasingam D, Harding K. NICE's draft guideline on intrapartum care. *BMJ* 2014;348:g4279.
- Bottomley C, Van Belle V, Mukri F, et al. The optimal timing of an ultrasound scan to assess the location and viability of an early pregnancy. *Hum Reprod* 2009;24:1811–1817.
- O'Herlihy C. Deaths in early pregnancy. In: Lewis G (ed.), Centre for Maternal and Child Enquiries (CMACE), *Saving Mothers' Lives: Reviewing Maternal Deaths to Make Motherhood Safe 2006–2008. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom*. *BJOG* 2011;118(Suppl. 1):1–203.
- Irish Health Service Executive (HSE). National miscarriage misdiagnosis review. April 2011. <http://www.rte.ie/news/2011/0418/miscarriagereview1.pdf> [accessed 3 July 2014].
- Royal College of Obstetricians and Gynaecologists. *Addendum to GTG No. 25 (October 2006): The Management of Early Pregnancy Loss*. 2011. <http://www.rcog.org.uk/files/rcog-corp/Addendum%20to%20GTG%20No%2025.pdf> [accessed 3 July 2014].
- Jeve Y, Rana R, Bhide A, et al. Accuracy of first-trimester ultrasound in the diagnosis of early embryonic demise: a systematic review. *Ultrasound Obstet Gynecol* 2011;38:489–496.
- Abdallah Y, Daemen A, Kirk E, et al. Limitations of current definitions of miscarriage using mean gestational sac diameter and crown-rump length measurements: a multicenter observational study. *Ultrasound Obstet Gynecol* 2011;38:497–502.
- Abdallah Y, Daemen A, Guha S, et al. Gestational sac and embryonic growth are not useful as criteria to define miscarriage: a multi-center observational study. *Ultrasound Obstet Gynecol* 2011;38:503–509.
- Doubilet PM, Benson CB, Bourne T, et al.; Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med* 2013;369:1443–1451.
- Condous G, Okaro E, Khalid A, et al. Do we need to follow-up complete miscarriages with serum human chorionic gonadotrophin levels? *BJOG* 2005;112:827–829.
- Trinder J, Brocklehurst P, Porter R, et al. Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial). *BMJ* 2006;332:1235.
- Goldsmith H. Ectopic pregnancy and miscarriage: summary of NICE guidance. *BMJ* 2012;345:e8136.
- Nielsen S, Hahlin M, Platz-Christensen J. Randomised trial comparing expectant with medical management for first trimester miscarriages. *BJOG* 1999;106:804–807.
- Van Calster B, Abdallah Y, Guha S, et al. Rationalizing the management of pregnancies of unknown location: temporal and external validation of a risk prediction model on 1962 pregnancies. *Hum Reprod* 2013;28:609–616.
- Mol BW, Lijmer JG, Ankum W, et al. The accuracy of single serum progesterone measurement in the diagnosis of ectopic pregnancy: a meta-analysis. *Hum Reprod* 1998;13:3220–3227.
- Cordina M, Schramm-Gajraj K, Ross JA, et al. Introduction of a single visit protocol in the management of selected patients with pregnancy of unknown location: a prospective study. *BJOG* 2011;118:693–697.
- Guha S, Ayim F, Ludlow J, et al. Triaging pregnancies of unknown location: the performance of protocols based on single serum progesterone or repeated serum hCG levels. *Hum Reprod* 2014;29:938–945.
- Kirk E, Papageorghiou AT, Condous G, et al. The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. *Hum Reprod* 2007;22:2824–2828.
- Brown DL, Doubilet PM. Transvaginal sonography for diagnosing ectopic pregnancy: positivity criteria and performance characteristics. *J Ultrasound Med* 1994;13:259–266.
- Condous G, Okaro E, Khalid A, et al. The accuracy of transvaginal sonography for the diagnosis of ectopic pregnancy prior to surgery. *Hum Reprod* 2005;20:1404–1409.
- Kirk E, Daemen A, Papageorghiou AT, et al. Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination? *Acta Obstet Gynecol Scand* 2008;87:1150–1154.
- Barnhart K, van Mello NM, Bourne T, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Fertil Steril* 2011;95:857–866.
- Moeller K, Moeller C, Thomsen S, et al. Success and spontaneous pregnancy rates following systemic methotrexate versus laparoscopic surgery for tubal pregnancies: a randomized trial. *Acta Obstetrica et Gynecologica* 2009;88:1331–1337.
- Nurmohamed L, Moretti ME, Schechter T, et al. Outcome following high-dose methotrexate in pregnancies misdiagnosed as ectopic. *Am J Obstet Gynecol* 2011;205:533.e1–533.e3.

- 26 Agency for Healthcare Research and Quality. *Medical Management of Ectopic Pregnancy*. 2008. <http://www.guidelines.gov/content.aspx?Id=12625#Section427> [accessed 3 July 2014].
- 27 Condous G, Kirk E, Lu C, *et al*. There is no role for uterine curettage in the contemporary diagnostic workup of women with a pregnancy of unknown location. *Hum Reprod* 2006;21:2706–2710.
- 28 Seeber BE, Sammel MD, Guo W, *et al*. Application of redefined human chorionic gonadotropin curves for the diagnosis of women at risk for ectopic pregnancy. *Fertil Steril* 2006;86:454–459.
- 29 Mavrelou D, Nicks H, Jamil A, *et al*. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. *Ultrasound Obstet Gynecol* 2013;42:102–107.
- 30 Bourne T, Barnhart K, Benson CB, *et al*. NICE guidance on ectopic pregnancy and miscarriage restricts access and choice and may be clinically unsafe. *BMJ* 2012;346:f197.
- 31 Harb HM, Knight M, Jurkovic D, *et al*. UKEPSS: The UK Early Pregnancy Surveillance Service for uncommon disorders of early pregnancy and acute gynaecology. *The Obstetrician & Gynaecologist* 2014;16:226–227.