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The hCG ratio can predict the ultimate viability of the intrauterine pregnancies of uncertain viability in the pregnancy of unknown location population

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BACKGROUND: To determine whether hCG ratio at 48 h can predict ultimate viability of intrauterine pregnancies of uncertain viability (IPUVs) in the pregnancy of unknown location (PUL) population. METHODS: Prospective observational study from June 2001 to October 2004. All women classified with PUL had serum hCG levels measured at 0 and 48 h to calculate hCG ratio (hCG 48/hCG 0 h). All women were followed up until final diagnosis: failing PUL, viable and non-viable intrauterine pregnancy (IUP), ectopic pregnancy. Those PULs found to have an IPUV at follow-up transvaginal ultrasound scan (TVS) were included in final analysis. RESULTS: During the study period, 12 572 consecutive first trimester women were scanned. One thousand and three (8%) women were classified PULs. Three hundred and seventy-nine (37.8%) PULs were confirmed IPUVs at follow-up scan. Complete data from 334 IPUVs were analyzed: 82.6% (276/334) viable IUPs and 17.4% (58/334) non-viable IUPs. Median hCG ratio was greater in viable IUPs [2.32, inter-quartile range (IQR) 1.16–4.77] compared with non-viable IUPs 1.83 (IQR 0.97–4.60). Sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratios of an hCG ratio >2.00 for the prediction of a viable IUP are 77.2%, 95.8%, 86.6%, 90.9%, 15.5, 0.24, respectively. In our population, an hCG ratio >2.00 increases the odds for a viable IUP from 0.42 to 6.46 post-test. CONCLUSIONS: The hCG ratio is significantly higher in those IPUVs which become viable IUPs compared with non-viable IUPs. New cut-offs for the hCG ratio need to be evaluated for the prediction of viability in the IPUV group of PULs.

Keywords: intrauterine pregnancy; pregnancy of unknown location; hCG; hCG ratio; pregnancy viability

Introduction

Since the introduction of early pregnancy units (EPUs), the management of early pregnancy complications has changed radically. Earlier access for women to consultation and high resolution ultrasound has resulted in increasing number of non-diagnostic first trimester scans or pregnancies of unknown location (PULs). The descriptive term PUL has been introduced officially since October 2006 (Royal College of Obstetricians and Gynaecologists, 2006). This is defined as an early pregnancy (positive urinary hCG) with no signs of intrauterine pregnancy (IUP) or extrauterine pregnancy on transvaginal ultrasound scan (TVS) (Condous *et al.*, 2006a; Royal College of Obstetricians and Gynaecologists, 2006). Although there is significant published data to support the use of the hCG ratio as a predictor of IUP, in fact, these data really apply to the prediction of intrauterine pregnancies of uncertain viability (IPUVs) (Royal College of Obstetricians and Gynaecologists, 2006). Approximately one-third of PULs are early developing IPUVs, too small to be visualized on TVS. Over two-third of this group of IPUVs, when followed up with TVS after confirmation of location, will be viable IUPs. Thus, to date, it is follow-up ultrasound which is used to determine the viability of these IPUVs. To the best of our knowledge, there are no data on the use of maternal serum markers to determine the ultimate viability of this IPUV group of PULs.

Although there is a body of evidence to suggest that the change of serum hCG over time, calculated at 48 h, correlates well with failing pregnancies and IPUVs (Condous *et al.*, 2006b), to date there has not been any data which attempt to determine the ultimate viability of these IPUVs utilizing serum maternal markers. We know that a serum hCG increase over 48 h of more than 66% is a good predictor of an IPUV (Condous *et al.*, 2004a); however, there is no way of knowing which of these IPUVs will be viable on follow-up scan.

The aim of this study was to determine if the hCG ratio alone at 48 h is able to predict the future viability of the IPUV subgroup of the PUL population.

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Materials and Methods

This was a non-interventional prospective observational study. All pregnant women attending the EPU at St George's Hospital, London, between 25 June 2001 and 9 October 2004, underwent a TVS using a 5 MHz probe (Aloka SSD 900, 2000 or 4000; Keymed Ltd, Southend, UK and Aloka Co. Ltd, Tokyo, Japan). Indications for sonography included lower abdominal pain with or without vaginal bleeding, poor obstetric history and determination of gestational age. Demographic variables recorded included the woman's age and gestational age at presentation. Women classified with a PUL were eligible for inclusion unless they were clinically unstable or had an acute abdomen or blood in the pouch of Douglas according to the ultrasound images at the time of the initial scan. PULs were defined by TVS as there being no sign of either an IUP or extrauterine pregnancy or retained products of conception in a woman with a positive pregnancy test.

All women classified with a PUL had blood taken at presentation to measure the levels of hCG (World Health Organization, Third International Reference 75/537) using automated electrochemiluminescence immunoassays. Serum hCG ≥5 U/l represented a positive pregnancy test. The levels of the hCG were then again measured 48 h later according to the unit's protocol.

The hCG ratio, defined as the hCG at 48 h divided by the hCG at 0 h, for each PUL was calculated. All women were followed up until final diagnosis was established: failing PUL, persisting PUL, ectopic pregnancy or viable/non-viable IUP. These diagnoses were established using the criteria described in previous studies published by this unit (Condous *et al.*, 2004a,b, 2005; Kirk *et al.*, 2006). The patients with IPUVs were included in the final analysis. The same primary investigator (G.C.) followed up all women and was responsible for collecting demographic data, biochemical results and the final outcomes.

If the serum hCG rise over 48 h period was >66% (i.e. the hCG ratio >1.66), the women were classified initially as having an early IPUV. A rescan was arranged for 1 week later to confirm the location. An early IPUV was confirmed ultrasonically with the presence of gestational sac eccentrically placed within endometrial cavity. These early IPUVs were then subsequently followed up with another ultrasound scan after a further 7 days to establish viability. Therefore, all IPUVs were subjected to two serum hCG levels (0 and 48 h) and three TVS—one to diagnose the PUL, one to confirm an IPUV and a third and final scan to confirm viability of the IPUV. Those PULs found to have IPUV at follow-up scans were in final analysis. Viable IUP was defined on ultrasound as presence of embryo with visible cardiac activity. Non-viable was defined as >6 mm crown-rump length (CRL) and nil cardiac activity, or CRL ≤ 5 mm with no fetal heart rate (FHR) at first scan and then no FHR at the intermediate scan on Day 7.

The initial hCG ratio of those IPUVs which ultimately became viable on follow-up scan was compared with that of the non-viable IPUVs. Statistical analyses were conducted with Statistical Analysis System (SAS) Version 9.1, Cary, NC, USA. Quantitative data were summarized by the median and the inter-quartile range (IQR). Differences between groups were investigated by computing the confidence interval (CI) on the difference in medians.

Having analyzed the data in the different IUP outcome groups, i.e. viable and non-viable, we attempted to establish new cut-off rules for the hCG ratio in order to maximize prediction of viability and non-viablity in the IPUV group of PULs.

Results

A total of 12 572 consecutive first trimester women were scanned during the study period, of whom 1003 (8%) women were classified as PULs. Three hundred and seventy-nine (37.8%) were demonstrated to be IPUVs at follow-up scan.

Of the 379 IPUVs eligible for the study, 14 did not have information regarding their viability (missing values) and 31 cases were lost to follow-up. Eighteen of the PULs were persisting PULs, therefore were excluded from the analysis. Consequently, total number of PULs considered in the study was 940, including 334 IPUVS with complete data. After ultrasound scan, 82.6% (276/334) had a viable IUP confirmed and the remaining 17.4% (58/334) were confirmed as having a non-viable IUP at follow-up ultrasound scan.

The hCG ratio statistics for both viable and non-viable IUPs are presented in Tables I and II and in Fig. 1. Table I shows that the median value of the hCG ratio for the viable IUPs was 2.27 (IQR 1.16–4.77) versus 1.83 (IQR 0.97–4.60) for the non-viable IUPs. The difference between the medians of both groups is 0.44 (0.31–0.56, 95% CI).

We tried to establish the optimal cut-off for the hCG ratio in order to predict viability versus non-viability in the IPUVs. In Fig. 1, the Kernel estimated density of the hCG ratio per viability group is reported. The figure shows that a value of 2.00 can be an appropriate cut-off to differentiate viable from non-viable IUPs.

In Table II, the distribution of the different PUL outcomes according to the hCG ratio intervals is reported. We have previously reported on the cut-off of 0.87 to predict failing PUL (Condous *et al.*, 2006b). We decided to take 2.00 as a cut-off to differentiate between viable and non-viable IUPs. The sensitivity (SENS), specificity, positive predictive value (PPV), negative predictive value and positive and negative likelihood ratios of an hCG ratio >2.00 for the prediction of a viable IUP are 77.2%, 95.8%, 86.6%, 90.9%, 15.5, 0.24, respectively. In our population, an hCG ratio >2.00 increases the pre-test probability odds for a viable IUP from 0.42 to 6.46 post-test.

Table I: hCG ratio in viable and non-viable IUP.

Group	*N*	Median	IQR	Diff median (95% CI)
hCG ratio				
Viable IUP	276	2.27	3.61	0.44 (0.31–0.56)
Non-viable IUP	58	1.83	3.63	

IQR, inter-quartile range; CI, confidence interval.

Table II: Distribution of PUL outcomes according to hCG ratio intervals.

	hCG ratio ≤0.87	hCG ratio 0.87–<1.66	hCG ratio 1.66–<2	hCG ratio ≥2	Total
Failing PUL	476 (89.3%)	49 (9.2%)	0	8 (1.5%)	533
Viable IUP	0	18 (6.5%)	45 (16.3%)	213 (77.2%)	276
Non-viable IUP	0	16 (27.6%)	23 (39.7%)	19 (32.8%)	58
Ectopic	11 (15.1%)	51 (69.9%)	5 (6.8%)	6 (8.2%)	73
Total			694	246	940

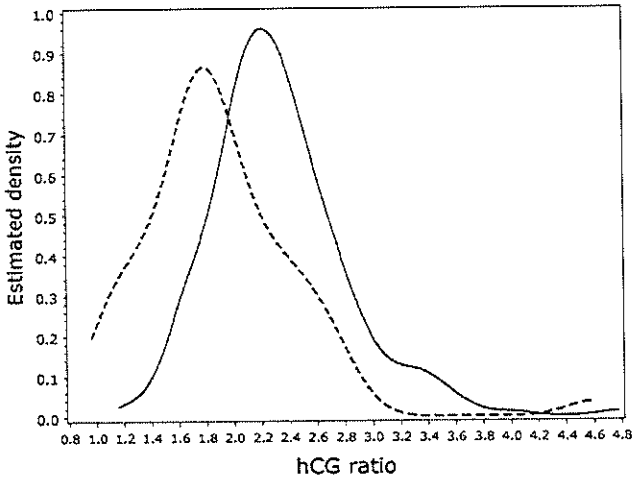


Figure 1: Kernel estimated density of the HCG ratio in viable (continuous line) and non-viable (dotted line) intrauterine pregnancies. Kernel estimated density of the hCG ratio per viability group.

Discussion

In our previously published studies, the hCG ratio when incorporated into mathematical models performed very well when applied to the PUL population at St George's Hospital EPU (Condous *et al.*, 2005, 2006a; Kirk *et al.*, 2006). According to the current unit's protocol, women diagnosed with a PUL at the first scan should undergo determination of the hCG ratio at 48 h. If the hCG ratio is >1.66, this subgroup of women will almost certainly have an IPUV and currently have a repeat scan after 1 week to confirm the diagnosis of an IPUV. This interval is based on our experience in the follow-up of PULs that has demonstrated no serious adverse outcome in the 7 days interval of expectant management. However, although the second scan after 7 days can almost always confirm the location of pregnancy, it may be too early to determine the viability of the pregnancy at this stage. Women with a confirmation of an IPUV are therefore rescanned 2 weeks thereafter to establish viability. Viability is established by ultrasound visualization of fetal cardiac activity. Theoretically, this should always be evident when the CRL of the embryo is over 6 mm (Levi *et al.*, 1990), which means between Week 5 and Week 6.

The hCG curve of an early viable IUP has been defined by Barnhart *et al.* (2004). They described the median slope for a rise of hCG after 2 days to be 2.24 (a 124% rise), an observation confirmed by our result of 2.27. However, a viable IUP was defined as TVS confirmation of gestational sac with a yolk sac or fetal pole. In our study, we tried to give complementary information defining viability as ultrasound visualization of fetal cardiac activity after 1 and 2 weeks from the diagnosis of IPUV.

In this study, we found that new cut-offs for the hCG ratio can be valuable in predicting final viability of the IPUVs. This has the potential to avoid the repeat scan 2 weeks after the IPUV is originally confirmed in order to determine embryo viability. We observed that both viable and non-viable IUPs have median hCG ratio values >1.66 and that the median hCG ratio is higher in the viable IUPs compared with the non-viable IUPs. We tried to investigate if it was feasible to set hCG ratio thresholds for an early prediction of the pregnancy viability in the IPUVs group. We set an interval of 1.66–2 for a non-viable IUP and a threshold of ≥2 for a viable IUP. Although the SENS of an hCG cut-off of 2 is low (77%), the PPV is high (92%) due to the high prevalence of viable IUP in the PUL population. Thus, in our population, the hCG ratio can be used not only for the prediction of IPUVs but also for the early screening of ultimate viability. Therefore, in PULs, in the case where the hCG ratio is >2.00, after confirmation of location with a scan at 7 days, we can potentially avoid the viability scan after 14 days and directly book the woman for the Nuchal scan at 11 to 13+6 weeks. In this way, we would be able to diagnose correctly and book for the Nuchal scan, without unnecessary interventions and without an increased risk of missing ectopic pregnancies, in the 87% of IPUVs. However, ~8% of the IPUVs booked for the Nuchal scan will be non-viable at 11 to 13 + 6 weeks. Although it is unlikely that these women will progress without symptoms until 11 to 13 + 6 weeks, we acknowledge that the unnecessary grief caused to these women must be taken into consideration in evaluating the most cost-effective strategy.

Indications for the first scan included lower abdominal pain with or without vaginal bleeding, poor obstetric history and determination of gestational age. One limitation of our study is that data on the persistence of pain or bleeding at 1 or 2 weeks are not available for analysis. However, in one of our previous studies, we have demonstrated that clinical information does not improve the performance of our model in predicting the outcome of PULs (Condous *et al.*, 2007).

In conclusion, a re-evaluation of what the initial hCG ratio at 48 h actually predicts needs to be carried out. The data which are more than a quarter of a century old, i.e. an hCG ratio >1.66 (Kadar *et al.*, 1981), in fact, should be applied to the IPUVs. In this study, we have created new cut-offs which are very useful in predicting viability in the IPUV group of PULs. In the future, the hCG ratio >2.0 may result in booking IPUVs directly for their Nuchal scan, thus potentially reducing the need for repeat ultrasound scans to determine viability.

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