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A prospective evaluation of a single-visit strategy to manage pregnancies of unknown location

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BACKGROUND: The aim was to assess whether women with a pregnancy of unknown location (PUL) can be safely excluded from potentially unnecessary multiple clinic visits. METHODS: A single-visit protocol was developed based upon data from 200 consecutive PULs. PULs were divided into groups according to the probable risk of ectopic pregnancy. Those PULs with an initial serum progesterone ≤10 nmol/l or a serum HCG of ≤25 U/l were deemed to be at low risk and classified as resolving or failing PULs. Those PULs with an initial serum progesterone of >50 nmol/l, regardless of serum HCG, were thought to be a probable intra-uterine pregnancy (IUP) and were also classified as being low risk. Those PULs with an initial serum progesterone of 10–50 nmol/l and a serum HCG of >25 U/l were classified as being at high risk. This protocol was then tested prospectively on 318 consecutive PULs. Management was based solely on the basis of an initial transvaginal ultrasound scan (TVS) and a single measurement of HCG and progesterone taken at the time of initial consultation. RESULTS: A total of 5544 consecutive women were scanned, of which 560 (10.1%) women were classified as PULs. Forty-two were lost to follow-up and therefore 518 (9.34%) were analysed. In the training set of 200 PULs, there were 111 (55.5%) failing PULs, 67 (33.5%) IUPs and 22 (11%) ectopic pregnancies. In the test set of 318, there were 189 (59.4%) failing PULs, 114 (35.8%) IUPs and 15 (4.7%) ectopic pregnancies. For the training group, the sensitivity and specificity of a single visit to detect low-risk PULs were 77 and 82%, respectively. The positive (PPV) and negative predictive values (NPV) were 97 and 31%, respectively. For the test group of 318 PULs, the sensitivity and specificity were 84 and 33%, respectively. The PPV and NPV were 96 and 9.4%, respectively. CONCLUSIONS: A single-visit strategy based on commonly used criteria eliminates 84% of non-ectopic pregnancies correctly from the system. However, as 67% of ectopic pregnancies are discharged without adequate follow-up, a single-visit strategy should not be used as an alternative to the current multi-visit strategy used in most units.

Key words: ectopic pregnancy/HCG/pregnancies of unknown location/progesterone/single visit

Introduction

Pregnancies of unknown location (PULs) are currently managed in most units with at least two-visits to the Early Pregnancy Unit (EPU). Having failed to identify a pregnancy on transvaginal sonography (TVS), blood is taken at presentation and at 48 h to measure serum HCG and progesterone. This is thought to enable the clinician to make a judgement about the likelihood of the PUL being a failing PUL, an intra-uterine pregnancy (IUP) or an ectopic pregnancy. From previously published data, changing levels of serum HCG and measurements of initial serum progesterone can predict viability (Hahlin *et al.*, 1995; Banerjee *et al.*, 1999) Current strategies, including the use of discriminatory zones and the concept of a suboptimally rising serum HCG, do not help locate the pregnancy (Condous *et al.*, 2004a).

Women with a PUL who exhibit abnormally rising serum HCG levels or mid-range serum progesterone values often need multiple visits to the clinic before the final outcome is clear. Although PULs account for only 10% of EPU cases, they result in a disproportionate amount of the workload for the staff. The prospect of being able to reduce the number of visits and investigations in women with a PUL is very appealing. If so, the clinician could triage these women as being at low risk or high risk for ectopic pregnancy after one visit, thus enabling a unit to direct resources and energies into those women at high risk for ectopic pregnancy, without compromising care and safety. A single-visit strategy could therefore have cost–benefit implications. The possible psychological morbidity to the women associated with multiple visits could also be reduced.

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To date, there are no published data on the safety and feasibility of a single-visit strategy in such women. In this study, we developed a new protocol based on a single blood test taken at presentation, and evaluated this protocol to see if a second visit could be eliminated in the management of PUL.

Materials and methods

Women were recruited to this non-interventional prospective study between June 25, 2001 and April 14, 2003. All women classified as a PUL at their first visit to the EPU, St George's Hospital, London, had serum HCG and progesterone measured. A PUL was defined on the basis of a TVS, there being no signs of either an intra- or extra-uterine pregnancy or retained products of conception in a woman with a positive urinary pregnancy test. All PULs were followed-up with serum hormone measurements and an ultrasound scan until a final diagnosis was obtained. These outcomes were a failing PUL, an IUP or an ectopic pregnancy.

A failing PUL was confirmed when there were persistent negative sonographic findings in the presence of falling serum HCG levels, ultimately reaching the detection level (i.e. <5 U/l). An IUP was confirmed sonographically during follow-up with the presence of a gestational sac eccentrically placed within the endometrial cavity. The diagnosis of ectopic pregnancy was based upon the positive visualization of an adnexal mass (Condous, 2004).

Ultrasonographic diagnosis of an ectopic pregnancy was based on the following grey-scale appearances: (i) an inhomogeneous mass adjacent to the ovary and moving separate from this—we have called this the blob sign (Condous *et al.*, 2004b); (ii) a mass with a hyper-echoic ring around the gestational sac referred to as the bagel sign (Condous, 2004); or (iii) a gestational sac with a fetal pole with or without cardiac activity. The diagnosis was confirmed subsequently at laparoscopy with histological confirmation of chorionic villi in the Fallopian tube. If an ectopic pregnancy was not visualized, but there was a high index of suspicion based on symptomatology, clinical findings and suboptimal rises of serial serum HCG levels, a laparoscopy was performed with or without an evacuation of the uterus.

Study design

This was a retrospective development of a protocol, followed by a prospective trial.

Although the data set originally consisted of three types of outcome, i.e. a failing PUL, an IUP or an ectopic pregnancy, the final evaluation of the protocol focused on a binary classification problem. The aim was to distinguish the low-risk PULs, i.e. failing PULs, those representing complete miscarriages and self-limiting forms of ectopic pregnancies, and small IUPs from the high-risk PULs, i.e. those representing aggressive forms of ectopic pregnancy based on a single blood test and TVS. After determining the appropriate cut-off values on the initial serum progesterone and HCG levels, the low-risk PULs could potentially be eliminated from requiring a second visit using this approach.

For this purpose, we tried to find a set of cut-off values based on the two raw biochemical measurements. Serum progesterone levels have been advocated as a diagnostic tool in the non-invasive diagnosis of ectopic pregnancy. In a meta-analysis, serum progesterone measurements can identify women at risk for ectopic pregnancy and those who need further follow-up (Mol *et al.*, 1998). Several cut-off values for initial serum progesterone levels have been described in the literature for predicting outcome of PULs. For example, a low initial serum progesterone level, i.e. <20 nmol/l, has been used to identify spontaneous pregnancy resolution (Banerjee *et al.*, 2001). Conversely, a high initial serum progesterone level, i.e. >60 nmol/l, can be used to discriminate between normal IUPs and abnormal pregnancies (Banerjee *et al.*, 2001). Cut-off values for serum progesterone may vary according to different populations, institutions and laboratories. These aforementioned cut-off values were adapted according to the training data from the first 200 consecutive PULs in order to develop the protocol.

This protocol was then tested prospectively on the next 318 consecutive PULs. Management of low-risk PULs would therefore be based solely on the basis of an initial TVS and a single measurement of HCG and progesterone taken at the time of initial consultation.

Statistical analysis

Univariate analysis has been performed on the training and test data, respectively. Descriptive statistics were obtained for all three groups of data. Scatter plots for the two predictive variables were generated for a visual check of the data sets. The single-visit protocol was evaluated in terms of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio of a positive test [LR(+)] and likelihood ratio of a negative test [LR(−)]. The simple kappa coefficient was also given for the 2×2 table of each diagnostic test to assess how the predicted outcome agreed with the true outcome of the PULs.

Table I. Characteristics of the PULs for different outcome groups reported as mean ± SD and the range of the variables within each group

Diagnosis	Progesterone (nmol/l)	HCG (U/l)	Gestational age (days)	Age (years)
Training data ($n = 200$)				
Failing PUL ($n = 111$)	11.80 ± 18.0 1 (1–103)	582.62 ± 870.4 1 (6–4303)	48.87 ± 15.63 (14–94)	31.14 ± 6.4 9 (18–49)
IUP ($n = 67$)	68.55 ± 27.54 (15–190)	799.90 ± 1293.93 (64–9417)	39.03 ± 13.68 (25–91)	28.79 ± 5.7 9 (18–40)
Ectopic ($n = 22$)	29.36 ± 18.1 7 (6–81)	1409.09 ± 2283.65 (69–8027)	44.05 ± 13.20 (19–85)	29.95 ± 4.1 1 (21–38)
Test data ($n = 318$)				
Failing PUL ($n = 189$)	8.42 ± 13.16 (1–75)	328.65 ± 663.1 4 (6–5688)	46.26 ± 11.64 (15–89)	30.53 ± 6.3 5 (15–45)
IUP ($n = 114$)	73.18 ± 28.23 (6–154)	618.94 ± 564.4 5 (20–3632)	39.14 ± 12.39 (20–85)	28.82 ± 5.5 4 (18–43)
Ectopic ($n = 15$)	68.13 ± 49.62 (5–191)	649.40 ± 719.8 2 (90–2779)	51.92 ± 19.04 (32–93)	31.40 ± 4.5 5 (24–41)

PUL = pregnancy of unknown location; IUP = intra-uterine pregnancy.

Results

A total of 5544 consecutive women were scanned, of which 560 women were classified as PULs. Forty-two were lost to follow-up and therefore 518 (9.34%) consecutive PULs were analysed. Table I reports the characteristics of the PULs in both the training and test set. In the training set of 200 PULs, there were 111 (55.5%) failing PULs, 67 (33.5%) IUPs and 22 (11%) ectopic pregnancies. In the training set, 69.4% of women presented with lower abdominal pain and 30.6% without. In the training set, 33.7% presented without any vaginal bleeding, 34.7% had vaginal bleeding without clots and 31.6% had vaginal bleeding with clots.

In the test set of 318, there were 189 (59.4%) failing PULs, 114 (35.8%) IUPs and 15 (4.7%) ectopic pregnancies. This difference in prevalence of ectopic pregnancy between the training and the test sets may be attributable to improved detection of ectopic pregnancies. As the ultrasonographers became more experienced, more ectopic pregnancies were diagnosed at presentation, resulting in fewer ectopic pregnancies being classified and included in the study as PULs. All women in both training and test sets were clinically stable.

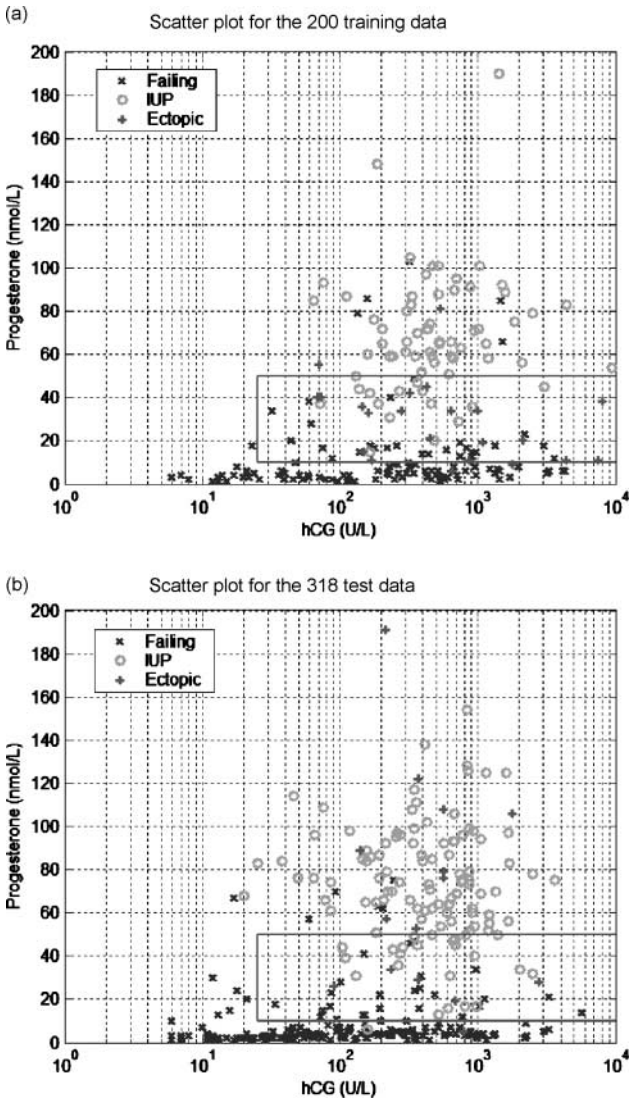

Figure 1. Scatter plots of HCG and progesterone levels for PULs in (**a**) the training data and (**b**) the test data. PULs located within the rectangle, i.e. with a serum progesterone level of 10–50 nmol/l and a serum HCG level of >25 IU/l, are deemed as high-risk for ectopic pregnancies in the single-visit protocol.

To analyse the data, we configured a scatter plot of the serum hormone levels and the final outcomes as observations (see Figure 1). There were two cut-off values for serum progesterone of 10 and 50 nmol/l, and one cut-off value for serum HCG of 25 U/l.

A single-visit protocol was developed in which PULs were divided into low-risk and high-risk PULs. Those PULs with an initial serum progesterone of ≤10 nmol/l or a serum HCG of ≤25 U/l were thought to be resolving or failing PULs and were classified as low risk for ectopic pregnancy. Those PULs with an initial serum progesterone of >50 nmol/l, regardless of serum HCG, were again deemed as low risk for ectopic pregnancy and were classified as viable IUPs. These were collectively referred to as low-risk PULs. Those PULs with an initial serum progesterone of 10–50 nmol/l and a serum HCG of >25 U/l were classified as being at high risk for ectopic pregnancy. These were collectively referred to as high-risk PULs, i.e. possible ectopic pregnancies.

The 'true' diagnoses versus the 'predicted' diagnoses for both the 200 training PULs and 318 test PULs are represented in Table II.

When the protocol was developed on the first 200 PULs, the sensitivity and specificity of a single visit to detect low-risk PULs were 77.0 and 81.8%, respectively. The PPV and NPV were 97.2 and 30.5%, respectively. The positive and negative LRs were 4.23 and 0.28, respectively. When the protocol was tested prospectively on the next 318 PULs, the sensitivity and specificity of a single visit to detect low-risk PULs were 84.2 and 33.3%, respectively. The PPV and NPV were 96.2 and 9.4%, respectively. The LR(+) ratio fell to 1.26, whilst the LR(−) increased to 0.48 on the test set. The small kappa coefficient of 0.08 for the prospective test demonstrates that the predicted outcome agreed poorly with the final true diagnoses.

We also generated the optimal conservative protocol, in which all the ectopic pregnancies in the training data were regarded as being high-risk PULs and accordingly would require follow-up (see Table III). This protocol was constructed by tuning the cut-off points according to the empirical range (see Table I) of the two hormone levels for ectopic pregnancies in the 200 training data. Under this conservative protocol, PULs with an initial serum progesterone between 5 and 81 nmol/l and a serum HCG of >50 U/l were classified as high-risk PULs, while the others were classified as low-risk PULs. This conservative protocol gave a specificity of 100%, i.e. all the ectopic pregnancies would require follow-up. The sensitivity was only 47% for detection of low-risk PULs. A total of 117 of the 200 (58.5%) women were deemed high-risk PULs. When testing this conservative protocol on the 318 test group, although 127 of the 318 (40%) women were deemed high-risk PULs, six of the 15 (40%) ectopic pregnancies would have been discharged without further follow-up.

Table II. Evaluation of a single-visit protocol: true diagnosis versus predicted diagnosis

Predicted diagnosis	True diagnosis		Total	
	Non-ectopic pregnancy	Ectopic pregnancy		
Training data ($n = 200$)				
Non-ectopic PULs	137	4	141	PPV = 97.16%
Ectopic PULs	41	18	59	NPV = 30.51%
Total	178	22	200	
	Sensitivity = 76.97%, LR(+) = 4.23	Specificity = 81.82%, LR(−) = 0.28		Kappa = 0.34
Test data ($n = 318$)				
Non-ectopic PULs	255	10	265	PPV = 96.23%
Ectopic PULs	48b	5	53	NPV = 9.43%
Total	303	15	318	
	Sensitivity = 84.16%, LR(+) = 1.26	Specificity = 33.33%, LR(−) = 0.48		Kappa = 0.08

The protocol considers a PUL as a low-risk PUL when the progesterone level is <10 or >50 nmol/l, or the HCG level is <25 IU/l, otherwise as a high-risk PUL requiring a second visit.
PULs = pregnancies of unknown location; LR = likelihood ratio; PPV = positive predictive value; NPV = negative predictive value.

Table III. Evaluation of the optimal conservative single-visit protocol: true diagnosis versus predicted diagnosis

Predicted diagnosis	True diagnosis		Total	
	Non-ectopic pregnancy	Ectopic pregnancy		
Training data ($n = 200$				
Non-ectopic PULs	83	0	83	PPV = 100%
Ectopic PULs	95	22	117	NPV = 18.80%
Total	178	22	200	
	Sensitivity = 46.63%, LR(+)=∞	Specificity = 100.00%, LR(−) = 0.53		Kappa = 0.16
Test data ($n = 318$)				
Non-ectopic PULs	185	6	191	PPV = 96.86%
Ectopic PULs	118	9	127	NPV = 7.09%
Total	303	15	318	
	Sensitivity = 61.06%, LR(+) = 1.53	Specificity = 60.00%, LR(−) = 0.65		Kappa = 0.05

The protocol considers a PUL as a low-risk PUL when the progesterone level is <5 or >81 nmol/l, or the HCG level is <50 IU/l, otherwise as a high-risk PUL requiring a second visit.
PULs = pregnancies of unknown location; LR = likelihood ratio; PPV = positive predictive value; NPV = negative predictive value.

The overall number of visits required to diagnose the 37 ectopic pregnancies was 113. The overall number of days required to diagnose these ectopic pregnancies was 282 days. The median number of visits required to diagnose an ectopic pregnancy was three (range 2–6). The median number of days required to diagnose an ectopic pregnancy was 5 days (range 2–25 days). Corresponding data were not available for the failing PUL or IUP groups.

In the failing PUL group, there were no adverse outcomes and the intervention rate was 0%. In the IUP group, there were no adverse outcomes and the intervention rate was 4.4%. In the ectopic pregnancy group, there were no adverse outcomes and the intervention rate was 100% (see Table IV). All women were managed expectantly, with an overall rate of intervention of 9.5% (49 out of 518). This included 12 cases treated with single dose methotrexate (50 mg/m^2), 22 cases treated with laparoscopic salpingectomy, three cases treated with laparoscopic salpingotomy, one case treated with laparoscopic partial oophorectomy and three cases requiring laparotomy. There were nine negative laparoscopies; eight in the IUP group (six women in this group also underwent evacuation of retained products of conception) and one in the ectopic pregnancy group (this woman underwent a second laparoscopy and salpingectomy).

Table IV. Final diagnoses and intervention rates

Diagnosis	Frequency	Cumulative percentage (%)	Intervention rates (%)	Maternal mortality (%)
1	300	57.92	0	0
2	181	92.86	4.4	0
3	37	100.00	100	0
Total	518	100.00	9.5	0

Final diagnoses: 1, failing PUL; 2, IUP; 3, ectopic pregnancy.

Discussion

In 8–31% of women who present to an EPU, the pregnancy site will not be visualized by TVS and these women are classified as having a 'pregnancy of unknown location' (PUL). (Hahlin *et al.*, 1995; Banerjee *et al.*, 1999, 2001; Condous, 2004; Condous *et al.*, 2004a). This is a descriptive term rather than a pathological entity. PUL is defined

by TVS as there being no signs of either an intra- or extra-uterine pregnancy or retained products of conception in a woman with a positive urinary pregnancy test. In this clinical situation, there are three possible outcomes: a failing PUL, an IUP or an ectopic pregnancy that is too early to visualize on TVS. The location of failing PULs remains unknown and a proportion will be failing ectopic pregnancies that are never visualized on TVS.

Women with a PUL should be managed expectantly on the basis of measurements of serum levels of HCG and progesterone. Expectant management has been shown to be safe, reduce the need for unnecessary surgical intervention and is not associated with any serious adverse outcomes (Cacciatore *et al.*, 1988; Hajenius *et al.*, 1995; Hahlin *et al.*, 1995; Banerjee *et al.*, 1999, 2001; Mol and Van der Veen, 1999; Condous *et al.*, 2004a). Nevertheless, 9–29% of these women will require surgical intervention due to a worsening clinical condition or non-declining serum HCG (Hahlin *et al.*, 1995; Banerjee *et al.*, 1999, 2001; Dart *et al.*, 1999).

Expectant management can be on an out-patient basis, and currently a multi-visit strategy is used in the management of PUL. This is thought to enable the clinician to predict the outcome in most cases. From previously published data, it is apparent that changing serum HCG levels and the initial serum progesterone can be used to predict viability (Hahlin *et al.*, 1995; Banerjee *et al.*, 1999; Condous *et al.*, 2004a). Current strategies, including the use of discriminatory zones and a suboptimally rising serum HCG, do not locate the pregnancy (Condous *et al.*, 2004a). Women with possible ectopic pregnancies in this group of PULs often have multiple visits to the EPU before a diagnosis is confirmed.

The results from this study appeared at first to be encouraging, with 84% of non-ectopic pregnancies being correctly eliminated from the system on the basis of a single visit (one blood test and one TVS). Sixty-seven percent of the ectopic pregnancies in this study would also have been discharged without follow-up. Even using the conservative protocol, 40% of ectopic pregnancies would still be missed. It is uncertain whether failing to follow-up this group of ectopic pregnancies is a problem, as not all ectopic pregnancies are dangerous and many may resolve without intervention. The difficulty lies in selecting the ectopic pregnancies that can be safely left to resolve and those who require more aggressive treatment. At least 15% of ectopic pregnancies will resolve spontaneously and can be managed expectantly (Condous *et al.*, 2003). These may be thought of as self-limiting ectopic pregnancies. Indeed, even when we re-analyse the data, accepting this conservative spontaneous resolution rate in ectopic pregnancies, we can still see that 57% of the ectopic pregnancies discharged without further follow-up would have persisted, causing possible harm to the women. The issue of concern is that to date there is no way of predicting which ectopic pregnancies are likely to be self-limiting and which are likely to be dangerous. Even ectopic pregnancies with serum HCG levels <10 U/l can rupture (Hochner-Celnikier *et al.*, 1992).

The majority of ectopic pregnancies in the study had serum progesterone >50 nmol/l and were misclassified as IUPs, i.e. low-risk PULs. This group of women would have been discharged without further follow-up and could have been complicated by tubal rupture (Stovall *et al.*, 1989), haemorrhage and death (Lewis and Drife, 2004). The majority of ectopic pregnancies are missed with this single-visit approach.

Laparoscopy is currently considered the gold standard for the diagnosis of ectopic pregnancy (Ankum *et al.*, 1993a). However, TVS and serum HCG measurements have been shown to be very useful as a diagnostic tool in suspected ectopic pregnancies (Ankum *et al.*, 1993b). In an ideal study, it is essential to have a gold standard that is applied to all subjects so that there is no diagnostic suspicion bias. The universal use of laparoscopy would give the most accurate representation of the prevalence of ectopic pregnancies in a PUL population.

We acknowledge that all subjects in the training set, however, did not have a laparoscopy. Although using this approach on all women with a PUL in this study would have ruled out the diagnosis of an ectopic pregnancy, it is difficult to justify this on ethical grounds. Laparoscopy is invasive and not without risks. In the clinical situation where pregnant women are not only clinically stable but also relatively asymptomatic, it is difficult to justify its use. As the vast majority of PULs are non-ectopic pregnancies (Hahlin *et al.*, 1995; Banerjee *et al.*, 1999, 2001; Condous *et al.*, 2004a), non-invasive diagnostic techniques including serum hormone measurements and TVS were used for all three groups. (Ankum *et al.*, 1993b) The ectopic pregnancy group also underwent laparoscopy for treatment as well as diagnostic confirmation. Consequently, there was a bias that enters from selecting those at high risk for the more invasive test. Although laparoscopy is accepted to be the gold standard, it does have its limitations. It does not confer 100% sensitivity. Some early ongoing ectopic pregnancies are too small to be visualized at the time of laparoscopy, i.e. false-negative laparoscopies and a proportion of ectopic pregnancies are self-limiting and are never seen. There was one false-negative laparoscopy during the study period.

It is important to make the distinction between ectopic pregnancies diagnosed on ultrasound at presentation and those women classified as a PUL. The diagnosis of ectopic pregnancy can be made reliably using ultrasound prior to surgery. A total of 87–93% of ectopic pregnancies can be diagnosed using TVS (Cacciatore *et al.*, 1990; Shalev *et al.*, 1998). In this study, we adopted the well accepted two-dimensional grey-scale imaging criteria for the diagnosis of ectopic pregnancy as described by Brown and Doubilet (1994). In our own unit, we have reported 93.2% of ectopic pregnancies being detected using TVS alone prior to surgery (Rosello *et al.*, 2003). There was a diagnostic suspicion bias prevalent in the training set, and hence in the test set, as it was these women who underwent laparoscopy. It is important to remember that these were not the only women to undergo laparoscopy. Women without ultrasonographic evidence of an ectopic pregnancy with suboptimally rising serum HCGs or those with clinical suspicion of an ectopic pregnancy also underwent laparoscopy.

Based on our study, a single-visit approach to the management of PUL will lead to a significant number of women with ectopic pregnancies being discharged without follow-up. This cannot be treated with complacency as the majority of these ectopic pregnancies are dangerous and will not resolve without intervention. Conversely, a significant proportion of those women who needed a second visit based on the new protocol were in fact IUPs, i.e. low-risk PULs.

A single-visit strategy based on commonly used criteria eliminates almost 84% of non-ectopic pregnancies correctly from the system. However, as 67% of ectopic pregnancies are discharged without adequate follow-up, a single-visit strategy should not be used as an alternative to the current multi-visit strategies. We conclude that a single-visit approach to the management of PUL is not a safe practice based on the current criteria used for patient selection and should not be recommended.

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