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Rationalizing the follow-up of pregnancies of unknown location

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BACKGROUND: To develop a strategy to rationalize the follow-up of pregnancies of unknown location (PULs) based on the predicted outcome using a mathematical model. METHODS: Prospective interventional study. Women classified with a PUL had serum hCG levels taken at 0 and 48 h. A logistic regression model was used to predict PUL outcome at 48 h. Women were managed according to the model's prediction. If the model predicted an intrauterine pregnancy (IUP) or ectopic pregnancy (EP), women underwent a repeat scan on day 7; if the model predicted a failing PUL and the hCG ratio was also <0.87, these women were discharged; if the model predicted a failing PUL and the hCG ratio was ≥0.87, serum hCG was repeated on day 7. RESULTS: Three hundred and sixty-three PULs were included; the final clinical outcomes were 22 (63.1%) failing PULs, 111 (30.6%) IUPs and 23 (6.3%) EPs. 88.7% (322/363) had the location of their pregnancy confirmed in the time period according to the study protocol, i.e. day 2 for failing PULs, day 7 for IUPs and EPs. By day 7, 97.5% (354/363) had been given a diagnosis and could be eliminated from any further follow-up. Only one woman (0.3%) underwent surgical intervention for the diagnosis of her pregnancy location—a diagnostic laparoscopy and surgical evacuation. CONCLUSION: The logistic regression model developed could be used as a basis on which to rationalize the management of PULs as it can successfully minimize their follow-up by reducing the number of visits, scans and blood tests, as well as intervention rates.

Keywords: pregnancy; ectopic; unknown location; regression model; hCG

Introduction

More than 90% of women with a positive urinary pregnancy test attending an early pregnancy unit (EPU) will have their pregnancy visualized on a transvaginal ultrasound scan (TVS) (Banerjee *et al.*, 2001; Condous *et al.*, 2004a). The remainder will be classified as pregnancies of unknown location (PULs) with no sign of an intrauterine pregnancy (IUP) or an extra-uterine pregnancy on TVS. These women often undergo a protracted period of follow-up involving repeated scans and blood tests in order to confirm the location and viability of the pregnancy. A single-visit strategy based on the initial serum progesterone and hCG levels to categorize women into either high risk or low risk of ectopic pregnancy (EP) has been developed and tested prospectively on a total of 518 PULs (Condous *et al.*, 2005a). Although it correctly eliminated 84% of non-EPs from further follow-up, its safety was challenged, as 67% of EPs would also have been discharged without adequate follow-up. Our unit has also previously developed a logistic regression model (M1) based on the hCG ratio (hCG 48 h/hCG 0 h) to predict the outcome of PULs (Condous *et al.*, 2004b) with a sensitivity of 91.7% for EP. The same model has also been used in a comparative study along with predictions made by experienced nurse practitioners. It was found to have a sensitivity of 86.8%, for EP and to compare favourably with the subjective interpretation of serum hCG levels by experienced operators (Kirk *et al.*, 2006). More recently, a new logistic regression model (M4) has been developed that performs significantly better than M1 (Condous *et al.*, 2007). This new model is based on the logarithm of the hCG average [(hCG 0 h + hCG 48 h)/2], the hCG ratio and its quadratic effect, where the predicted probability for the different classes are computed using these formulas:

$$P_{\text{ectopic}} = \frac{e^{z2}}{1 + e^{z1} + e^{z2}}$$

$$P_{\text{failing PUL}} = \frac{e^{z1}}{1 + e^{z1} + e^{z2}}$$

$$P_{\text{IUP}} = \frac{1}{1 + e^{z1} + e^{z2}}$$

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where

$$z1 = \log\left(\frac{P_{\text{failing}}}{P_{\text{IUP}}}\right) = 5.88 - 1.18 \cdot \text{LhCGmean} - 5.56 \cdot \text{hCGratioc} + 2.05 \cdot \text{hCGratioc}^2$$

$$z2 = \log\left(\frac{P_{\text{ectopic}}}{P_{\text{IUP}}}\right) = 0.39 - 0.06 \cdot \text{LhCGmean} - 0.26 \cdot \text{hCGratioc} - 3.93 \cdot \text{hCGratioc}^2$$

$$z2 - z1 = \log\left(\frac{P_{\text{ectopic}}}{P_{\text{failing}}}\right) = -5.49 + 1.12 \cdot \text{LhCGmean} + 5.30 \cdot \text{hCGratioc} - 5.98 \cdot \text{hCGratioc}^2$$

In a study of 376 PULs, M4 gave an area under the receiver operator characteristic (ROC) curve of 0.978 for failing PUL, 0.974 for IUP and 0.900 for EP. It performed better than M1, which gave an area under the ROC curve of 0.965, 0.969 and 0.842, respectively (Condous *et al.*, 2007). Although these strategies enable the likely location of the pregnancy to be predicted within 48 h, in reality it is often significantly longer before the true location of the pregnancy is confirmed either after TVS or surgical intervention in the form of either laparoscopy or surgical evacuation. During this time period, women may have multiple blood tests to measure serum hCG and progesterone levels and undergo numerous TVS examinations until the pregnancy is visualized or hCG levels decrease. This non-standardized approach represents a significant workload for clinicians and is inconvenient for patients. Strategies aimed at safely reducing the amount of follow-up in this group of women are needed. At present, there is no standardized management for asymptomatic haemodynamically stable women classified as PULs with regard to the timing of these repeat serum hormone levels and TVS examinations. The aim of this study was to develop a protocol for the management of PULs and test it prospectively within the EPU setting.

Materials and Methods

This was a prospective interventional study performed between the 21 February 2005 and the 20 February 2006 at the EPU at St George's Hospital, London. Women with a positive pregnancy test underwent a TVS examination using a 5 MHz transducer for B mode imaging (Aloka SSD 900, 2000 or 4000, Aloka Co., Japan). Women either self-referred or were referred by their General Practitioner, Mid-wife or the Accident and Emergency Department. Reasons for presentation were recorded and included: vaginal bleeding and/or lower abdominal pain, unsure dates, previous early pregnancy complication, such as previous EP or spontaneous abortion and maternal anxiety.

The inclusion criteria were: all women with an PUL and an hCG level less than 10 000 IU/L and were clinically stable and had no signs of haemoperitoneum on TVS. Women were classified as having a PUL if there was no evidence of an IUP or EP on TVS. An IUP was diagnosed if there was an intrauterine gestational sac ± a fetal pole ± fetal cardiac activity, or heterogeneous tissue within the endometrial cavity suggestive of retained products of conception. An EP was diagnosed on TVS if no IUP was seen and one of the following was visualized: (i) an inhomogeneous adnexal mass ('blob sign') separate from the ovary (Condous *et al.*, 2005a,b), (ii) an empty extra-uterine gestational sac with a hyperechoic ring ('bagel sign') in the adnexal region (Goldstein and Timor-Tritsch, 1995) or (iii) a yolk sac or fetal pole ± cardiac activity in an extra-uterine sac in the adnexal region. As persistent PULs probably represent missed EPs and behave biochemically like the ectopic group, they were analysed as EPs. A cut-off hCG level of 10 000 IU/l was used as it is known that below this level the rate of serum hCG change over time does not increase significantly, i.e. it is linear (Kadar *et al.*, 1990). The model, M4, therefore does not have to be used within specific ranges of gestational age, provided the serum hCG levels are less than 10 000 IU/Ul.

The exclusion criteria were: all women whose pregnancy was located on the initial scan, either intra- or extra-uterine; all women who were clinically unstable and/or had signs of haemoperitoneum on TVS and those in whom the initial serum hCG measurement was >10 000 IU/l.

If the initial serum hCG levels were >1000 IU/l without a history of heavy bleeding, then these women underwent a repeat scan within 24 h in order to ascertain if there was an early IUP sac or misdiagnosed EP.

Women classified as a PUL fulfilling the inclusion criteria had blood taken for serum hCG levels at 0 h (time of presentation) and 48 h later. The model used for this study was the logistic regression model M4, based on the logarithm of the hCG average, the hCG ratio and its quadratic effect (Condous *et al.*, 2007). The model was incorporated into a Microsoft Office Excel 2003 (Microsoft Corp., Redmond, WA, USA) package and was installed on the desktop of the central EPU computer. We weighted M4's estimated probabilities of failing PUL, IUP, and EP using weights 1, 1, 6, respectively, in order to optimize the detection of the EP group within this PUL population. This optimal weighting was established after the model was tested on retrospectively collected data (444 PULs) and was found to have a sensitivity of 87.1% for the detection of EP and sensitivities of 82.1% and 84.2% for the detection of IUPs and failing PULs, respectively.

Women were then managed according to the model's prediction. If the model predicted an IUP or EP women were rescanned on day 7, where day 0 was the day of presentation. Day 7 was chosen as the optimal time to re-scan as; previously the mean time to diagnosis from the preliminary scan in 40 PULs subsequently diagnosed with EP was 7.3 days (range 1–25 days) (Condous *et al.*, 2006). A woman was diagnosed with an IUP or EP on TVS according to the previously mentioned criteria. If the model predicted a failing PUL, the serum hCG level was repeated on day 7, to check that it was still decreasing. After 200 PULs had been managed, the protocol was reviewed as a high proportion of women did not return for this confirmatory serum hCG level on day 7. It was changed so that if the hCG ratio was <0.87, a failing PUL could be confirmed at 48 h. This hCG ratio cut-off has a sensitivity of 92.7% [95% confidence interval (CI): 85.6–96.5] and a specificity of 96.7% (95% CI: 90.0–99.1) for the detection of failing PUL (Condous *et al.*, 2007). If the hCG ratio was >0.87, a serum hCG was repeated on day 7. Figure 1 summarizes the protocol for the management of the PULs based on the model's prediction. If a woman was still classified as a PUL on day 7 after a repeat TVS, repeat hCG levels were taken and further TVS examinations repeated as indicated. In the event of TVS not being diagnostic, a laparoscopy or surgical evacuation of the uterus was performed to confirm pregnancy location in symptomatic women after 7 days. All women with PULs were given patient information leaflets containing details of follow up and 24-h contact numbers in the case of an emergency. They were asked to return to the EPU or Accident and Emergency Department if they had any change in their symptoms, in

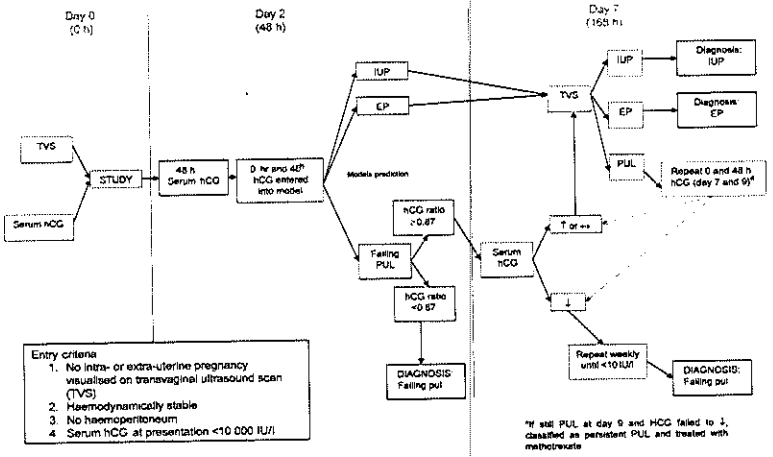

Figure 1: Flow diagram for management protocol for PULs according to model predictions

particular severe pain or heavy bleeding. The number of women returning to the EPU before the scheduled time of the next follow-up visit was recorded along with the indication for re-presenting. The need for hospital admission and length of stay were also recorded.

Statistical analysis

The model M4 was applied to the data, which resulted in estimated probabilities of failing PUL, IUP, and EP for all cases. These estimated probabilities were not where weighted by 1, 1, 6, respectively. Our prediction then was the outcome for which probability weight was maximal. ROC curves for all three outcomes were computed using a widely used non parametric procedure (Hanley and McNeil, 1982). Statistical analyses were conducted with SAS (version 8.2 for windows) (SAS Institute Inc., Cary, USA).

Results

During the 1-year study period, 5322 women presented to the EPU. Of these, 534 women (10%) were classified as PULs and were the number intended to treat. In total, 363 PULs were managed according to the model's prediction and therefore these were included in the final analysis. The 171 other PULs were excluded either because of incomplete data or because they were not managed according to the study's protocol. No women were excluded because they were thought to be at a higher risk of EP. Of the 171 PULs excluded from the final analysis, 40 (23.4%) did not attend for a second hCG level at 48 h and 36 (21.1%) did not attend for either a final TVS to confirm pregnancy location or have a repeat hCG level taken. Of the remaining 95 PULs, there were 22 (23.2%) failing PULs, 61 (64.2%) IUPs and 12 (12.6%) EPs or persistent PULs. All were excluded because of inappropriate scheduling

Table 1: Predicted outcomes of PULs according to the model and the true outcomes after follow-up

True/Predicted	Failing PUL	IUP	EP	Total
Failing PUL	220	0	2	222
IUP	0	82	4	86
EP	9	29	17	55
Total	229	111	23	363

of follow-up visits, i.e. predicted failing PULs not brought back for a repeat hCG at day 7, if initial hCG ratio >0.87, and repeat TVS examinations for predicted EPs and IUPs not performed at day 7 ± 1 day. For example, all of the predicted IUPs did not have their second scan until an average of 13 days after presentation. Of the 363 PULs included in the study, the model predicted 222 (61.2%) to be failing PULs, 86 (23.7%) to be IUPs and 55 (15.1%) to be EPs. After follow-up, 229 (63.1%) were subsequently diagnosed as failing PULs, 111 (30.6%) were IUPs and 23 (6.3%) were EPs (Table 1). The model gave an area under the curve of 0.995 for predicting failing PUL, 0.987 for the prediction of IUP and 0.894 for the prediction of EP (Figure 2). The commonest presenting complaint was vaginal bleeding, with 65.0% of women having vaginal bleeding, with or without lower abdominal pain (Table 2). The hCG levels at 0 h ranged from 7-9785 IU/l and at 48 h were 1-7970 IU/l (Table 3).

Failing PULs

Of the 229 women with failing PULs, 220 (96.1%) were given the diagnosis on the basis of the hCG ratio being < 0.87. The

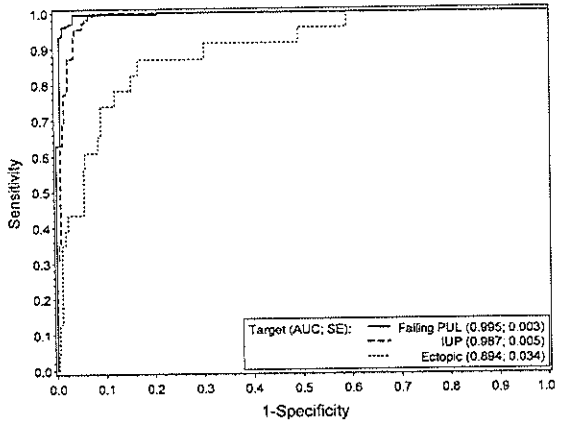

Figure 2: Receiver operator characteristic curves, and area under curve (AUC), for predicting failing PUL, IUP and EP

Table 2: Reasons for presentation in women classified with PULs attending the EPU

Reason for presentation	Final pregnancy outcome			Total % (*n*)
	Failing PULs % (*n*)	IUPs % (*n*)	EPs % (*n*)	
Bleeding	27.9 (64)	30.6 (34)	30.5 (7)	28.9 (105)
Bleeding and pain	53.3 (122)	4.5 (5)	17.4 (4)	36.1 (131)
Pain	3.1 (7)	20.7 (23)	4.3 (1)	8.5 (31)
Unsure dates	0.9 (2)	3.6 (4)	8.7 (2)	2.2 (8)
Previous miscarriage	2.2 (5)	8.1 (9)	4.3 (1)	4.1 (15)
Previous EP	1.3 (3)	4.5 (5)	8.7 (2)	2.8 (10)
Other	11.4 (26)	27.9 (31)	26.1 (6)	17.4 (63)
Total	229	111	23	363

other nine women needed a repeat hCG level to confirm the diagnosis. Six of these returned for a third blood test on day 7 and the other three on days 10–14. Two hundred and eleven (95.9%) of the 220 women with an hCG ratio <0.87 required just one TVS examination and two blood tests. The other nine women returned for repeat blood tests and review after 48 h because of continued bleeding and anxiety. In total, only five women with failing PULs (2.2%) were reviewed in the EPU at 24 h after presentation—four self-referred because of increased lower abdominal pain and one was asked to return as the initial hCG level was greater than 3000 IU/l and there had not been a history of heavy vaginal bleeding with clots and only one of these women with lower abdominal pain required admission overnight.

Intrauterine pregnancy

Of the 111 women with an IUP, 81.1% ($n = 90$) were confirmed as an IUP on TVS on day 7 (± 1 day). Of these women, 97.8% (88/90) required only two TVS examinations and two blood tests to measure hCG levels.

Twenty-one women of these 111 women (18.9%) returned to the EPU by day 5 for review and 19 subsequently had their IUPs confirmed within this time period. The other two women did not have their pregnancies visualized but did on the next review at day 7. Thirteen out of these 21 women were asked to return at 48 h for a TVS as their initial hCG levels were >1000 IU/l (1028–4397 IU/l). They all had their IUPs visualized on scan at 48 h. Six of the 21 women returning before day 5 returned because of increased pain and two women returned as anxious. Only two women did not have their IUPs visualized until day 14 after further repeat blood tests. They both had low initial hCG levels—44 IU/l and 212 IU/l.

Ectopic pregnancies

In the 23 women classified and treated as EPs, there were 21 tubal EPs, one interstitial EP and one persistent PUL. According to the model, 17 of these women with EPs were predicted to be EPs and four were predicted to be IUPs, so 21/23 would all have been brought back for a repeat ultrasound scan at day 7. Two women with hCG levels <375 IU/l were predicted to have failing PULs, with hCG ratios of <0.87. Both of these returned for an hCG level on day 7, when one was rescanned and noted to have an EP. Although asymptomatic and still with an hCG level <400 IU/l, she chose to undergo a laparoscopic salpingectomy due to a previous history of two EPs. The other case had a further hCG level on day 9, which had not decreased and a repeat scan still did not confirm pregnancy location. She was therefore treated on day 11 as a persistent PUL with systemic methotrexate. Overall, 12 women (52.2%) had their EPs diagnosed when they returned

Table 3: Serum hCG levels and final pregnancy location

		Serum hCG levels		hCG parameters	
		0 Hours	48 Hours	hCG ratio	Mean hCG
Failing PULs	Median (IU/l)	264	90	0.357	180
(n = 229)	IQR (IU/l)	681	271	0.221	469.5
	Range (IU/l)	7–9785	1–4595	0.001–1.809	5–6607
IUPs (n = 111)	Median (IU/l)	713	1358	2.105	1018.5
	IQR (IU/l)	943	1855	0.626	1432.5
	Range (IU/l)	43–4397	108–7970	0.898–3.356	75.5–5988
EPs (n = 23)	Median (IU/l)	519	630	1.263	578.5
	IQR (IU/l)	643	993	0.671	847
	Range (IU/l)	185–1718	155–2824	0.416–2.543	187.5–2269
All	Median (IU/l)	415	296	0.524	411
	IQR (IU/l)	930	1017	1.476	1080
	Range (IU/l)	7–9785	1–7970	0.001–3.356	5–6607

IQR, Interquartile range.

on day 7 ± 1 day. Two women (8.7%) were reviewed and scanned on day 7 and still classified as PULs but subsequently had their EPs diagnosed on day 9 after a third set of blood tests and scan. Seven women (30.4%) were reviewed again before day 5 and were diagnosed with an EP—four because they were in pain, one because of bleeding, one because of maternal anxiety and another was asked to return as she had high hCG levels at 0 and 48 h (1718 IU/l and 2216 IU/l). Two of the four women with pain were admitted overnight prior to diagnosis of their EP. Only one woman (4.3%) in the ectopic group underwent surgical intervention in order to help diagnose the location of her pregnancy. She underwent a diagnostic laparoscopy and evacuation of products of conception, however both were negative and her interstitial EP was subsequently diagnosed on TVS after 26 days. She was successfully treated with methotrexate. Seven other EPs were also treated with methotrexate. One case was managed expectantly and 13 surgically: 11 laparoscopic salpingectomies and 2 laparoscopic salpingostomies.

Number of Visits

Using the developed protocol, 65.3% (237/363) of PULs seen during the study period were given a diagnosis by 48 h and therefore eliminated from any further follow-up (Fig. 2). After 48 h, only 126 women were still classified as PULs (34.7%). By day 7 ± 1 day, another 117 women had the location of their pregnancy confirmed. After day 7, only nine women (2.5%) remained classified as PULs. So within seven days of follow-up, 97.5% of PULs had been given a final diagnosis (Fig. 3). Table 4 shows the expected number of blood tests and TVS examinations that would have been needed according to the model's prediction and the actual number of visits performed. An additional 49 TVS examinations were performed and an additional 44 serum hCG measurements.

In total, 88.7% (322/363) had the location of their pregnancy confirmed in the time period according to the study protocol, i.e. day 2 for failing PULs and day 7 for IUPs and EPs. Thirty three (9.1%) women due for review on day 7 re-presented to the EPU before that time. Only one woman (0.3%) underwent a surgical intervention for the diagnosis of her pregnancy location, a laparoscopy and surgical evacuation of the uterus. The overall intervention rate in this study was 6.1% (22/363). Seven women received methotrexate, one woman received methotrexate and then underwent a laparoscopic salpingectomy, one woman had a negative laparoscopy and surgical evacuation and then received methotrexate, 11 women had laparoscopic salpingectomies and 2 women had laparoscopic salpingostomies.

Discussion

In this prospective interventional clinical trial, we have demonstrated the validity of using a logistic regression model in the management of PULs. The classification of PUL outcome at 48 h using model M4 rationalized the follow-up of these women. It is well accepted that women with a PUL can be safely managed expectantly (Banerjee *et al.*, 1999; Condous *et al.*, 2004a, 2006, 2007; Kirk *et al.*, 2006). We believe that the modern management of women with a PUL should focus on ways of standardizing the number of visits and intervention rates. In this study, not only have we standardized the management of women with a PUL, but we have also addressed the issues of reducing the number of visits, scans and blood tests as well as the intervention rates. Although there is no consensus about appropriate intervention rates in women with PUL, published data suggest that with experience, rates as low as 9–10.8% are achievable (Banerjee *et al.*, 2001; Condous *et al.*, 2006). In this study, the intervention rate was significantly lower (6.1%) than published data. One interpretation of this very low-intervention rate is that adherence to predetermined methodical protocols, based on the use of mathematical models in PUL management, can improve management. Only one of the women with a PUL in this study (0.3%) needed surgical intervention to classify the location of the pregnancy, a laparoscopy with surgical evacuation of the uterus. We can therefore conclude that management according to the model and protocol used in this study does not lead to an increased intervention rate.

In this study, almost 90% of those women included were successfully managed according to the set protocol, with the majority of IUPs (80.2%) being confirmed on the basis of

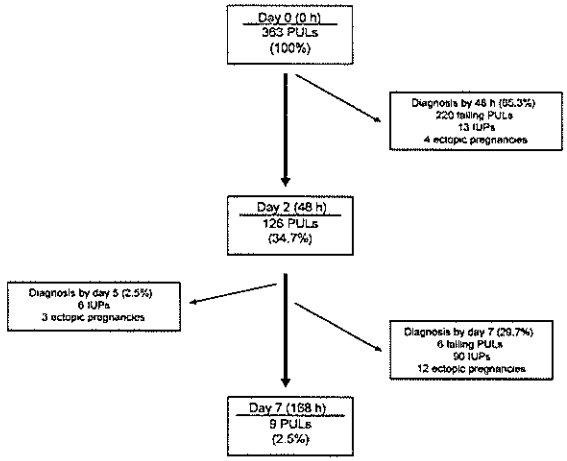

Figure 3: Flow diagram showing the timing of the final diagnosis of PULs

Table 4: Expected verses true number of visits required until final diagnosis made

	Failing PULs	IUPs	EPs	Total
Expected				
Number of cases	222	86	55	363
Number of TVS examinations per case	1	2	2	
Total number of TVS examinations	222	172	110	504
Number of serum hCG measurements per case	2	2	2	
Total number of serum hCG measurements	444	172	110	726
True				
Number of cases	229	111	23	363
Total number of TVS examinations	259	233	61	553
Total number of serum hCG measurements	479	227	64	770
Additional tests				
TVS examinations performed				49
Serum hCG measurements taken				44
% additional TVS examinations				13%
% additional serum hCG measurements				12%

TVS, transvaginal ultrasound scan.

two ultrasound scans and two serum hCG measurements, within 7 ± 1 day, and the majority of failing PULs (93.0%) being confirmed within 2 days after only one ultrasound examination and two serum hCG measurements. Just over half of all the EPs (52%) were diagnosed on the basis of two ultrasound examinations and two serum hCG measurements within 7 ± 1 day. Two of the EPs were predicted as failing PULs. One of these was managed successfully with methotrexate and one chose to undergo a laparoscopic salpingectomy as she had previously had an EP on the same side. Four of the EPs were predicted to be IUPs. All were diagnosed as EPs within 7 ± 1 day. They were all managed laparoscopically with no complications. Only an additional 49 TVS examinations and 44 serum hCG measurements were performed, meaning that one in seven PULs needed an extra TVS examination and one in eight PULs needed an extra serum hCG measurement.

Importantly, over 60% of PULs could be eliminated from further follow-up at 48 h and seven days after presenting, only 2.5% of women remained classified as PULs. In our study, with a PUL rate of 8.6%, 354 women (97.5%) had been given a diagnosis by day 7 and therefore could be discharged. In units with higher PUL rates, this could mean even more follow-up visits could be avoided with obvious financial benefits.

Less than 10% of women (35) represented to the EPU before the scheduled follow-up visit at day 7. There were 5 failing PULs, 22 IUPs and 8 EPs, so the majority (77.1%) were non-EP and therefore low risk. None of the women diagnosed with EP had any serious morbidity whether or not they presented before or at the time of the scheduled follow-up visit. In particular, there were no ruptured EPs; all surgical procedures were carried out laparoscopically with no one requiring a laparotomy or blood transfusion. There were also no known complications in any of the women with IUPs or failing PULs.

The criticisms of this study may be that a large number of PULs were excluded due to inappropriate scheduling of follow-up visits and that two cases of possible EP with decreasing hCG levels were misclassified as failing PULs. The two women (0.5%, 2/363) classified as failing PULs who were subsequently diagnosed as an EP and a persistent PUL could have posed a problem, if they had not returned for an hCG level at

day 7. Both had low initial hCG levels (<375 IU/l), which decreased by >25% in 48 h, and only one of them actually had an EP subsequently visualized on TVS. Neither woman was symptomatic and as both were treated, one with a laparoscopic salpingectomy and one with systemic methotrexate, the natural progression of these EPs is not known. It may be that both would have eventually resolved without intervention, as may have other EPs treated in this study. Indeed, it is not known in any study what the incidence of EP is in the failing PUL group. The woman who underwent a salpingectomy elected to do so, given a history of two previous EPs. Given the increased risk of EP in such a woman, it may be fair to exclude PULs with a previous history of EP from management according to such a protocol. However, this may be unnecessary as nine other women also had a previous EP and posed no management problem (Table 2). Due to the difficulty we had in getting women to return at day 7 for a repeat hCG in the predicted failing PUL group, it may be appropriate to ask such women to perform a home pregnancy test in 2 weeks time, and if still positive then to return to the EPU for a repeat hCG level and TVS. It remains a challenge to identify ways in which adherence to the management protocol can be improved. One possible suggestion is to apply the protocol to a smaller unit with a different patient population to see if compliance is improved.

At present, there is no standardized management for asymptomatic haemodynamically stable women classified as PULs with regard to the number and timing of repeat serum hormone levels and TVS examinations. In fact, many women undergo multiple serum hCG measurements, repeat TVS examinations and follow-up visits until the location of the pregnancy is confirmed. There is no current consensus about the timing of these repeat investigations, and it is at the discretion of the lead clinician, which in our experience even in the same hospital can vary considerably. Repeat investigations that are likely to be inconclusive have implications for the woman, her family and the healthcare system, in terms of psychological morbidity and financial resources. There are many suggested strategies for the prediction of the likely outcome of PULs. This, however, is the first study to develop a strategy based on the predicted PUL outcome at 48 h, which potentially results in a decrease in follow-up and intervention rates. We have demonstrated that this protocol for repeat serum hCG measurements and ultrasound examinations based on M4's PUL prediction can work in clinical practice. Further studies are now needed to test the reproducibility of this model and follow-up protocol in other units.

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