The effect of morphological types of extrauterine ectopic pregnancies and their effect on the accuracy of pre-operative ultrasound diagnosis

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Abstract

Objectives: To investigate the impact of the different morphological types of extra-uterine ectopic pregnancy on the accuracy of pre-operative ultrasound diagnosis.

Methods: We performed a retrospective study of all pregnant women who underwent emergency surgery for presumed extra-uterine ectopic pregnancy in a single Early Pregnancy Unit between January 2009 and December 2017. The pre-operative ultrasound findings were recorded including the exact location and morphological type (I-V) of extra-uterine ectopic pregnancy. The ultrasound findings were compared with the operative and histological findings.

Results: A total 26401 women presented with early pregnancy complications during the study period including 1241 (4.7%, 95% CI 4.5-5.0) women who were diagnosed with an extra-uterine ectopic pregnancy. Surgery was performed in 721 cases (58.1%, 95% CI 55.3-60.8) out of which 710 (98.5%, 95%CI 97.6% to 99.4%) were diagnosed with an extrauterine ectopic pregnancy on a preoperative ultrasound scan. The remaining 11 women had severe pain and significant haemoperitoneum and were managed surgically as emergency without an ectopic pregnancy having been seen on the scan. The diagnosis of ectopic pregnancy was confirmed at laparoscopy in all 721 cases. The positive predictive value of pre-operative ultrasound for the diagnosis of extra-uterine ectopic pregnancy was 99.4% (95% CI 98.6-99.8) with a sensitivity of 98.5% (95% CI 97.3-99.1). There was no statistically significant difference in the accuracy of pre-operative ultrasound diagnosis for the five morphological types of extra-uterine ectopic pregnancy ($P>0.05$).

Conclusions: The positive predictive value of pre-operative ultrasound diagnosis of extra-uterine ectopic pregnancy is very high. Different ultrasonographic morphological types of

extrauterine ectopic pregnancy had no significant effect on the accuracy of pre-operative diagnosis.

Introduction

Ectopic pregnancy (EP) is a common condition with approximately 35,000 women diagnosed each year in the United Kingdom[1]. Some EPs have a potential to cause significant maternal morbidity and prompt diagnosis is essential to facilitate timely intervention[1,2]. However, a significant proportion of EPs are tubal miscarriages. In these cases conservative management can be used successfully and help to avoid the complications and costs associated with surgical treatment[3].

Traditionally the diagnosis of an extra-uterine ectopic pregnancy (EUEP) was made at surgery and confirmed on histological examination[4–6]. The first successful non-invasive diagnosis of tubal EP using transabdominal ultrasound was described by Kobayashi in 1969[7]. That was an pivotal step in the clinical diagnosis of EUEP; however, the accuracy of transabdominal ultrasound was low, with a reported sensitivity and specificity of around 50%[7]. Improvements in ultrasound technology, particularly the introduction of transvaginal ultrasound (TVS), have significantly enhanced the diagnostic accuracy and ultrasound has become a standard tool for assessment of women with suspected early pregnancy complications[8–11].

Many studies have been published describing the use of TVS for the diagnosis of tubal EP. The reported diagnostic accuracy figures vary widely and many authors continue to advocate the use of serum β-hCG and other biochemical markers to reduce the number of false negative diagnoses[12,13]. Some authors believe that in many cases ultrasound findings are non-specific and they propose that a conclusive diagnosis of tubal EP can only be made in cases when a gestational sac containing an embryo or a yolk sac is visible, whilst the other morphological

types should be classified as "probable" EP[12]. This approach has been questioned by others, who showed that conclusive ultrasound diagnosis of tubal EP could be made in most cases regardless of the morphological type[14].

In this study, we assessed the overall accuracy of the ultrasound diagnosis of all types of EUEP in a large group of women who were all managed surgically. We also examined the positive predictive value (PPV) of the different morphological types of EP using surgery as the reference standard.

Materials and methods

This was a retrospective study carried out at a single large specialist Early Pregnancy Unit (EPU). We included all women with presumed ultrasound diagnosis of EUEP who were managed surgically between January 2009 and December 2017. All women underwent a pre-operative TVS using high-end ultrasound equipment (Voluson E8, GE Medical Systems, Milwaukee, WI, USA). The majority of the examinations were carried out by clinical fellows in early pregnancy and gynecology, who were all Level II operators[15], under the supervision of senior gynecologists, the majority of whom were expert Level III operators[15].

The diagnosis of EUEP was based on findings of a structure outside the uterus with typical morphological features of an EUEP and classified based on the below characteristics:

I. A gestational sac containing an embryo with visible cardiac activity
II. A gestational sac containing an embryo with no visible cardiac activity
III. A gestational sac containing only a yolk sac, with no visible embryo
IV. An empty gestational sac, with no visible additional structures
V. A solid, homogenous swelling

Haemoperitoneum was classified as mild, moderate or severe based on the location and quality of the blood seen[16], as described below:

- Mild: presence of echogenic fluid in the pouch of Douglas.
- Moderate: presence of blood clots within the pouch of Douglas.
- Severe: presence of blood clots within the pouch of Douglas and the utero-vesical fold and/or above pelvic brim.

The location of the EP was defined based on the site of the pregnancy in relation to other pelvic structures[17], as followed:

- Tubal EP – a gestational sac or solid adnexal swelling, typically located high in the pelvis and separable from the ipsilateral ovary on palpation with the transvaginal ultrasound probe. The corpus luteum is visualised within the ipsilateral or contralateral ovary.
- Ovarian EP– identified within the ovarian cortex as a gestational sac or solid swelling surrounded by healthy ovarian tissue. A corpus luteum is usually, but not always, seen within the ipsilateral ovary. On palpation, it is not possible to separate the EP from the ovary. Doppler examination typically demonstrates blood supply to the EP separate form the vascular corpus luteum.
- Abdominal EP– solid swelling or gestational sac fixed deep in the pelvis within the pouch of Douglas. Pregnancy could also be implanted into the pelvic side wall or into the broad ligament with detectable blood supply on Doppler examination.

The serum β-hCG and progesterone levels were taken in all clinically stable patients. The results of these biochemical tests were used to facilitate selection of women with a visible EUEP for either surgical or conservative management. In all women with initial inconclusive ultrasound scan findings ('pregnancy of unknown location')[18] the results of the blood tests

were used to plan follow up visits, but never to make a presumptive diagnosis of EP or to trigger medical or surgical intervention.

In our Unit records of all women diagnosed with EP and those with 'pregnancy of unknown location' are stored in a dedicated clinical file which is updated on daily basis. In women selected for surgical management, intraoperative findings and histology reports are recorded electronically and checked by our nursing and clinical staff to determine the need for further follow up.

All women diagnosed with EUEP who presented with severe pain were managed surgically on an emergency base depending of the severity of the clinical symptoms. Other indications for surgery were the presence of a live embryo on ultrasound scan, EUEP measuring >3cm in mean diameter, moderate or severe haemoperitoneum, or initial β-hCG above 1500IU/L. Women with visible EUEPs and β-HCG levels rising above 1500IU/L on follow up visits were also managed surgically, as well as women who were suitable for conservative management but opted for surgery instead. Surgical management was also offered to pregnant women with non-diagnostic ultrasound findings who presented with severe pain and evidence of severe haemoperitoneum.

All women in this study proceeded to have minimally invasive (laparoscopic) surgical management, which was performed by the on-call clinical team. The approach to surgical treatment was standardised. For tubal EP, in the presence of a healthy contralateral tube, a salpingectomy was performed in preference to a salpingotomy. Salpingotomy was carried out in women with evidence of contralateral tubal abnormalities and at the woman's request[2]. In ovarian EP, the trophoblastic tissue was excised from the surrounding healthy ovarian cortex with the aim of preserving the ovary. Abdominal EPs were separated from the surrounding structures and excised from the pelvic side wall. Tubal EP where a salpingotomy was

performed and all abdominal and ovarian EP were followed up in the EPU to confirm that the β-HCG levels were declining, given the possibility of residual trophoblastic tissue.

Histological analysis was performed on all surgical specimen collected at surgery. Where an EP was not confirmed at surgery or on histological analysis, follow-up was carried out in the EPU with serial serum β-hCG to confirm diminishing levels.

Statistical analysis of the data was performed using Statistical Package for Social Sciences (SPSS, version 25, 2017). The baseline variables for normality of distribution were tested using Shapiro-Wilk test. The diagnostic performance of ultrasound for the diagnosis of ectopic pregnancy was expressed as PPV and sensitivity. These measures were calculated for each of the five ultrasonographic morphological groups.

We sought advice from the Joint Research Office of University College London and University College London Hospital regarding ethical approval and were advised that formal ethics approval was not needed for this study as the data were anonymised and were analysed within the EPU.

Results

During the study period, 26,401 pregnant women attended the EPU with clinical symptoms early pregnancy complications. Overall 1241/26401 (4.7%, 95% CI 4.5-5.0) were diagnosed with tubal, ovarian or abdominal EP on TVS. There were 721 (58.1%, 95% CI 55.3-60.8) women who were surgically managed for confirmed or suspected EP, whereas the others were managed either expectantly or medically. Flowchart of patients is shown in Fig.1

The mean age of the women who had surgery was 32.0 years (range 17-47). There were 270 (37.4%) multiparous and 79 (11%) had history of a previous EP. The mean gestational age at

time of diagnosis of EP was 6 weeks and 4 days (range 3 weeks and 6 days – 15 weeks and 5 days). This was based either on menstrual period dates or conception dates in women who had undergone assisted conception. The initial presenting clinical symptoms of women who received surgical treatment are shown in Table 1.

Presenting Symptom	**N (%, 95% CI)**
Pain & Bleeding	429/721 (59.5%, 95% CI 55.9-63.0)
Bleeding only	133/721 (18.4%, 95% CI 15.8-21.4)
Pain only	108/721 (15.0%, 95% CI 12.6-17.8)
Asymptomatic	51/721 (7.1%, 95% CI 5.4-9.2)

Table 1: Initial presenting symptoms

There were 598 out of 721 (82.9%, 95% CI 80.0-85.5) cases diagnosed with an EUEP at the first TVS and 94 (13.0%, 95% CI 10.8-15.7), 22 (3.1%, 0.95 CI 2.0-4.6) and 7 (0.97%, 95% CI 0.47-2.0) who required an additional one, two or three scans, respectively, before the diagnosis of EUEP was made.

In 11 (1.5%, 95% CI 0.9-2.7) cases, the patient presented in severe pain or were haemodynamically unstable with a positive pregnancy test and TVS showing significant haemoperitoneum with no evidence of intrauterine or extrauterine pregnancy. Although no EUEP was visualised on TVS in those cases, surgery was indicated, given the clinical suspicion and the presenting symptoms.

A blood test for β-hCG and progesterone levels was taken in 538/721 (74.6%, 95% CI 71.3-77.6) of the cases. The overall median β-hCG was 1720mU/l (IQR 701-3770) and the progesterone was 18.4nmol/l (IQR 18.4-37) on the most recent blood test prior to surgery. The median β-hCG (mU/L) levels in morphological types I, II and III were 9150 (IQR 4420-22560),

6660 (IQR 3250-15500) and 1980 (1140-2990) respectively, which were higher than those with morphological types IV and V, which were 1920 (1080-3320) and 761 (334-1940) respectively.

591/721 (82.0%, 95% CI 79.0-84.6) women were admitted for surgery after the initial TVS, whilst 130 (18.0% (95% CI 15.4-21.0) were initially managed conservatively and had surgery after a period of follow up. The indications for surgery are shown in Table 2.

Primary indication for surgery	**N (%, 95% CI)**
Significant haemoperitoneum	199 (27.6, 24.5-31.0)
High initial β-hCG >1500 IU/L	136 (19.0, 16.2-21.9)
Severe pain	122 (16.9, 14.4-19.8)
Rising β-hCG on follow up	119 (16.5, 14.0-19.4)
Live EUEP	87 (12.1, 9.9-14.7)
Patient choice	45 (6.2, 4.7-8.3)
Size of EUEP >3cm	13 (1.8, 1.1-3.1)
Total	721(100)

Table 2: Primary indications for surgery

Of the 721 cases who underwent surgery 717 EUEP were confirmed. The operative findings revealed 702 (97.4%, 95% CI 95.9-98.3) tubal, 12 (1.7%, 95% CI 1.0-2.9) ovarian and 3 (0.4%, 95% CI 0.1-1.2) abdominal EP. There were 13 (1.8%, 95% CI 1.1-3.1) heterotopic pregnancies with a concomitant intrauterine and tubal EP.

Overall 710 women were diagnosed with an EUEP on TVUSS out of which 706 (99.4%, 95% CI 98.6-99.8) had the pre-operative ultrasound diagnosis or EUEP confirmed at laparoscopy. There were four false positive cases, which were managed operatively due to associated severe pain and/or evidence of significant haemoperitoneum. Two women had haemorrhagic

corpus luteum at laparoscopy. In one case no EUEP was seen at laparoscopy, but at post-operative follow up a tubal EP was still visible on TVS; the serum β-hCG remained persistently high before eventually declining and the pregnancy resolved spontaneously without the need for any further intervention. The final case was followed up with post-operative serial β-hCG levels, which continued to rise for a week post operatively before reducing, with the pregnancy resolving without its site found on further TVS.

Of the 11 women who presented with severe pain and significant haemoperitoneum had immediate surgery before an EUEP was visualised on pre-operative TVS, all were found to have an EUEP at laparoscopy.

The overall PPV of TVS in the diagnosis of EUEP was 99.4% (95% CI 98.6-99.8) with a sensitivity of 98.5% (95% CI 97.3-99.1). The relative frequency and PPV of each ultrasonographic morphological type is shown in Table 3. There was no statistically significant difference in the accuracy of pre-operative ultrasound diagnosis for the five morphological types of extra-uterine ectopic pregnancy (P>0.05).

Morphological type	**n (%, 95% CI)**	**Positive Predictive Value % (95% CI)**
I: A gestational sac containing an embryo with visible cardiac activity	92 (12.8, 10.5-15.4)	100 (96.0-100)
II: A gestational sac containing an embryo with no visible cardiac activity	28 (3.8 ,2.7-5.6)	100 (87.9-100)
III: A gestational sac containing only a yolk sac, with no visible embryo	85 (11.8, 9.6-14.4)	100 (95.7-100)
IV: An empty gestational sac, with no	245	99.6 (97.8-99.9)

visible additional structures	(34.0, 30.6-37.5)	
V: A solid, homogenous mass	260 (36.1, 32.6-39.6)	98.9 (96.7-99.6)

Table 3: The relative frequency and PPV of TVS depending on morphological type of EUEP using laparoscopic diagnosis as the reference standard.

There were ten (1.4% 95% CI 0.8-2.5) cases where the laterality of the EUEP on pre-operative TVS differed from the operative findings.

The location of EUEP did not affect the sensitivity of ultrasound diagnosis as all ovarian and abdominal EPs were identified on pre-operative TVS. The diagnosis of abdominal pregnancy was confirmed in all three cases. However, 9/12 (75%) ovarian EP were initially misdiagnosed as tubal and 5/702 (0.7%) of tubal EP were misclassified as ovarian.

The presence of trophoblastic tissue was confirmed on post-operative histology in 681/716 (95.1%, 95% CI 93.3-96.5) following surgical excision of EUEP whilst in the remaining 35 the histology did not confirm the presence of trophoblastic tissue. Each of these cases was followed up with serial blood tests. In all of these women, the β-hCG returned to pre-pregnancy levels without the need for any further intervention.

The results are summarised in Figure 1.

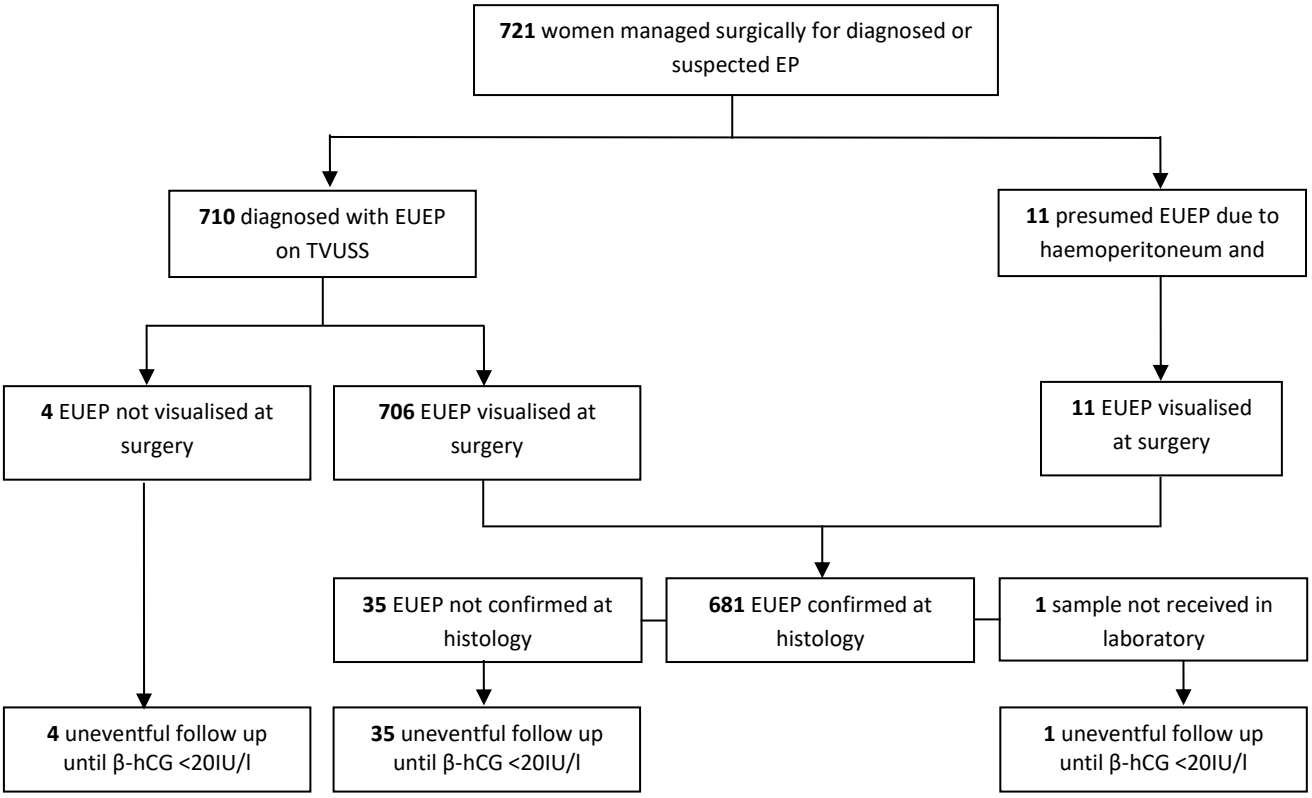

Figure 1: Flowchart of patients attending the EPU diagnosed with EUEP and managed surgically.

Discussion

The data of this study indicate that pre-operative ultrasound diagnosis of EUEP is highly sensitive (accurate?). The overall PPV was 99.4%. False positive diagnosis only occurred in EUEPs presenting as solid inhomogeneous swellings or with empty gestational sacs. They were very few of these cases in our cohort and we found no significant difference in the PPV between different morphological types of EUEP. This is an critical observation as 71% of all EUEPs undergoing surgery presented as empty sacs or solid swellings on TVS. This is similar to the findings by Condous et al who reported empty sacs and solid swelling in 58% of their population of EPs[21]. If these morphological types had been considered non-specific, nearly three quarters of all women with EUEPs in our study would have been offered additional blood

tests and follow-up scans. This type of approach not only increases costs of medical care but also caused further social disruption to patients and their family, and in addition would have also increased the risk of rupture and intra-abdominal bleeding due to delays in initiating surgical management.

The majority of EUEP (82.9%; 95%CI 80-85.5) in this study were detected on the initial ultrasound examination at a rate comparable to that published by Kirk et al [9,19] who an overall diagnostic rate of 73.9 % (95% CI 65.1-81.6) at the first visit. Although we measured β-hCG and progesterone in all women with initial non-diagnostic TVS, they were only used to plan follow up visits. In clinically stable women, the diagnosis of EUEP was always based on positive identification on TVS. Thus our results also indicate that using an arbitrary β-hCG level >1500IU/l to diagnose EUEP instead of TVS is not safe as 53% of women with clinically significant EUEP present with β-hCG levels below this threshold.

We found that in women with significant intra-abdominal bleeding it is not always possible to visualise an EUEP on TVS. All 11 women in our series who had positive urine pregnancy test and significant haemoperitoneum were diagnosed with ruptured EUEP at surgery. These findings suggest that the assessment of presence and quality of haemoperitoneum should be routinely performed in all women with clinical suspicion of EUEP.

One woman with a negative laparoscopy had continuing evidence of tubal EP on post-operative TVS with a persistently high serum hCG. These findings indicated that it is likely that the EP was missed at laparoscopy, rather than being misdiagnosed on ultrasound scan.

Three quarters of ovarian pregnancies in our series were misdiagnosed as tubal pregnancies on ultrasound scan. Ovarian pregnancies are often complicated by significant haemoperitoneum which makes the examination difficult due to tenderness and blurring of the ovarian and ectopic margins. We suggest ovarian pregnancy should be considered in differential diagnosis

of all women with EUEP and evidence of moderate or severe haemoperitoneum. However, in women with small, unruptured ovarian pregnancies the ultrasound diagnosis is usually straightforward which facilitates their detection and excision of ectopic villous tissue from the ovary at surgery.

We were unable to obtain histological confirmation of ultrasound and surgical diagnosis of EUEP in 4.9% of cases. This is in agreement with previous studies which have shown that in some women with spontaneous tubal miscarriage or rupture the villous tissue may be lost and thus cannot identified within the large volume of blood clots[20]. Traditionally histological identification of villous tissue or trophoblastic cells has been considered as the golden standard for the confirmation of the diagnosis of EP [21]. Our data shows that histological diagnosis is associated with a relatively higher false negative rate compared to surgery. This suggest that in modern clinical practice of EUEP, the surgical diagnosis would be a more appropriate reference standard. However, all women with negative histology should be followed by serial serum β-hCG to detect women in whom villous tissue may have been incompletely excised or missed. In some women, villous tissue left in the abdominal cavity may re-implant and continue to grow, which is another reason to arrange post-operative blood tests.

The issue of diagnostic reference standard is further complicated by the fact that in modern practice a large proportion of women with ultrasound diagnosis of EUEP are managed conservatively. In our study, 42% of women did not have surgery, the majority of which were managed expectantly. Ultrasound is the only method which can be used to follow-up???? EUEP in these women. The accuracy of TVS in these women could only be partially assessed by looking at the subgroup of women who had surgery following failed conservative management.

Another important finding of our study is that in 1.4% of cases the laterally of EUEP on TVUSS was not confirmed at surgery. These discrepancies are more likely to occur in women with acute uterine latero-flexion and in those with severe adhesions. Although we believe that laterality of EUEP should always be reported, this minor inaccuracy of TVS diagnosis should be recognised and laterality should not be specified when women are consented for salpingectomy or salpingotomy.

Operator dependence is one of major limitations of ultrasound and many diagnostic models have been developed over the years to facilitate detection of conditions which are difficult to diagnose, such as ovarian cancer. However, the studies have also shown that experienced ultrasound operators tend to perform better than many of the diagnostic models[22]. In our department we have minimised the effect of operator dependence by ensuring that expert examiners are always available to support sonographers and less experienced clinicians working together. Our protocols require that every diagnosis of EP is checked by an expert operator to minimise the risk of false positive findings. All women with non-diagnostic scans are also re-examined by experienced operators to reduce the risk of false negative diagnoses. As a result, the diagnostic output of the department is determined by the quality of the best and most experienced operator, regardless of the quality of other examiners. We believe that this unit setup is the one of key factors which enabled us to achieve such a high level of diagnostic accuracy.

In conclusion, our results show that with the optimal organisational set up ultrasound is a reliable method for diagnosis of EUEP regardless of its morphological type and exact location. We have also shown that this high level of accuracy could be achieved without reliance on the results of biochemical tests. This finding is of importance to clinical practice and it should help to provide safer and more cost-effective care to women with EUEPs.

References

1. Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J, Springett A.. Saving Mothers' Lives: Reviewing Maternal Deaths To Make Motherhood Safer: 2006–2008. British Journal of Obstetrics and Gynaecology. 2011;**118**:81-84.

2. Diagnosis and management of ectopic pregnancy: Green Top Guideline. British Journal of Obstetrics and Gynaecology. 2016;**123**:15–55.

3. Mavrelos D, Nicks H, Jamil A, Hoo W, Jauniaux E, Jurkovic D. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. Ultrasound in Obstetrics and Gynaecology. 2013;**42**:102–7.

4. Jauniaux E, Jurkovic D. Ectopic pregnancy: 130 years of medical diagnostic challenges. BJOG 2018; in press.

5. Beck P, Broslovsky L, Gal D, Tancer ML. The role of laparoscopy in the diagnosis of ectopic pregnancy: a plea for conservative management. International Journal of Gynaecology and Obstetrics. 1984;**22**:307-9.

6. Sowter M, Farquhar CM. Ectopic pregnancy: An update. Current Opinion in Obstetrics and Gynecology. 2004;**16**:289-93

7. Kobayashi M, Hellman LM, Fillisti LP. Ultrasound: An aid in the diagnosis of ectopic pregnancy. American Journal of Obstetrics and Gynecology. 1969;**103**:1131–40.

8. Brown D, Doubilet P. transvaginal sonography for diagnosing ectopic pregnancy: positivity criteria and performance characteristics. Journal of Ultrasound in Medicine. 1994;**13**:259–66.

9. Kirk E, Papageorghiou AT, Condous G, Tan L, Bora S, Bourne T. The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. Human Reproduction. 2007;**22**:2824–8.

10. Bignardi T, Alhamdan D, Condous G. Is ultrasound the new gold standard for the diagnosis of ectopic pregnancy? Seminars in Ultrasound, CT and MRI. 2008;**29**:114–20.

11. Casikar I, Reid S, Condous G. Ectopic pregnancy: Ultrasound diagnosis in modern management. Expert Rev Obstetrics Gynecol. Clinical Obstetrics and Gynecology. 2012;**55**:402-9

12. Cacciatore B, Stenman U, Ylöstalo P. Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000 IU/L. British Journal of Obstetrics and Gynaecology. 1990;**97**:904–8.

13. Kadar N, DeVore G, Romero R. Discriminatory hCG zone: its use in the sonographic evaluation for ectopic pregnancy. Obstetrics and Gynecology. 1981;**58**:156–61.

14. Nadim B, Infante F, Lu C, Sathasivam N, Condous G. Morphological ultrasound types known as ‘blob’ and ‘bagel’ signs should be reclassified from suggesting probable to indicating definite tubal ectopic pregnancy. Ultrasound in Obstetrics and Gynaecology. 2018;**51**:543–9.

15. Education and Practical Standards Committee, European Federation of Societies for Ultrasound in Medicine and Biology. Minimum training recommendations for the practice of medical ultrasound. Ultraschall Der Medizin. 2006;**27**:79–105.

16. Rajah K, Goodhart V, Zamora K, Amin T, Jauniaux E, Jurkovic D. How to measure size of tubal ectopic pregnancy on ultrasound. Ultrasound in Obstetrics and Gynaecology. 2018;**52**:103–9.

17. Jurkovic D, Mavrelos D. Catch me if you scan: Ultrasound diagnosis of ectopic pregnancy. Ultrasound in Obstetrics and Gynaecology. 2007;**30**:1–7.

18. Barnhart K, van Mello NM, Bourne T, Kirk E, Van Calster B, Bottomley C, Chung K, Condous G, Goldstein S, Hajenius PJ, Mol BW, Molinaro T, O'Flynn O'Brien KL, Husicka R, Sammel M, Timmerman D. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. Fertility and Sterility. 2011;**95**:857–66.

19. Lattouf I, Lu C, Pixton S, Reid S, Condous G. Is there a difference in the behaviour and subsequent management of ectopic pregnancies seen at first scan compared to those ectopic pregnancies which commence as pregnancies of unknown location? Australian and New Zealand Journal of Obstetrics and Gynaecology. 2016;**56**:107–12.

20. Farahani L, Sinha A, Lloyd J, Islam M, Ross JA. Negative histology with surgically treated tubal ectopic pregnancies – A retrospective cohort study. European Journal of Obstetrics and Gynaecology. 2017;**213**:98–101.

21. Condous G, Okaro E, Khalid A, Lu C, Huffel S, Timmerman D, Bourne T. The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery. Human Reproduction. 2005;**20**:1404–9.

22. Nunes N, Ambler G, Foo X, Naftalin J, Derdelis G, Widschwendter M, Jurkovic D. Comparison of two protocols for the management of asymptomatic postmenopausal women with adnexal tumours – a randomised controlled trial of RMI/RCOG vs Simple Rules. British Journal of Cancer. 2017;**116**:584.