

# There is no role for uterine curettage in the contemporary diagnostic workup of women with a pregnancy of unknown location

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**BACKGROUND:** The aim of this study was to generate and evaluate a new protocol that defined non-viability in the pregnancy of unknown location (PUL) population and therefore ensured no viable intra-uterine pregnancy (IUP) would be interrupted if uterine curettage was performed. A secondary aim was to evaluate published biochemical criteria that define non-viability in a PUL population to establish if these criteria could result in inadvertent termination of pregnancy (TOP) if uterine curettage was performed. **METHODS:** All clinically stable women classified as having a PUL were included in this study. Protocol 1 was developed retrospectively based on data from 500 consecutive PULs. Using this protocol, no cases of viable IUPs would undergo uterine curettage and the potential for TOP was eliminated. This protocol was then validated prospectively on the data from a further 503 consecutive PULs. Results were then compared with three established criteria (Protocols 2–4) for the use of uterine curettage as a diagnostic tool to classify the location of PULs. Protocol 2 defined non-viability when the hCG ratio (hCG at 48 h/hCG at 0 h) was  $\leq 1.66$ ; Protocol 3 advised uterine curettage at serum hCG levels of  $\geq 2000$  U/l or when the initial serum hCG was  $< 2000$  U/l with a serum hCG rise of  $< 35\%$  over 48 h (hCG ratio  $< 1.35$ ); Protocol 4 advised uterine curettage with a serum hCG rise of  $< 50\%$  over 48 h (hCG ratio  $< 1.50$ ). The number of uterine curettages performed and viable IUPs that would have undergone an unplanned TOP were recorded for all protocols. **RESULTS:** A total of 12 572 consecutive women were scanned: 1003 (8.0%) women were classified as PULs. Training set consisted of 500 PULs: 278 (55.6%) failing PULs, 176 (35.2%) IUPs and 46 (9.2%) ectopic pregnancies (EPs). Test set consisted of 503 PULs: 255 (50.7%) failing PULs, 203 (40.4%) IUPs and 45 (9.0%) EPs. Protocol 1 when developed retrospectively on the training set would have resulted in 293 uterine curettages and no potential TOP. Protocol 1 tested prospectively on 503 PULs would have resulted in 272 uterine curettages and no potential TOP. Three established criteria were tested on the entire data set ( $n = 1003$ ). Protocol 2 would have resulted in 114 uterine curettages and 14 (12.3%) potential TOPs; Protocol 3 would have led to 611 uterine curettages and seven (1.2%) potential TOPs; Protocol 4 would have resulted in 617 uterine curettages and three (0.5%) potential TOPs. No harm came to the women whose EP diagnosis was delayed. **CONCLUSIONS:** Established criteria for the use of uterine curettage in the management of PULs, including those advocated by the American Society for Reproductive Medicine (ASRM), can theoretically result in an inadvertent TOPs. On the basis of these data, a change in contemporary clinical practice should be considered to avoid further damage to wanted pregnancies. We conclude that uterine curettage should not be used in the routine diagnostic workup of women with a PUL.

*Key words:* pregnancy of unknown location/termination of pregnancy/transvaginal ultrasound/uterine curettage

## Introduction

As more pregnant women present at earlier gestations to the Emergency Department or to Early Pregnancy Units (EPUs), the number of women with no signs of an extra- or intra-uterine pregnancy (IUP) on transvaginal ultrasound scan (TVS) may also increase. These women are classified as having a pregnancy of unknown location (PUL). In many centres, the diagnosis of an ectopic pregnancy (EP) in a PUL population is based on documenting that there is no IUP. Uterine curettage is used as a diagnostic tool to differentiate an EP from a miscarriage in women with a PUL (Barnhart *et al.*, 2002). Under these circumstances, an endometrial biopsy that does not contain chorionic villi is considered to be diagnostic of an EP (Ollendorff *et al.*, 1987).

According to Barnhart *et al.*, the presumption that there is an EP present when there is no evidence of an IUP on TVS is not justified. In a recent study, this presumption was inaccurate in almost 40% of cases (Barnhart *et al.*, 2002). The authors in this study concluded that uterine curettage was necessary to differentiate EP from miscarriage to more accurately select woman for medical management of EP.

Before performing this invasive test, one must be certain that the pregnancy is non-viable (Carson and Buster, 1993; Pisarska *et al.*, 1998). There are many different biochemical thresholds that can be used to define non-viability in an early pregnancy. These are based on the sub-optimal rise in serum hCG over 48 h, absolute levels of progesterone of  $\leq 15.9$  nmol/l at presentation or even varying discriminatory zones for serum hCG levels (Kadar and Romero, 1988; Stovall *et al.*, 1990; Stovall *et al.*, 1992; Mol *et al.*, 1998; Barnhart *et al.*, 2002).

The question is whether there is a role for the use of uterine curettage in the contemporary diagnostic workup of women with a PUL. The aim of this study was to generate and evaluate a new protocol that defined non-viability in the PUL population and therefore would ensure no viable pregnancy would be interrupted if uterine curettage was performed. A secondary aim was to evaluate published biochemical criteria that define non-viability in a PUL population to determine if these criteria could result in inadvertent termination of pregnancy (TOP) if uterine curettage was performed.

## Materials and methods

We undertook a non-interventional prospective observational study of pregnant women attending the EPU at St George's Hospital, London, between 25 June 2001 and 9 October 2004. All pregnant women who presented to the EPU underwent a TVS, using a 5 MHz probe (Aloka SSD 900, 2000 or 4000; Keymed Ltd, Southend, UK and Aloka Co. Ltd., Tokyo, Japan). All clinically stable women classified as having a PUL were included in the final analysis. A PUL was defined on the basis of the initial TVS as there being no signs of either an IUP or extra-uterine pregnancy or retained products of conception, in a woman with a positive urinary pregnancy test (Condous *et al.*, 2004b, 2005a). These women had peripheral blood taken at presentation to measure the levels of serum hCG (World Health Organization, Third International Reference 75/537) and progesterone (Roche Elecsys 2010 Progesterone II test; Roche Diagnostics, Lewes, UK) using automated electrochemiluminescence immunoassays (ECLIAS). These levels were measured 48 h later, according to the unit's protocol.

If any of the following were present on TVS, these women were excluded from the PUL population:

- (i) visualization of any evidence of an intra-uterine sac at the first ultrasound scan;
- (ii) identification of an adnexal mass thought to be an EP at the initial ultrasound scan;
- (iii) those with an endometrial thickness of  $>15$  mm on TVS with the presence of heterogeneous, irregular tissues within the uterus thought to be an incomplete miscarriage or
- (iv) women who were clinically unstable or had a haemoperitoneum according to the scan images.

All women classified as having a PUL were followed up with serum hCG measurements, TVS and/or laparoscopy until the final clinical outcomes were established. The outcomes included a failing PUL, an IUP, an EP or a persisting PUL. These diagnoses were established using the criteria described in previous studies published by this unit (Condous *et al.*, 2004a,b; Condous *et al.*, 2005a,b,c,d,e; Condous *et al.*, 2006; Kirk *et al.*, 2006). The persisting PULs almost certainly represent ultrasonically missed EPs, and as they behaved biochemically like EPs, they were incorporated into the EP group in the final analysis.

## Study design

This was a retrospective development of a protocol, followed by a prospective trial. The data set was split into two sets according to the data collection time: one was called the model-building or training data set and the other was called the validation or test data set. The initial model-building data set was collected from 25 June 2001 until 15 April 2003 ( $n = 500$  consecutive women with a PUL). The subsequent validation data set was collected at the same unit, from 16 April 2003 until 9 October 2004 ( $n = 503$  consecutive women classified as having a PUL).

A new protocol, Protocol 1, was developed based on the use of uterine curettage as a diagnostic tool to differentiate EP from miscarriage in women with no signs of an extra-uterine pregnancy or IUP on TVS, i.e. a PUL. Protocol 1 was weighted to ensure that no cases of viable IUPs underwent uterine curettage, and therefore the potential for TOP was eliminated. Protocol 1 was developed on retrospective analysis of the model-building data from the first 500 consecutive PULs. In this protocol, stable women with a PUL and serum hCG level of  $\geq 2000$  U/l in conjunction with a serum progesterone level of  $<45$  nmol/l at presentation can have uterine curettage performed to establish the location of the PUL without interrupting an ongoing IUP. Similarly, stable women with serum hCG levels of  $<2000$  U/l at presentation and an hCG ratio (hCG at 48 h/hCG at 0 h) of  $\leq 1.15$ , i.e. serum hCG rise of  $\leq 15\%$  over 48 h, can also have uterine curettage without interrupting an ongoing IUP. This protocol was then validated prospectively on the data set of the next 503 consecutive women with PULs who attended the department.

## Model validation

Split sample analysis gives overly pessimistic estimates of a model's performance, with large variability (Steyerberg *et al.*, 2001). To make use of the data more efficiently and check the bias and variability of the results, we also have validated Protocol 1 using the regular bootstrap sampling technique (Efron and Tibshirami, 1993). In particular, 1000 bootstrap samples were drawn with replacement from the original data set (with 1003 patient data), and the proportion of the outcome was kept the same in each bootstrap sample as in the original data set.

The performance of Protocol 1 was then compared with the established criteria that use uterine curettage as a diagnostic tool to classify the location of PULs. The American Society for Reproductive Medicine

(ASRM) Practice Committee Report (2001) advocates the use of uterine curettage following endocrine documentation that suggests a non-viable pregnancy regardless of its location, i.e. when there is an abnormal rise in serum hCG in early pregnancy of  $\leq 66\%$  in 48 h (Kadar and Romero, 1988). For the purposes of this study, Protocol 2 was therefore according to Kadar and Romero and defined non-viability when there was an hCG ratio of  $\leq 1.66$  (Kadar and Romero, 1988); Protocol 3 was according to Barnhart *et al.* and advised uterine curettage at serum hCG levels of  $\geq 2000$  U/l or when the initial serum hCG was  $< 2000$  U/l with an hCG ratio of  $< 1.35$ , i.e. a serum hCG rise of  $< 35\%$  over 48 h (Barnhart *et al.*, 2002); Protocol 4 was according to Stovall *et al.* and advised a uterine curettage with an hCG ratio of  $< 1.50$ , i.e. a serum hCG rise of  $< 50\%$  over 48 h (Stovall *et al.*, 1990). These established protocols were tested on the total PUL population ( $n = 1003$ ).

### Primary outcome

In all the protocols, the number of uterine curettages that would have been performed in the PUL population, and in particular the number of viable pregnancies that would have undergone potential termination, was recorded.

Statistical analyses were performed using the SAS software package, version 9 (Cary, NC, USA).

### 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. The mean age and gestation at presentation were 30.2 years and 41.9 days, respectively. The mean serum hCG levels at 0 h and 48 h were 582.2 U/l and 690.2 U/l, respectively. The mean serum progesterone levels at 0 h and 48 h were 34.6 nmol/l and 30.6 nmol/l, respectively (Table I).

In the model-building (training) and validation (test) sets, there were 500 and 503 PULs, respectively (Table II).

When developed retrospectively, Protocol 1 would have resulted in 293 uterine curettages being performed on the PUL population, resulting in no TOPs (Table III). When Protocol

1 was validated prospectively, 272 uterine curettages would have resulted in no TOPs (Table III).

The other three protocols were tested on the total PUL population of 1003 PULs.

The contingency tables for the different protocols on the complete PUL population have been summarized in Table IV. Also reported in Table IV are some performance measures including the sensitivity of each protocol for advising uterine curettage and for detecting potential EPs and the false positive rate for advising uterine curettage in a woman with a viable IUP. For Protocol 1, the bootstrap estimate of the performance measures and their corresponding 95% confidence interval (CI) have been provided as well.

Protocol 2 would have resulted in 114 uterine curettages and 14 potential (12.28%) TOPs. Protocol 3 would have resulted in 611 uterine curettages and seven (1.15%) potential TOPs. Protocol 4 would have resulted in 617 uterine curettages and three (0.49%) potential TOPs (Table IV).

### Discussion

This study clearly demonstrates that uterine curettage should not be used in the routine diagnostic workup of women with a PUL. Current criteria for defining non-viability (Kadar and Romero, 1988; Stovall *et al.*, 1990; Barnhart *et al.*, 2002) in a PUL population may lead to the inadvertent termination of some wanted pregnancies if invasive diagnostic tests are used. This is in part due to the discriminatory zones for serum hCG levels being set too low as well as the serial rise in serum hCG being used to define pregnancy failure not being conservative enough. We advocate the non-invasive evaluation of pregnant women with a PUL. Ultrasound, and in particular TVS, is the single diagnostic tool of choice to positively identify EPs in women who present in the first trimester (Cacciatore *et al.*, 1990; Shalev *et al.*, 1998; Condous *et al.*, 2005b). In specialist scanning units, the diagnosis of an EP should be based on the positive visualization of an adnexal mass using TVS, rather than the routine use of uterine curettage to exclude chorionic villi. Invasive diagnostic tests such as uterine curettage with or without laparoscopy are rarely used in some units (Atri *et al.*, 2003), and this 'hands-off' approach should be encouraged in the modern management of women with a PUL.

An expectant 'wait and see' approach does not compromise the care of women with a PUL (Cacciatore *et al.*, 1988; Hahlin *et al.*, 1995; Hajenius *et al.*, 1995; Banerjee *et al.*, 1999; Mol and Van der Veen, 1999; Banerjee *et al.*, 2001; Condous *et al.*, 2004a). In a recent study, we demonstrated that PULs can be safely managed without the need for intervention based on the hCG ratio (Condous *et al.*, 2006). The use of non-invasive diagnostic techniques including high-resolution TVS in conjunction with serum hCG and progesterone measurements is the cornerstone of management of women with a PUL. (Ankum *et al.*, 1993; Condous *et al.*, 2003).

The exception to the use of uterine curettage is in the persisting PUL group, which only accounts for 2% of the total PUL population (Condous *et al.*, 2004b). The persisting PUL group is defined as those PULs whose serum hCG levels fail to decline, tend to be low ( $< 500$  U/l) and have reached a plateau. Under

**Table I.** Descriptive statistics for pregnancies of unknown location ( $n = 1003$ )

Variable	<i>n</i>	Mean	SD
Age (years)	1000	30.18	6.43
Gestation (days)	920	41.95	14.24
Endometrial thickness (mm)	993	11.77	25 0694
hCG (0 h)	1003	582.19	938.57
hCG (48 h)	1003	690.22	1014.78
hCG ratio	1003	1.23	0.93
Progesterone (0 h)	991	34.56	36.78
Progesterone (48 h)	966	30.57	36.35

**Table II.** Training and test sets—three outcome groups after incorporating the persisting PULs into the ectopic pregnancy group

Diagnosis	Training data ( $n = 500$ )		Test data ( $n = 503$ )	
	Frequency	%	Frequency	%
Failing PUL	278	55.60	255	50.70
Intra-uterine pregnancy	176	35.20	203	40.60
Ectopic pregnancy	46	9.20	45	8.95

PUL, pregnancy of unknown location.

**Table III.** Protocol 1 developed on the training set and tested prospectively

Diagnosis need for D&C	Retrospective test on the first 500 PUL data				Prospective test on the subsequent 503 PUL data			
	Failing PUL	Intra-uterine pregnancy	Ectopic pregnancy	Total	Failing PUL	Intra-uterine pregnancy	Ectopic pregnancy	Total
No	11	171	25	207	14	198	19	231
Yes	267	5 <sup>a</sup>	21	293	241	5 <sup>a</sup>	26	272
Total	278	176	46	500	255	203	45	503

D&C, uterine curettage; PUL, pregnancy of unknown location.

hCG ratio = hCG at 48 h/hCG at 0 h.

Perform uterine curettage if (i) hCG (0 h) ≥2000 U/l and progesterone (0 h) <45 nmol/l or (ii) hCG (0 h) <2000 U/l and hCG ratio <1.16.

<sup>a</sup>Nil in this group of IUPs were viable IUPs.

**Table IV.** Evaluation of the four protocols on the total PUL population (n = 1003)

Protocol	Need for D&C	Diagnosis				Performance measures		
		Failing PUL	IUP others	IUP viable	Ectopic pregnancy	Percentage of D&C	Sensitivity for ectopic pregnancy	False D&C rate for viable IUP
1	No	25	351	18	44	565/1003	47/91	0/565
	Yes	508	10	0	47	56.33%	51.65%	0.00%
						Bootstrap estimate (95% CI)		
						(52.8%, 60.51%)	(29.24%, 72.22%)	(0%, 1.70%)
2	No	505	339	4	41	114/1003	50/91	14/114
	Yes	28	22	14	50	11.37%	54.95%	12.28%
3	No	15	341	11	25	611/1003	66/91	7/611
	Yes	518	20	7	66	60.92%	72.53%	1.15%
4	No	11	340	15	20	617/1003	71/91	3/617
	Yes	522	21	3	71	61.52%	78.02%	0.49%

CI, confidence intervals; D&C, uterine curettage; IUP, intra-uterine pregnancy.

these circumstances, uterine curettage to confirm the absence of chorionic villi is a reasonable management option before giving medical treatment with methotrexate (Condous *et al.*, 2003).

In units that routinely use uterine curettage in women with a PUL, the lowering of the hCG ratio threshold from 1.5 (i.e. a serum hCG rise of <50% in 48 h) to 1.15 (i.e. a serum hCG rise of ≤15% in 48 h) would mean adopting an extremely conservative approach. This new hCG ratio threshold may result in failure or delay in the diagnosis of EP because uterine curettage is deferred or delayed. Advocates of uterine curettage might argue that the risk of diagnostic delay in the EP subgroup outweighs the risk of unintentional pregnancy termination. This controversy needs to be addressed. On the one hand, the number of EPs in the complete 1003 PUL set that would have been diagnosed with uterine curettage using the new hCG ratio threshold of 1.15 is 47/91 (51.65%) compared with 71/91 (78.02%) if the hCG ratio threshold had have been 1.5. Therefore, 24 EPs would have had their diagnosis delayed if the new policy was adopted. On the other hand, no ongoing IUPs in the validation set would have been potentially terminated if the new hCG ratio threshold of 1.15 was adopted, whilst three of 24 IUPs with an hCG ratio threshold of 1.5 would have potentially undergone a TOP in an effort to locate the pregnancy. The authors believe that the delay in diagnosing these 24 extra EPs is very unlikely to result in complications, whilst the use of the hCG ratio threshold of 1.5 certainly can cause potential harm to viable IUPs. In a recent study in our unit, the diagnosis of EP in the PUL population was made using TVS at follow-up visits;

routine curettage was not used. There were no adverse outcomes in this study (Condous *et al.*, 2005a). Therefore potential diagnostic delay at this very early stage of pregnancy does not have an impact on the morbidity or mortality in the EP subgroup.

Current strategies for the use of uterine curettage as a diagnostic tool in the management of PUL, including those advocated by the ASRM, are of concern as they are based on an inadequate knowledge of the status of the pregnancy. According to our data, these criteria may lead to performing uterine curettages in women with an ongoing IUP resulting in an inadvertent TOP in 0.5–12.3% of cases. Furthermore, in most cases, over 50% of the women undergo invasive surgical intervention that they may not require. On the basis of this study, we conclude that there is no role for the routine use of uterine curettage in the diagnostic workup of women with a PUL.

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