

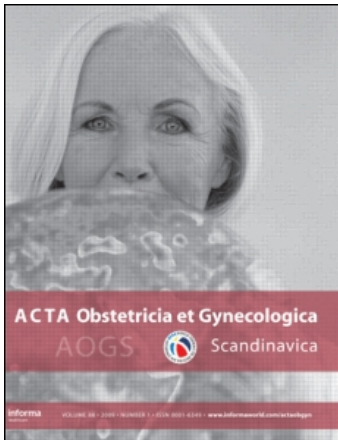
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Publisher Informa Healthcare

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Acta Obstetrica et Gynecologica Scandinavica

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title-content=t716100748>

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First Published:2008

To cite this Article Kirk, Emma, Daemen, Anneleen, Papageorgiou, Aris T., Bottomley, Cecilia, Condous, George, De Moor, Bart, Timmerman, Dirk and Bourne, Tom(2008)'Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination?',Acta Obstetrica et Gynecologica Scandinavica,87:11,1150 — 1154

To link to this Article: DOI: 10.1080/00016340802443822

URL: <http://dx.doi.org/10.1080/00016340802443822>

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ORIGINAL ARTICLE

Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination?

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Abstract

Objective. To compare the appearance and behavior of ectopic pregnancies (EPs) initially classified as pregnancies of unknown location (PULs) to those visualized on the initial transvaginal ultrasound scan (TVS). **Methods.** An observational study over a four-year period on women undergoing a TVS prior to diagnosis of a tubal EP. Demographic details, presenting symptoms, TVS findings, serum hCG and progesterone levels were recorded at the time of the initial TVS and at the time of diagnosis of the EP in those initially classified as a PUL. **Results.** 411 women with a tubal EP underwent a TVS prior to treatment. In 85.9% (353/411) the EP was visualized on the initial TVS while 14.1% (58/411) were initially classified as PULs. Those initially classified as PULs had significantly lower mean gestational age and mean initial human chorionic gonadotrophin (hCG) levels, and significantly higher mean progesterone level at presentation than those where the EP was visualized on the initial TVS. Of those with a PUL, 60.3% (35/58) had the EP subsequently visualized on TVS. At the time of diagnosis these EPs were significantly smaller ($p < 0.0001$); the appearance of the EPs, serum hCG and progesterone levels at the time of visualization on TVS were not significantly different from those visualized on the initial TVS. **Conclusion.** In women with EPs who are initially classified as PULs, failure of visualization of the EP on the initial TVS is likely to be due to the fact that they are too small and probably too early in the disease process.

Key words: Ectopic pregnancy, pregnancy of unknown location, transvaginal ultrasound, early pregnancy unit

Introduction

Transvaginal sonography has been shown to have an overall sensitivity of 87–99% for the detection of tubal ectopic pregnancy (EP) (1–5). However, not all of these EPs are visualized on the initial transvaginal scan (TVS): a proportion of women are initially classified as having a 'pregnancy of unknown location' (PUL). This is defined as a positive pregnancy test with no evidence of an intra-uterine or EP on TVS. In these women, the EP are usually visualized on subsequent TVS examinations, often after serial human chorionic gonadotrophin (hCG) measure-

ment. The true incidence and clinical relevance of EP in the PUL population is unknown. The majority of women classified as having a PUL will subsequently be diagnosed as having an early intra-uterine pregnancy or a failed PUL. These failed PULs are confirmed by observing decreasing serum hCG levels, but in most cases the location of the pregnancy is never identified. Whilst the majority will probably be failed intra-uterine pregnancies, a proportion will be failed EP.

In a prospective observational study of 5,240 women attending the Early Pregnancy Unit (EPU), the initial TVS detected 73.9% of EPs (95%,

CI = 65.1–81.6%) with a specificity of 99.9% (99.8–100%) (5). Of the remaining EPs the majority (93.5%) were detected on a subsequent ultrasound scan. An interesting finding was that serum hCG levels were significantly higher in those women diagnosed with EP at the initial TVS when compared to those with a PUL subsequently confirmed as an EP ($p < 0.001$). It is therefore possible that an EP derived from a woman initially classified as a PUL may be different to an EP visualized on the initial TVS examination.

The aim of this study was to examine why some EPs are not visualized on the initial TVS and whether these EPs have features that make them different to those visualized on the initial TVS.

Materials and Methods

Data were collected prospectively on all women with a tubal EP attending an EPU of a London teaching hospital over a four-year period (15 February 2002–14 February 2006, inclusive). The unit is open six days a week and any woman less than 14 weeks gestation with a positive pregnancy test is seen there. Women either present directly to the EPU or are referred after admission via the Accident and Emergency Department or the Acute Gynecology Unit. Reasons for presentation were recorded and included: pain, vaginal bleeding, pain and vaginal bleeding, unsure dates, previous EP and maternal anxiety. Maternal age and expected gestation according to the last menstrual period were also recorded.

The diagnosis of tubal EP was either made on TVS using a 5 MHz transducer for B mode imaging (Aloka SSD 900, 2000 or 4000, Aloka Co, Japan) or at the time of surgery. An ultrasonographic diagnosis was made using the criteria shown in Table I. At the time of the TVS, the following were recorded: endometrial thickness, size of the EP, appearance of the EP, and the presence or absence of free fluid or blood (hemoperitoneum) in the Pouch of Douglas.

Table I. Ultrasonographic criteria for the diagnosis of tubal EP.

Appearance	Diagnostic criteria
Inhomogeneous mass	An empty endometrial cavity with an inhomogeneous mass in the adnexal region.
Empty gestational sac ('bagel' sign)	An empty endometrial cavity with an empty ectopic gestational sac seen as hyper-echoic ring.
Gestational sac containing a yolk sac or fetal pole	An empty endometrial cavity with an ectopic gestational sac with a yolk sac and/or fetal pole with or without cardiac activity.

A surgical diagnosis was made at the time of laparoscopy or laparotomy by the finding of a distended Fallopian tube and confirmed histologically after removal of either the products of conception alone (salpingostomy) or with a portion of the Fallopian tube (salpingectomy). Serum hCG levels (World Health Organization, Third International Reference 75/537) and progesterone levels (Roche Elecsys 2010 Progesterone II test, Roche Diagnostics, Lewes, UK) were taken and recorded at the time of diagnosis of the EP. Women in whom the diagnosis of EP was not made on the initial TVS were initially classified as a PUL and had serum hCG levels and progesterone levels recorded at the time of their initial presentation and at 48 hours. The diagnosis of EP was subsequently made using the criteria above.

Tubal EP were managed expectantly, medically or surgically. The type of management depended on clinical signs and symptoms, TVS findings and serum hCG levels, according to unit guidelines. Indications for surgical management included: pain, hemodynamic instability, positive fetal cardiac activity on TVS, hemoperitoneum on TVS and a serum hCG $> 5,000$ IU/L. Medical management was in the form of a single systemic dose of methotrexate (50 mg/m^2), administered according to the protocol developed by Stovall et al. (6).

One hundred and fifty two of the tubal EPs in this study had been included in our previous publication on the accuracy of TVS for the diagnosis of EP prior to surgery and 110 tubal EPs had been included in our publication on the diagnostic effectiveness of an initial TVS in detecting EP (4,5).

Statistical analysis

The Mann–Whitney U test was used to compare continuous non-parametric variables between the two groups and the Fisher's exact test to compare dichotomous variables. For the variables of serum hCG and progesterone a log-transformation was performed. Following this, the Shapiro Wilk test showed no evidence of non-normality and a Q-Q plot showed that the data conformed to a Gaussian distribution. Parametric two-sample t -test with equal variance was used to perform subsequent analysis. Two sided p values are reported. Statistical analysis was performed using SAS Version 9.1 for Windows (SAS Institute Inc, Cary, USA).

Results

During the study period, 422 women were diagnosed with a tubal EP. Of the 422 women,

411 (97.4%) underwent a TVS prior to treatment. The remaining 11 women underwent primary surgical management with no prior ultrasound examination, due to hemodynamic instability.

Of the 411 remaining women, 353 (85.9%) had the EP visualized on the initial TVS while 58 (14.1%) were initially classified as PULs. The ultrasound appearance of the EPs visualized on the initial TVS were of an inhomogeneous mass in 222 cases (62.9%), an empty gestational sac in 77 cases (21.8%) and a gestational sac containing a yolk sac or fetal pole in 54 cases (15.3%).

Those initially classified as PULs had a lower mean gestational age (mean 41.4 days \pm standard deviation (SD) 13.5) when compared to those who had their EP visualized on the first scan (45.6 days \pm 14.5), Table II. They also had a lower median initial serum hCG (median 635 IU/L nmol/L, interquartile range (IQR) 234–2,030) and a higher median serum progesterone (30 nmol/L, IQR = 19–45) when compared to those who had their EPs visualized on the first scan (1,286 IU/L, IQR = 478–3,826 and

19 nmol/L, IQR = 9–36, respectively). Those cases in which the EP was visualized on the initial scan were also more likely to have a hemoperitoneum or anechoic free fluid in the Pouch of Douglas (Table II).

Of the 58 women initially classified as having a PUL one underwent a laparoscopy because of pain and the suggestion of hemoperitoneum on TVS, and was subsequently diagnosed with an EP at the time of surgery. The other 57 women had measurement of serial hCG levels and repeat TVS examinations, and an EP was visualized in 35 (61.4%) women; in the other 22 women the EPs were diagnosed at the time of surgery. In this group, the mean time from presentation to visualization on TVS was 7.8 days \pm 6.9. The TVS appearances of these EPs were of an inhomogeneous mass in 25 women (71.4%), an empty gestational sac in nine (25.7%) and a gestational sac containing a fetal pole in one woman (2.9%). There were no significant differences in the appearances of the EPs whether they were visualized on the initial TVS or subsequent examinations

Table II. Characteristics of women where EPs were visualized on the initial scan and those initially classified as PULs.

	Initial TVS result		
	Ectopic pregnancy	PUL	<i>p</i> -Value
<i>n</i>	353	58	–
Obstetric history			
Maternal age (years) mean (SD)	30.4 (5.9)	32.0 (6.30)	0.0551*
Gestational age (days) mean (SD)	45.6 (14.5)	41.4 (13.5)	0.0317*
Previous delivery >24/40, <i>n</i> (%)	157 (47.7)	33 (60.0)	0.1091 [^]
Previous miscarriage, <i>n</i> (%)	65 (19.8)	12 (21.8)	0.7177 [^]
Previous EP, <i>n</i> (%)	32 (9.7)	8 (14.6)	0.3365 [^]
Previous TOP, <i>n</i> (%)	69 (21.0)	13 (23.6)	0.7222 [^]
Presenting symptoms			
Bleeding, <i>n</i> (%)	216 (61.2)	39 (67.2)	0.4657 [^]
Pain, <i>n</i> (%)	233 (66.0)	34 (58.6)	0.2997 [^]
TVS findings			
Endometrial thickness (mm) mean (SD)	10.1 (5.7)	11.1 (5.3)	0.098*
Hemoperitoneum, <i>n</i> (%)	138 (39.3)	13 (22.4)	0.0129[^]
Anechoic free fluid, <i>n</i> (%)	203 (57.8)	24 (42.1)	0.0311[^]
Initial serum levels			
hCG (IU/L) Median (IQR, 25th quantile–75th quantile)	1,286 (3,384, 478–3,826)	635 (1796, 234–2,030)	0.0010[°]
Progesterone (nmol/L) median (IQR, 25th quantile–75th quantile)	19 (27, 9–36)	30 (26, 19–45)	0.0095[°]
Management of ectopic pregnancy			
Expectant, <i>n</i> (%)	26 (7.4)	3 (5.2)	0.3934 [^]
Medical, <i>n</i> (%)	50 (14.2)	12 (20.7)	
Surgical, <i>n</i> (%)	277 (78.4)	43 (74.1)	

Note. Significant results are highlighted in bold.

TVS, transvaginal scan; SD, standard deviation; TOP, termination of pregnancy; hCG, human chorionic gonadotrophin; IQR, Interquartile range.

*Mann–Whitney *U* test (two-sided).

[^]Fisher's exact test (two-sided).

[°]Two-sample *t*-test with equal variance after log-transformation (parametric test).

[^]Chi-square test.

Table III. Differences in the ultrasound appearance and serum hormone levels of EPs visualized on the initial TVS and those visualized on subsequent TVS examination.

	TVS to visualize ectopic pregnancy		
	Initial TVS	Subsequent TVS	<i>p</i> -Value
<i>n</i>	353	35	–
Mean size of ectopic mass on TVS (mm)			
Mean (SD)	22.2 (9.3)	15.4 (5.3)	<0.0001*
Appearance of ectopic pregnancy on TVS			
Inhomogeneous mass, <i>n</i> (%)	222 (62.9)	25 (71.4)	0.1029 [^]
Empty gestational sac, <i>n</i> (%)	77 (21.8)	9 (25.7)	
Gestational sac containing a yolk sac or fetal pole, <i>n</i> (%)	54 (15.3)	1 (2.9)	
Serum levels at time of diagnosis			
hCG (IU/L) Median (IQR, 25th quantile–75th quantile)	1,286 (3,384, 478–3,826)	1,259 (2,657, 340–2,997)	0.2431 [°]
Progesterone (nmol/L) Median (IQR, 25th quantile–75th quantile)	19 (27, 9–36)	20 (17, 11–28)	0.7334 [°]

Note. Significant results are highlighted in bold.

TVS, transvaginal scan; SD, standard deviation; HCG, human chorionic gonadotrophin; IQR, Interquartile range.

*Mann–Whitney *U* test (two-sided).

[^]Fishers exact test.

[°]Two-sample *t*-test with equal variance after log-transformation (parametric test).

(Table III, $p = 0.1029$). The mean size of the ectopic mass, however, was significantly smaller in those initially classified as PULs (mean diameter $15.4 \text{ mm} \pm 5.3$ compared to $22.2 \text{ mm} \pm 9.3$, $p < 0.0001$) (Table III). The serum hCG and progesterone levels at the time of diagnosis of the EPs were not significantly different between the two groups (both $p > 0.2$, Table III).

Linear regression analysis was performed to test for correlation between serum hCG levels and the size of the EP. For the EPs visualized on the initial TVS, hCG and size were correlated ($r = 0.1846$; $p = 0.0008$). There was no significant correlation for the EPs visualized on a subsequent scan ($r = 0.2768$; $p = 0.1386$). When considering all EPs visualized on the initial or subsequent scan, a significant correlation was also found ($r = 0.1919$; $p = 0.0003$). The size increased with increasing serum hCG levels.

Discussion

In this study, 388 of the 411 women with tubal EP had this visualized on TVS prior to treatment. This gives an overall sensitivity of 94.4% for the detection of EP, which is consistent with data published from other units (1–3,7). In keeping with our previous publication (5), the majority (85.9%) were visualized on the initial TVS examination.

The mean gestational age at presentation was significantly lower in women initially classified with a PUL when compared to those women where the EP was visualized on the initial TVS examination. Serum hCG levels at the time of the initial TVS examination were also significantly lower in women

classified as a PUL. However, serum hCG levels at the time of visualization of the EP on TVS were not significantly different between those visualized on the initial scan and those visualized on subsequent examinations. This suggests that the failure of visualization on the initial TVS for some EPs is due to the gestational age being too early, with correspondingly low serum hCG levels.

Although, there was no significant difference in serum hCG levels at the time of diagnosis, the mean ectopic mass size at the time of visualization on TVS was smaller in those initially classified as PULs. This may be because of the examining sonographer, aware of the serum hCG levels and absence of an intra-uterine pregnancy, may have a higher index of suspicion during ultrasound. Nevertheless, there was no difference in the appearance of the EPs: in both groups the majority were visualized as an inhomogeneous mass. The precise relationship between the size of an ectopic mass, the appearance of an EP on TVS and serum hCG levels is uncertain. A study published in 1990 on 120 women with tubal EPs found that the serum hCG levels correlated with the size of ectopic gestational sacs but not with the diameter of inhomogeneous adnexal masses (8). It was also found that in most of the women with an ectopic gestational sac serum hCG levels were high and increasing while in those with an inhomogeneous mass they were lower and decreasing. The authors suggested that detection of a sac-like adnexal ring on TVS implies an intact Fallopian tube with a gestational sac that is growing, while detection of an inhomogeneous mass may represent a collapsed sac,

which is less likely to contain active trophoblastic tissue.

Our findings suggest that visualization of an inhomogeneous mass may indicate either an early developing EP as seen in the group initially classified as a PUL; or a failing EP as in the group visualized on the initial TVS. This is supported by the finding that initial progesterone levels were significantly lower in those visualized on the initial TVS when compared to those visualized on subsequent examinations. Low serum progesterone levels have been shown to be predictive of pregnancy failure (9). This finding should, however, be interpreted with caution, as it does not mean that EPs diagnosed in the PUL population always have increasing serum hCG levels. In the majority of cases, we probably only subsequently visualize on TVS those EPs with increasing serum hCG levels. Women classified as PULs, with decreasing serum hCG levels and low progesterone levels often do not have the scan repeated. The true incidence of EP in this PUL population is therefore not known.

We had hypothesized that if a woman had pain or a previous EP, her EP would have been more likely to be visualized on the initial TVS (as the sonographer may have been more concerned about the possible diagnosis). However, this was not the case. In fact, patient symptomatology and previous obstetric history were not significantly different between the two groups. Perhaps, not surprisingly, the finding of anechoic free fluid or blood in the Pouch of Douglas was more common in those women who had their EPs visualized on the initial TVS.

Conclusion

Women with EPs who are initially classified as having a PUL, do not have their EPs visualized on the initial TVS as they are too small and probably too early in the disease process. They therefore,

represent EPs not yet seen on scan as they have been scanned too early in their development and may be of more clinical significance than previously thought.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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