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ORIGINAL ARTICLE *Early pregnancy*

The optimal timing of an ultrasound scan to assess the location and viability of an early pregnancy

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BACKGROUND: The objective of this study was to determine the optimal gestational age at which to establish the location and viability of an early pregnancy using transvaginal ultrasonography (TVS).

METHODS: This was a prospective study of 1442 women undergoing initial TVS at no more than 84 days gestation. Logistic regression analysis was performed to determine the relationship between gestational age and the ability to confirm viability or non-viability, in women with and without symptoms of pain and bleeding.

RESULTS: The commonest TVS finding prior to 35 days was a pregnancy of unknown location, from 35 to 41 days an early intrauterine pregnancy of uncertain viability and from 42 days a viable intrauterine pregnancy. Miscarriage could only be diagnosed on initial TVS after 35 days. There was no difference between the ability to make a diagnosis for women with certain or uncertain dates ($P = 0.719$). The chance of confirming viability increased rapidly per day of gestation until 49 days and thereafter plateaued. Of the 29 ectopic pregnancies diagnosed, 72% presented prior to 49 days gestation and all of these women presented with pain, bleeding or a previous ectopic pregnancy history.

CONCLUSIONS: The ability to confirm viability or non-viability is significantly related to gestational age. In asymptomatic women with no previous ectopic pregnancy TVS should be delayed until 49 days. Our data suggest that this would reduce the number of inconclusive scans, without an associated increase in morbidity from missed ectopic pregnancies.

Key words: first trimester / pregnancy / diagnosis / transvaginal ultrasound / viability

Introduction

Transvaginal ultrasonography (TVS) is commonly performed during the early first trimester of pregnancy to confirm pregnancy location, viability or gestational age (Bignigg and Read, 1991). The optimal timing of such an early first trimester ultrasound scan is unclear. As commercially available human chorionic gonadotrophin (hCG) assays can detect pregnancy from the time of a missed period there seems to be a trend for women to present earlier for ultrasound assessment. There is also a tendency for asymptomatic women to undergo routine scans for viability in the early first trimester. However this may be associated with an increase in the rate of inconclusive ultrasound findings (Jauniaux *et al.*, 2005).

Performing an ultrasound assessment in pregnancy too early may lead to the finding of a pregnancy of unknown location (PUL) or an intrauterine pregnancy of uncertain viability (IPUVI) with the need for serial serum hCG measurements and further ultrasound assessment (Banerjee *et al.*, 1999; Elson *et al.*, 2003; Falco *et al.*, 2003; Condous *et al.*, 2004). Conversely, if ultrasound assessment is deferred based on arbitrary limits for gestation, there may be physical or psychological morbidity or mortality associated with a delay in the diagnosis of a spontaneous early pregnancy loss (Nikcevic *et al.*, 1998) or an ectopic pregnancy (Mol and van der Veen, 1997; Lewis, 2007).

The first objective of this study was to test the hypothesis that there is a positive association between gestational age and the ability to make a definitive diagnosis of viability or non-viability at first TVS assessment in a general Early Pregnancy Unit (EPU) population. The second objective was to determine whether there is an optimal

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time for an ultrasound scan to be performed, in both asymptomatic and symptomatic women, in order to limit the number of PUL and IPUVI findings while giving a definitive answer regarding viability and identifying the majority of women with pathology present within the cohort studied.

Methods

This was a prospective observational cohort study of all women attending an EPU with a positive pregnancy test from January to October 2006. The EPU is open 6 days a week and receives self-referrals as well as referrals from other health care practitioners. Women attend for a number of reasons, including abdominal pain, vaginal bleeding, uncertain menstrual dates, maternal anxiety or a history of a previous early pregnancy complication. The criteria for inclusion in this study were natural conception, first attendance in the index pregnancy, a history of a positive pregnancy test and a gestational age from the first day of the last menstrual period (LMP) of no more than 84 days. There was no minimum gestational age for inclusion. Women were included regardless of the indication for their presentation except where they presented with complications following delivery, termination of pregnancy or recently diagnosed early pregnancy loss. Women who were unable to report an LMP date (whether certain or uncertain) were excluded as a menstrual gestational age could not be calculated. For women presenting with more than one pregnancy during the study period, only the first pregnancy was included in the analysis.

Prior to TVS all women completed a detailed demographic and symptom questionnaire. TVS was performed using a 5 MHz transducer for B mode imaging (Aloka SSD 900, 2000, 4000 or GE Voluson 730). All operators were experienced sonographers (specialist nurse, midwife or gynaecologist). Ultrasound findings were contemporaneously entered onto an electronic database (Viewpoint PIA database, LB Systems, Vienna, Austria).

The TVS outcomes were pre-defined using the recommended criteria described in Table I. Where the history and ultrasound findings were suggestive of complete miscarriage the pregnancy was classified as a PUL as an intrauterine pregnancy had not been previously identified and 6% of such cases are known to be associated with an ultimate diagnosis of ectopic pregnancy (Condous *et al.*, 2005a, b). Depending on the outcome of the assessment, women were managed according to standard departmental protocols. Women with inconclusive TVS findings (PUL or IPUVI) were managed expectantly. This involved serial measurements of serum hCG, serum progesterone and a repeat TVS for PUL, or a repeat TVS after an interval of 7–14 days for IPUVI. The number of further serum biochemical tests and ultrasound assessments to confirm a diagnosis of viable pregnancy, miscarriage or ectopic pregnancy was recorded.

In this study gestational age was defined as the number of days from the first day of the LMP. 'Certain dates' was defined as being sure of the LMP and a regular cycle length of between 26 and 30 days. Where an LMP was reported but cycles were irregular, less than 26 days, more than 30 days, the woman was not sure of the date or they had used hormonal contraception, been pregnant or breastfed in the 3 months prior to pregnancy, this was defined as 'uncertain dates'.

Statistical analysis

SAS 9.1.3 service pack 4 was used for statistical analysis. The ability to make a diagnosis and pregnancy outcome for women with certain and uncertain dates was analysed using the Fisher exact test or the χ^2 test as appropriate. Analysis was performed separately for women with certain and uncertain dates in order to determine the influence of certainty of dates on the ability to confirm viability or non-viability. The Spearman correlation coefficient was calculated to assess the relationship between gestational age and the number of follow-up biochemistry or ultrasound assessments needed to confirm a diagnosis. Logistic regression analysis was used to determine the likelihood of making a diagnosis according to gestational age in both asymptomatic and symptomatic women.

Table I Criteria for the classification of findings at transvaginal ultrasound assessment in the Early Pregnancy Unit at first attendance

Diagnostic	Viable intrauterine pregnancy	An intrauterine gestational sac containing a fetal pole with visible cardiac activity
	Ectopic pregnancy	An empty endometrial cavity with: (i) an inhomogeneous adnexal mass or (ii) an extrauterine gestational sac with or without a yolk sac and/or fetal pole (Condous *et al.*, 2005a, b)
	Miscarriage	(i) An intrauterine gestational sac containing a fetal pole with a crown-rump length (CRL) of >6 mm with no cardiac activity or (ii) An empty intrauterine gestational sac with a mean diameter >20 mm or (iii) The presence of heterogeneous, hyperechoic irregular tissues within the uterine cavity (Farquharson *et al.*, 2005)
Non-diagnostic	IPUVI	(i) An empty intrauterine gestational sac measuring <20 mm in diameter or (ii) an intrauterine gestational sac containing a fetal pole with a CRL <6 mm with no fetal cardiac activity (RCR/RCOG guideline, 1995)
	PUL	An empty endometrial cavity, with no evidence of an intrauterine gestational sac or retained products of conception and no visualized extra-uterine pregnancy (Condous *et al.*, 2005a, b; RCOG, 2006)

Results

During the study period 1767 pregnancies were assessed with TVS. Of the 1442 (81.6%) fulfilling the inclusion criteria, 893 (61.9%) had certain dates and 549 (38.1%) uncertain dates. Reported gestational age ranged from 7 to 84 days (median 49 days). Median maternal age was 32 years (range 15–50 years). Median gravidity was 2 (1–12) and median parity was 0 (0–10). Maternal ethnicity was reported as white in 62%, black in 14%, Asian in 12% and mixed/other in 6% (6% did not report ethnicity). Symptoms of pain or bleeding were reported by 1065/1442 (73.9%) and 377/1442 (26.1%) were asymptomatic. Specific indications for ultrasound assessment are shown in Table II. In 544/1442 (37.7%) of pregnancies there was more than one indication for assessment.

Table II Indications for assessment in the study population (n = 1442)

Indication*	Number of women (%)
Bleeding	722 (50.1)
Pain	717 (49.7)
Uncertain dates	259 (18.0)
Previous miscarriage	170 (11.8)
Anxiety	66 (4.6)
Previous ectopic pregnancy	52 (0.4)
Hyperemesis	6 (0)
Missing	1 (0)

*Women commonly present with more than one indication for assessment.

Viability or non-viability was confirmed at first scan in 509/893 (57.0%) of women with certain dates and 307/549 (55.9%) of women with uncertain dates ($P = 0.6881$, χ^2 test). Table III shows the distribution of ultrasound outcomes. There were no significant differences in outcome between the certain and uncertain dates groups ($P = 0.4375$, χ^2 test). Fig. 1 illustrates the frequency of the TVS findings according to gestational age.

For the women in whom viability or non-viability could not be confirmed at initial TVS, serum biochemistry was needed in 227/626 (36.3%) and further ultrasound assessment in 461/626 (73.6%). A correlation was found between gestational age and the number of blood tests (Spearman correlation coefficient = − 0.20, $P < 0.0001$) and between gestational age and the number of repeat ultrasound assessments (Spearman correlation coefficient = −0.14, $P < 0.0021$).

Pain and bleeding

In asymptomatic women logistic regression analysis demonstrated that prior to 49 days gestation the odds of confirming viability or non-viability at first assessment increased by 20.0% per day (95% confidence intervals (CI) 16.5–23.7%) and by 2.3% per day (95% CI 0.8–3.9%) thereafter (Fig. 2). In symptomatic women (reporting either pain or bleeding), the odds of confirming viability or non-viability depended upon gestational age in the same way as in the case of asymptomatic patients. For an equal gestational age however, the odds was 25.5% lower for symptomatic than for asymptomatic patients.

The number of women who presented before 49 days with no symptoms was 177. Of these a diagnosis could be made at first assessment in 62 (35.03%). The number of women presenting before 49 days with pain or bleeding was 505. Of these a diagnosis could be made at first assessment in 173 (34.26%).

Inconclusive scans

The overall inconclusive scan rate was 43%. About 397 (28%) women were initially classified as having an IPUVI and 229 (16%) classified as having a PUL. Within the IPUVI group, 178 (45%) pregnancies were found to be non-viable (miscarriage) at follow-up. In 142 women with initially inconclusive scans despite presenting at more than 36 days gestation (when the fetal heart beat would normally be expected to be visible), the pregnancy was subsequently found to be viable at follow-up assessment. Fourteen women presented with a clinical history of suspected complete miscarriage but were classified as PUL as no pregnancy had been previously visualized on ultrasound scan.

Ectopic pregnancy

The incidence of ectopic pregnancy in the study population was 2% (28/1442). The median gestation at the time of presentation and first TVS was 45 days (range 19–81 days) and at the time of diagnosis of ectopic pregnancy was 48 days (range 19–81 days). Table IV describes the characteristics of the ectopic pregnancies according to whether the initial presentation and TVS was before or after 49 days gestation. Table V shows the distribution of the ectopic pregnancies according to whether the gestational age was greater than or less than 49 days and the presence or absence of symptoms, with a calculation of the number of scans performed in each group for each ectopic pregnancy diagnosed.

Two women who presented without symptoms at less than 49 days were found to have ectopic pregnancies. In both cases the indication for TVS was a history of a previous ectopic pregnancy. In one of these cases the diagnosis of a viable ectopic pregnancy was made at first presentation at 43 days gestation. In the other case, the woman presented at 36 days and was found to have a PUL, with the diagnosis of ectopic pregnancy (with a visible gestation sac but no fetal pole) subsequently made by TVS at 41 days gestation.

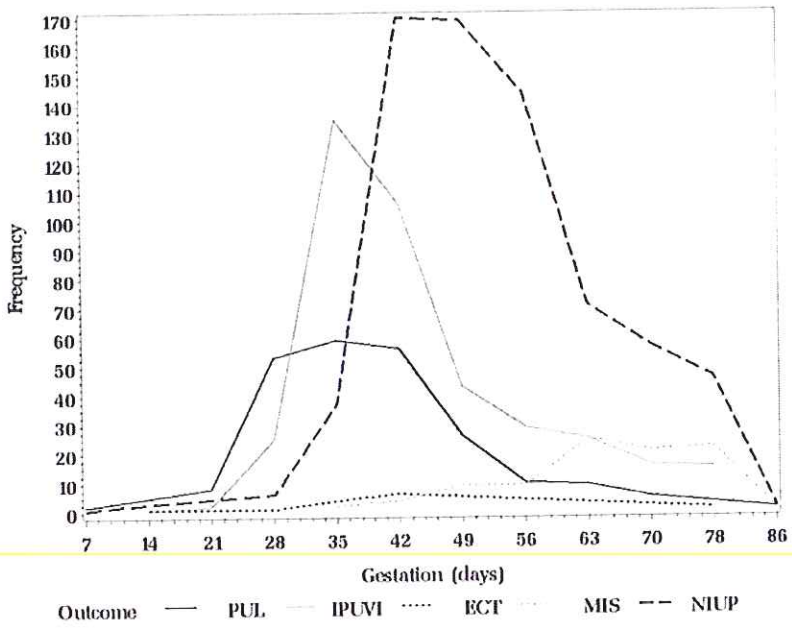
Discussion

This study confirms the hypothesis that there is a positive association between reported gestational age and the ability to make a definitive diagnosis of viability or non-viability at the time of the first early pregnancy assessment. In the population studied, prior to 35 days gestation the most common outcome was a PUL, from 35 to 41 days the most

Table III Outcome of initial TVS assessment in women with certain and uncertain dates

	Diagnostic			Non-diagnostic		
	Normal intrauterine pregnancy	Miscarriage	Ectopic	IPUVI*	PUL†	Total
Uncertain dates	273 (18.9%)	29 (2.0%)	5 (0.4%)	148 (10.3%)	94 (6.5%)	549 (38.1%)
Certain dates	432 (30.0%)	64 (4.4%)	13 (0.9%)	249 (17.3%)	135 (9.4%)	893 (61.9%)
Total	705 (48.9%)	93 (6.5%)	18 (1.3%)	397 (27.5%)	229 (15.9%)	1442 (100%)

*Intrauterine pregnancy of uncertain viability. †Pregnancy of unknown location.



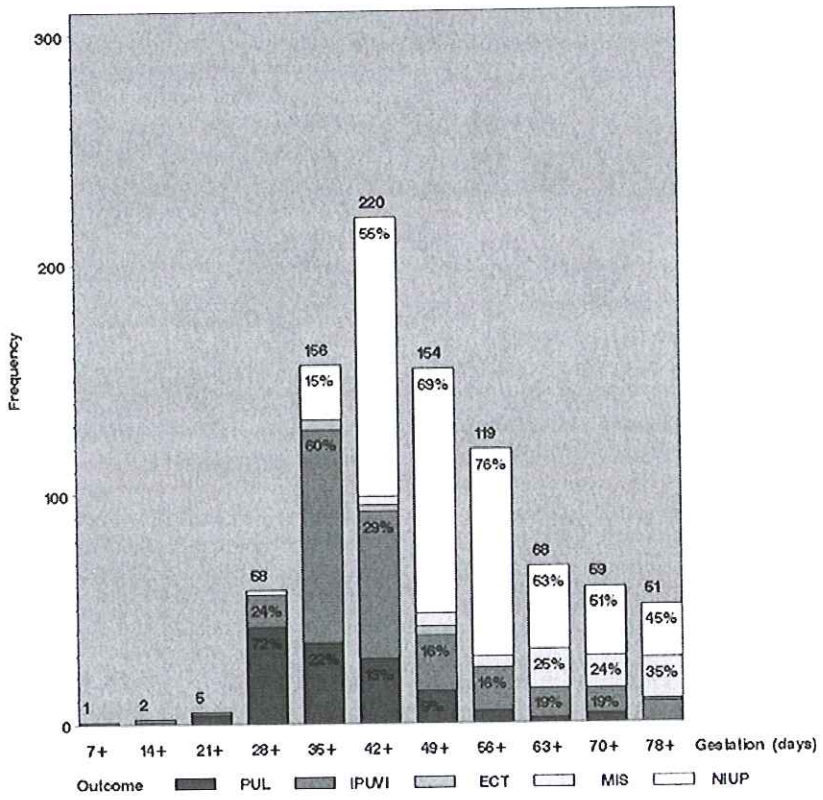


Figure 1 (**a**) Graph illustrating frequency of diagnostic outcome according to gestational age ($n = 1442$); (**b**) Histogram showing the actual frequencies of each diagnosis according to the gestational age at presentation ($n = 1442$).

PUL = pregnancy of unknown location; IPUVI = intrauterine pregnancy of uncertain viability; ECT = ectopic pregnancy; MIS = miscarriage; NIUP = normal intrauterine pregnancy (fetal heart pulsation visible).

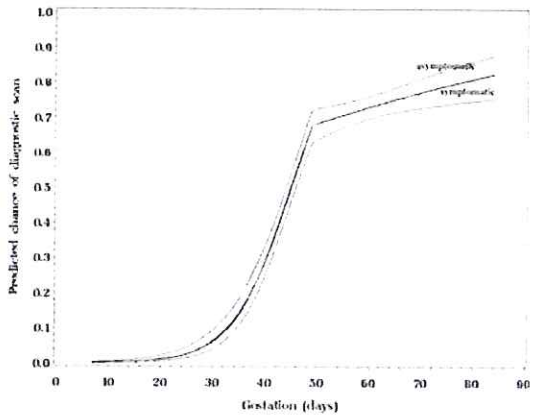


Figure 2 Logistic regression model of the increase in likelihood of making a diagnosis for each 1 day increase in gestational age.

The estimated curves are shown, with 95% CI, for women with and without symptoms.

common outcome was an IPUVI and from 42 days it was a viable intrauterine pregnancy (Fig. 1). Miscarriage could not be diagnosed at an initial scan until at least 35 days, and most miscarriages were diagnosed when the first assessment was between 63 and 85 days. As long as an LMP date could be recalled, maternal reporting of certain or uncertain dates did not influence the likelihood of being able to confirm viability or non-viability.

The logistic regression analysis (Fig. 2) suggests that to minimize the number of women characterized as having a PUL or IPUVI, with the burden of the associated follow up blood tests or ultrasound scans, 'viability' scans should be deferred until 49 days gestation but that there is minimal benefit in delaying beyond this stage. In asymptomatic women, the chance of delaying a diagnosis of ectopic pregnancy by deferring TVS until 49 days is small, with only two out of 177 women in this group being diagnosed with an ectopic pregnancy, both of whom had a history of a previous ectopic pregnancy and who would therefore have been considered at high-risk. Consequently we conclude that if ultrasound had been deferred until 49 days in women without previous ectopic pregnancy and with no symptoms of pain and bleeding, it is unlikely that any woman would have come to harm from an ectopic pregnancy not having been diagnosed. In symptomatic women, the likelihood of ectopic pregnancy being diagnosed if first assessment was before 49 days was higher (one ectopic diagnosis per 28 scans) and therefore deferring TVS in a symptomatic woman has a considerable chance of missing or delaying the diagnosis of an ectopic pregnancy. Delay in the diagnosis of ectopic pregnancy may lead to rupture with significant morbidity or mortality (Mol and Van der Veen, 1997; Lewis, 2007). Earlier diagnosis may improve the success of conservative treatment for unruptured ectopic pregnancy (Trio *et al.*, 1995; Atri *et al.*, 2001) and this may improve subsequent fertility (Fernandez *et al.*, 1998; Roussos *et al.*, 2000).

The prediction of ectopic pregnancy from demographics, obstetric history and symptoms is challenging. In our EPU population the overall prevalence of ectopic pregnancy is 1 in 43 (2.3%) (Kirk *et al.*, 2007). This study shows that for women presenting with symptoms of pain and bleeding the chance of a diagnosis of ectopic pregnancy is three times higher than for women without symptoms. This is consistent with previous evidence that pain and bleeding at presentation have similar odds ratios for the diagnosis of ectopic pregnancy (Barnhart *et al.*, 2006).

Our study also shows that presentation at less than 49 days gestation is associated with a three times higher risk of a diagnosis of ectopic pregnancy than presentation after 49 days. We therefore

Table IV Characteristics of ectopic pregnancies in women presenting before or after 49 days gestation (n = 1442)

		<49 Days	≥49 Days
Total number of women undergoing TVS		682	760
Number of ectopic pregnancies		20	8
Mean gestational age at presentation (range)		41 (19–48) days	55 (49–81) days
Pain		12 (60%)	5 (63%)
Bleeding		15 (75%)	6 (75%)
Asymptomatic		3 (15%)	2 (25%)
Ectopic appearance	Inhomogeneous mass	13 (65%)	4 (50%)
	Gestation sac (bagel)	4 (20%)	3 (38%)
	Viable	3 (15%)	1 (13%)
Median ectopic mass diameter (range)*		14.4 (8–33) mm	18.7 (13–23) mm
Free fluid		13 (65%)	4 (50%)
Echogenic free fluid		2 (10%)	1 (13%)
Median hCG (range)*		810 (58–23 988) IU/l	1370 (110–24 326) IU/l
Management	Surgical	13 (65%)	4 (50%)
	Medical	4 (20%)	3 (38%)
	Expectant	3 (15%)	1 (13%)

hCG: human chorionic gonadotrophin.
*Excludes one molar ectopic pregnancy.

Table V Ectopic pregnancy incidence per number of transvaginal ultrasound examinations performed according to the gestational age at presentation (more or less than 49 days) and the presence of symptoms (pain or bleeding)

		<49 Days	≥49 Days
Asymptomatic	Number of scans	177	200
	Number of ectopic pregnancies	2	2
	Number of scans to detect one ectopic pregnancy	89	100
Symptomatic	Number of scans	505	560
	Number of ectopic pregnancies	18	6
	Number of scans to detect one ectopic pregnancy	28	93

suggest that although no strategy can ensure that an ectopic pregnancy will not be missed with 100% certainty, it is likely that women without symptoms and who have not had a previous ectopic pregnancy can be safely managed by deferral of TVS assessment until 49 days gestation unless symptoms of pain and bleeding develop in the meantime. However, while our data suggest 49 days seems a good cut-off on which to base scanning policy in asymptomatic women, it must be remembered that this is based on only 28 ectopic pregnancies and needs confirmation in larger trials.

We do not know why women presented to the EPU at the gestational ages at which they did, especially those who were asymptomatic. Although this may be a strength of the paper as it resulted in a broad range of gestational ages which could be examined, there may be potential bias if women were preferentially attending at a certain gestation because either they or their referring practitioner had a gestational age at which they believed a scan was necessary. Another potential limitation of the study is that we identified a certain time point when a viable or non-viable pregnancy was determined. We cannot know from this data whether the result would have been the same had the scan been performed a few days earlier. The only way to determine this would be to scan women every day which would not be practical.

No previous clinical studies have reported on the potential benefit of screening for either ectopic pregnancy or pregnancy viability. However an interesting theoretical economic evaluation of the potential benefit of screening asymptomatic women for ectopic pregnancy suggested that a screening program with TVS and serum hCG measurement would reduce the number of patients with ruptured ectopic pregnancy from 2.1 to 0.61 per 100 screened women, if the prevalence of ectopic pregnancy was at least 6% (Mol *et al.*, 2002). The medical and economic benefit of screening with a lower prevalence of ectopic pregnancy was limited.

We now aim to prospectively test our management strategy of offering scans to asymptomatic women only after 49 days gestation, unless they have had a previous ectopic pregnancy diagnosis. We will aim to determine whether the psychological and financial cost of unnecessary biochemical and ultrasound follow-up in asymptomatic women with no previous history of ectopic pregnancy can be avoided by deferring assessment in such women, without an increase in morbidity from delayed diagnosis of ectopic pregnancy.

It is interesting that our study showed that even after 49 days gestation 20–25% of TVS findings remained inconclusive. This is likely to be due to three factors. First, some women presented with a clinical history suggestive of complete miscarriage but no previously visualized intrauterine gestational sac and were therefore classified as a PUL until the diagnosis of non-viable pregnancy was confirmed by declining serum hCG levels (14 women in this study). Second, some pregnancies fail at an early gestation without spontaneous expulsion of the small (<20 mm) gestational sac and women with these findings therefore needed reassessment after at least 7–14 days to confirm non-viability (178 women in this study). Third, some women considerably overestimated their gestational age, accounting for a finding of PUL or IPUVI when, had the gestational age been correct, a viable pregnancy would have been visualized (142 women).

It is known that the fetal heart pulsation may be visible on TVS from 37 days gestation in normal pregnancies (Jurkovic *et al.*, 1995). The gestational age at which an intrauterine pregnancy may be deemed to be non-viable, in women without bleeding and regular certain dates, is 46 days (Rempen, 1990). This study shows that in an unselected population of women attending an EPU, in whom true gestational age cannot be confirmed, there is a much wider range of gestation during which a scan may fail to confirm either viability or non-viability and therefore be non-diagnostic. Therefore although we would expect a fetal heart beat to be visible from 37 days, TVS at this gestation results in a high number of inconclusive scans.

Women tend to present for reassurance regarding fetal viability rather than to determine whether they have an ectopic pregnancy. Inconclusive scan findings create maternal anxiety and can be costly in terms of resources incurred by blood tests and follow-up ultrasound assessment. This study shows that the potential cost of unnecessary further investigation is considerably higher if such an assessment is performed before 49 days gestation and that deferral until after 49 days is most likely to be associated with being able to give a definitive answer regarding pregnancy viability or non-viability, allowing a more efficient use of resources. By deferring to 49 days we estimate that 94 inconclusive (PUL or IPUVI) scans and 27 blood tests would have been safely avoided in our study population. As the demand for ultrasound assessment to confirm viability increases, there is a need to develop evidence-based protocols to safely minimize the number of these inconclusive scans. This study provides new evidence on the relationship between gestational age and initial TVS outcome.

Conclusion

We have confirmed the hypothesis that there is a significant positive relationship between gestational age and the ability to confirm viability or non-viability at first assessment independent of the certainty of the reported LMP date or regularity of the menstrual cycle. Our data suggest that TVS assessment in asymptomatic women without a previous history of ectopic pregnancy can be safely deferred until 49 days gestation. This would reduce the number of inconclusive scans, and

thus the need for unnecessary blood tests and repeat TVS assessment, without an associated cost of missing the diagnosis of ectopic pregnancy. However in women with symptoms of pain or bleeding or with a previous history of an ectopic pregnancy, ultrasound should not be deferred due to the risk of serious morbidity associated with a missed diagnosis of an ectopic pregnancy.

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