Rationalising the change in defining non-viability in the first trimester

Fernando Infante[1]
MBBS (U Valle, Col.), MPH (UNSW), MRANZCOG

Ishwari Casikar[1]
MBBS

Uche Menakaya[1]
MBBS, MCE, DRANZCOG, MRANZCOG

George Condous[1,2]
MBBS, FRCOG, FRANZCOG, MD

[1]Acute Gynaecology, Early Pregnancy and Advanced Endosurgery Unit
Sydney Medical School Nepean
University of Sydney
Nepean Hospital
Penrith
New South Wales
Australia

[2]OMNI Gynaecological Care, Centre for Women's Ultrasound and Early Pregnancy
St Leonards
Sydney
New South Wales
Australia

Correspondence to email ferchoinfante@yahoo.com.au

Abstract

Introduction: With the publication of four papers in late 2011, international cut-offs for definitions of non-viability in the first trimester of pregnancy were challenged. These definitions were inconsistent across different international guidelines. For example, a gestational sac with absent yolk sac or embryo and a mean diameter of ≥ 16 mm would be classified as a miscarriage in the USA, whereas the same sac would have to measure ≥ 20 mm in the UK or Australia to meet this definition. Likewise, an embryo with no detectable heartbeat and a CRL of ≥ 5 mm would also meet criteria for missed miscarriage in the USA, compared to a CRL ≥ 6 mm in the UK or Australia.

Methods: Later in 2011 and then in 2012, guidelines across the three countries were updated and are now consistent, defining an empty gestational sac with a mean diameter of > 25 mm as a non-viable pregnancy and/or an embryo with CRL > 7 mm and no detectable heartbeat. In this paper we explore the rationale that led to these changes in order to potentially avoid wrongly diagnosing miscarriage at the decision boundary measurements and in turn avoiding inadvertent termination of potentially viable pregnancies.

Conclusion: Although reducing women's anxiety and making a definitive diagnosis as early as possible is desirable, the need for absolute certainty is paramount before diagnosis of the death of an early pregnancy is made.

Keywords: crown rump length, intra-uterine pregnancy of uncertain viability, miscarriage, transvaginal scan.

Introduction

The transvaginal ultrasound scan (TVS) has long ago become the gold standard diagnostic tool for the assessment of women in the first trimester of pregnancy. This has now also been endorsed by the Royal College of Obstetricians and Gynaecologists (RCOG) as an integral component of assessment.[1] Identification of key structures including the gestational sac eccentrically placed within the endometrial cavity is key to determining pregnancy location,[2] while the presence of a fetal or embryonic pole with visible cardiac pulsations is key to determining pregnancy viability.[3] However determining non-viability in the clinically stable woman poses a significant challenge when no cardiac activity can be visualised in the embryo, or when no embryo can be visualised inside the intra-uterine gestational sac. The term *Intra-uterine pregnancy of uncertain viability* (IPUV) has been applied to any situation where a diagnosis of viability cannot be made.[4] The rate of IPUV at the first visit may vary from 10–29% of all intra-uterine pregnancies.[1,5] Experienced operators using TVS can visualise cardiac activity in an embryo whose crown-rump length (CRL) is as small as 1.3 mm.[6] However at CRL < 5 mm, up to one third of embryos will not have detectable heart activity on TVS.[7,8] In fact, the lower threshold for a CRL at which cardiac activity should be seen has not been established with absolute certainty. Similarly, lower cut-offs for the size of the gestational sac, expressed as the mean sac diameter (MSD), at which the yolk sac or the embryonic pole should be visualised have also not been established beyond absolute doubt. Naturally this has major implications for the diagnosis, counselling and management of women with early pregnancy loss. Prior to 2012, the sonographic criteria to define IPUV and non-viable pregnancy varied internationally. It is therefore possible to assume that misdiagnosis could have lead to inadvertent termination of wanted pregnancies. One of the most commonly used guidelines for diagnosing miscarriage in the United Kingdom (UK) was the 'Management of Early Pregnancy Loss' – Green top guideline number 25, developed by the RCOG.[1] These guidelines defined an IPUV as an intra-uterine gestational with a MSD of < 20 mm with no obvious yolk sac or embryo; or a CRL of < 6 mm with no embryonic cardiac activity. They recommended that in order to confirm or refute viability, a repeat scan at a minimal interval of one week was necessary. From this, it could have been inferred that a miscarriage could be diagnosed at the first scan if the MSD was ≥ 20 mm with no yolk sac or embryo; or if the CRL was ≥ 6 mm with no embryonic cardiac activity. It is important to

note that the level of evidence to support these guidelines was level IV, which is expert opinion only.

The American College of Radiology had, prior to 2012, published less conservative measurements in their *First Trimester Bleeding* guidelines.[4] They defined miscarriage on the basis of an empty sac with a MSD ≥ 16 mm, or, if present, an embryo with a CRL measuring > 5 mm with no observable cardiac activity In Australia, the Australian Society of Ultrasound in Medicine (ASUM) had similar recommendations for MSD and CRL diagnostic criteria as the RCOG in the UK.[8]Following the publication of four papers that questioned and examined the evidence hitherto supporting these guidelines,[6,9–11] the RCOG published an amendment to its 2006 guideline in October 2011.[12] ASUM followed suit in November 2011 and then the American College of Radiology in 2012.[13,14] There is now consensus among the three sets of guidelines, with diagnostic criteria for defining non-viability on the basis of CRL size without detectable heart beat, increased to ≥ 7 mm; and on the basis of empty sac with MSD, increased to ≥ 25 mm.[12–14]

Methods

What is the rationale behind these changes and do we now have all the evidence we need to formulate such cut-offs beyond any doubt?

It is important to take a closer look at the four papers mentioned above.[6,9–11] Jeve, *et al.* published a systematic review on the accuracy of first trimester ultrasound to make a diagnosis of miscarriage.[9] The authors found only eight papers of acceptable quality for analysis; six of them were prospective and two were retrospective cohort studies. The papers had been published between 1986 and 1994.[15–22] The reference standards against which findings were measured in each paper varied from clinically diagnosed miscarriage, diagnosis of miscarriage in a further scan, histopathology, failure of embryo development, falling levels of serum human chorionic gonadotrophin and evaluation of fetal status on second-trimester ultrasound. Only half the studies had access to a transvaginal probe. None of the studies evaluated the reproducibility of their early pregnancy measurements. The main findings of this review were that previously used criteria for defining non-viability in the first trimester were not entirely accurate. Considering that a major decision such as uterine evacuation may follow the diagnosis of early fetal demise, any criterion used to determine such diagnosis would at least need to have 100% specificity, i.e. no viable pregnancies should be classified as non-viable. This means that the false positive rate (FPR) should be 0%. If a diagnostic test states there has been fetal demise, there can be no doubt left for the mother if surgery is then arranged. Otherwise the inadvertent termination of a potential live pregnancy could occur. In particular, the authors found that an empty gestational sac with MSD ≥ 25 mm and a missing yolk sac in a gestational sac with MSD ≥ 20 mm appeared to be the most accurate thresholds for the diagnosis of early embryonic demise, with an estimated specificity of 100% and consequent FPR rate of 0%. However as confidence intervals for both thresholds lied between 0.96–1.00, this would mean that up to four in every 100 diagnoses may be a false positive one. That is to say, for every 100 tests among women with an intra-uterine pregnancy where these criteria would be used to define non-viability, there might be up to four live pregnancies.[9] An important factor influencing these findings was the relatively small sample size of the studies analysed.

Abdallah, *et al.* studied over one thousand pregnancies diagnosed as IPUV across four different hospitals in a multi-centred prospective trial.[10] The end point was ongoing pregnancies at the 11–14 week scan. They found that for every 100 pregnancies classified as non-viable due to an empty sac with MSD ≥ 16 mm, up to four could be viable (FPR of 4.4%); for every 200 pregnancies classified as non-viable due to an empty sac with MSD ≥ 20 mm, one pregnancy could be viable (FPR of 0.5% for this cut-off). Interestingly, there were no false-positive tests results for miscarriage when a cut-off of MSD ≥ 21 mm was used. Regarding the presence of an embryo with no detectable cardiac activity, up to 8 pregnancies could be viable for every 100 tests advising non-viability based on CRL with cut-offs of both 4 and 5 mm (FPR 8.3%). There were no false-positive results using a CRL cut-off of ≥ 5.3 mm. A weakness of this study was the relatively small number of cases at or around the critical decision boundaries used to define to miscarriage.[10]

An important aspect to consider when the CRL and MSD fall near the decision boundaries is that of the intra and inter-observer reproducibility of measurements. By way of example, Sonologist A could measure a CRL of 5 mm, whereas Sonologist B might measure it as 5.4 mm. Or Sonologist A could if asked to review their images off-line, at a later time, repeat the same measurement and obtain a different value. To test this, Pexsters, *et al.* asked two independent sonographers, both gynaecologists with specialist training in obstetric and gynaecological sonography, to determine CRLs and MSDs in a set of 54 viable pregnancies between 6 and 9 completed weeks. The sonographers were also asked to take two measurements of CRL per pregnancy. A total of 44 pregnancies were assessed by both practitioners. The authors found that the limits of agreement for CRL were ± 8.91 and ± 11.37% for intra-observer agreement, and ± 14.64% for inter-observer agreement. This means that for a CRL measurement of 6 mm the prediction interval for the second observer was 5.4–6.7 mm. Similarly for the MSD, the inter-observer limits of agreement were ± 18.78%; for an MSD measurement of 20 mm, the prediction interval for the second observer was 16.8–24.5 mm. Therefore determining that a pregnancy is non-viable when the CRL is measured as 6 mm in an embryo with no demonstrable heart activity, or when an empty sac's MSD measures 20 mm, might have the potential of misdiagnosis by over-estimating smaller measurements in a pregnancy that should still be classified as IPUV.[6] The more conservative cut-offs now used by International guidelines are meant to account for such variations in intra and inter-observer measurements.

What about guidelines to re-assess IPUVs to determine viability or non-viability at a later time? There is consensus among the international guidelines, with little evidence to underpin it, that measurements should be repeated 7–10 days later, but the expected findings to prove or disprove viability are unclear. It had been previously thought that in a normal pregnancy, the CRL should increase by approximately 1 mm per day between 7 and 12 weeks.[11,23] In the fourth paper discussed here, Abdallah at el looked at a subset of the 1060 pregnancies from their main

study.[10,11] A total of 359 pregnancies were analysed. The main finding was that there was considerable overlap between viable and non-viable pregnancies (as determined at the 11–14 week mark) in terms of the MSD growth rate. In spite of the fact that MSD growth was significantly higher in viable than non-viable pregnancies (mean 1.003 vs. 0.503 mm/day; $P < 0.001$, 95% CI of difference 0.403–0.596) there was no cut-off below which a viable pregnancy could be safely excluded. On the other hand, the failure of either a yolk sac or embryo to be visualised on repeat scan was always associated with miscarriage, in this particular study. CRL growth rates were also significantly different between viable and non-viable pregnancies (mean 0.673 vs. mean 0.148 mm/day; 95% CI of difference 0.345–0.703). However the minimum growth rate for CRL that could differentiate between a viable and a non-viable pregnancy was as low as 0.2 mm per day. In other words, if a CRL grew only 1.4 mm in a week, it could still correspond to a viable pregnancy.[11]

Conclusion

Based on the recent evidence, current International guidelines have been modified. However, is it possible that the new cut-offs are not conservative enough? What is the optimal interval between scans to follow up IPUVs before making a definite diagnosis of non-viability? A recently published paper made a point of how the association between failure to identify embryonic structures within a gestational sac on two scans 7 and 14 days apart and definite empty sac miscarriage, as reported by Abdallah, *et al*.,[11] was based on a relatively small number of cases. Thus, larger prospective studies are required to confirm this apparent unequivocal sign of miscarriage.[4]

The rationale for hasting a definite diagnosis of non-viability is to reduce the anxiety of uncertainty for the couple, reduce the follow up required and allow commencement of earlier definitive management. Health care costs implications need to be taken into account as well. From a clinical perspective, delaying definite diagnosis of miscarriage and its subsequent management, in the stable and usually mildly symptomatic or asymptomatic patient does not pose any major risk to the mother. Several studies have proven that expectant management is safe; and that waiting 7 days reduces the risk of intervention by 30%.[24,25] However it is important to also consider that definitive management of miscarriage must be guided by the principle of patient's autonomy and informed consent, in conjunction with the ability of the unit managing the patient to offer expectant, medical and/or surgical treatment. Surgical curettage still offers the greatest evacuation rate, the least risk of needing unplanned admission and the shortest duration of bleeding.[26] The patient should be allowed to weigh this against the small risk of surgical and anaesthetic complications.

The current guidelines and recommended cut offs have been introduced to avoid inadvertent termination of potentially viable pregnancies at the decision boundary measurements. The challenge now is to prospectively validate these new ultrasound cut-offs for MSD and CRL to diagnose miscarriage in a large study population. Although reducing women's anxiety and making a definitive diagnosis as early as possible is desirable, the need for absolute certainty is paramount before diagnosis of the death of an early pregnancy is made.

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