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Physical resolution of tubal ectopic pregnancy on ultrasound imaging following successful expectant management

BIOGRAPHY

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KEY MESSAGE

A complete physical resolution of tubal ectopic pregnancies managed expectantly is achieved within 78 days following the return of beta-HCG to non-pregnant levels in 95% of women. This information will help to improve safety of expectant management of ectopic pregnancies and improve counselling of women who are planning further pregnancies.

ABSTRACT

Research question: What is the time required for complete physical resolution of tubal ectopic pregnancies diagnosed on ultrasound imaging in women undergoing successful expectant management?

Design: A prospective observational cohort study of 177 women who had successful expectant management of tubal ectopic pregnancy, who attended a single Early Pregnancy Unit between January 2014 and December 2018. All participants were monitored until their serum beta-human chorionic gonadotrophin (beta-HCG) dropped to non-pregnant concentrations and with 2-weekly follow-up ultrasound scans until resolution of the pregnancy.

Results: A total of 112/177 (63.3%, 95% confidence interval [CI] 55.7–70.4) of tubal ectopic pregnancies were indiscernible on ultrasound 2 weeks after serum beta-HCG had returned to non-pregnant concentrations. In 8/177 (4.5%, 95% CI 2.0–8.7), physical resolution took longer than 78 days. There was a positive correlation between biochemical and physical resolution of tubal ectopic pregnancy ($r = 0.21$, $P = 0.006$).

Conclusions: Physical resolution of tubal ectopic pregnancy is often prolonged and is positively correlated with initial and maximum beta-HCG concentrations. Results of this study indicate that beta-HCG resolution cannot be used as the end-point of expectant management of tubal ectopic pregnancy, which should be considered when counselling women and planning for future pregnancies.

KEYWORDS

INTRODUCTION

Tubal ectopic pregnancy (TEP) is the most common of ectopic gestation. Traditionally the treatment of TEP was surgical due to the perceived risk of maternal morbidity and mortality associated with conservative management (*Kobayashi et al., 1969*). Advances in non-invasive diagnosis have enabled earlier diagnosis of TEP, usually before serious complications occur, which facilitated the use of medical treatment with methotrexate (*Mol et al., 2008*). In addition, improved sensitivity of transvaginal ultrasound (TVUS) imaging has enabled detection of small, failing TEP, which are often destined to resolve naturally without the need for any medical interventions (*Dooley et al., 2019*). This has led to the introduction of expectant management, which has now been recognized as an acceptable option to manage clinically stable women diagnosed with small TEP associated with low serum beta-human chorionic gonadotrophin (beta-HCG) concentrations (*National Institute for Health and Care Excellence, 2019*). Previous studies have shown that nearly a third of all women diagnosed with TEP on ultrasound imaging can be successfully managed expectantly, thus avoiding the costs, complications and side-effects of medical or surgical treatment (*Mavrelos et al., 2013*).

There has been a previous investigation of the serum beta-HCG clearance times in clinically stable women diagnosed with TEP who were managed expectantly, in which it was demonstrated that the median time for beta-HCG to reduce to non-pregnant concentrations is 18 days and that the clearance time is directly associated with the maximum and initial rate of decline of the serum beta-HCG concentration (*Mavrelos et al., 2015*). Although the decline of the serum beta-HCG to non-pregnant concentrations is considered to be the end-point of successful non-surgical treatment of TEP, there are reports in the literature of women with a negative pregnancy test presenting with ruptured TEP (*Kalinski and Guss, 2002*; *Lonky and Sauer, 1987*). Additionally, there are published reports of chronic TEP, with women presenting with a negative pregnancy test and found to have a persistent solid adnexal swelling on ultrasound examination (*Drakopoulos et al., 2014*; *Savelli et al., 2013*). In view

of this, it is likely that trophoblastic tissue will persist within the Fallopian tube for some time after all clinical and biochemical signs of pregnancy have resolved. Previous studies have investigated small cohorts of women who have been managed with methotrexate therapy, with follow-up ultrasound scans until the ectopic pregnancy was no longer visible (*Brown et al., 1991*). The study by *Brown et al. (1991)* demonstrated that in approximately 40% of cases, the ectopic pregnancy remained visible on ultrasound scan after the serum beta-HCG had returned to non-pregnant concentrations; and one case took 180 days to resolve. It is not known, however, in what proportion of women managed non-surgically the trophoblastic tissue will remain within the Fallopian tube, how long it will take to resolve and what the possible associated short- and long-term risks are.

The aim of this study was to monitor the changes in size of TEP which were successfully managed expectantly, after the resolution of serum beta-HCG concentrations. The length of time taken for full physical resolution of TEP was assessed and all complications during this follow-up period were recorded.

MATERIALS AND METHODS

This was a prospective observational cohort study performed at a single Early Pregnancy Unit (EPU), carried out over a 5-year period between January 2014 and December 2018. All women who had a positive urine pregnancy test and presented to the clinic either with suspected early pregnancy complications or with a history of previous miscarriage or ectopic pregnancy were included. All women were assessed clinically and underwent a TVUS using high-end equipment (Voluson E8, GE Medical Systems, Milwaukee, WI, USA). All examinations were performed either by a consultant gynaecologist experienced in early pregnancy care or by a clinical fellow working under their direct supervision. Clinical data, ultrasound images and the results of biochemical tests were stored on a dedicated clinical database (PIA Fetal Database, version 2.23; Viewpoint Bildverarbeitung GmbH, Munich, Germany) and were available for review during a woman's follow-up visit.

The ultrasound diagnosis of a TEP was based on direct visualization of a

structure with typical appearance of an extrauterine pregnancy separable from the ipsilateral ovary (*Dooley et al., 2019*). The morphological type of the TEP was classified based on the following defined characteristics:

- Gestational sac containing an embryo, with visible cardiac activity.
- Gestational sac containing an embryo, with no visible cardiac activity.
- Gestational sac containing only a yolk sac, with no visible embryo.
- Empty gestational sac, with no visible additional structures.
- Solid, homogenous swelling.

Surgical management was offered to women who were diagnosed with a TEP and had presented with severe pain or were found to have significant hemoperitoneum on ultrasound examination. Where ultrasound revealed either a live embryo or TEP with a mean diameter of more than 3 cm, surgical management was also recommended.

Women who had no or only mild symptoms were offered expectant management, pending the results of the serum beta-HCG concentrations. Women were confirmed as eligible for expectant management if their initial serum beta-HCG concentration was less than 1500 IU/l. Where the concentration was above this, women were advised to have surgery. Medical management is not routinely offered in the study unit and is usually only considered in the context of clinical trials.

Women selected for expectant management were managed on an outpatient basis. An individualized follow-up plan was developed by one of the EPU consultants based on a woman's initial blood results and TVUS findings. They were advised to return to the clinic or the emergency department if they experienced increased abdominal pain, before their scheduled appointment. They were also advised against long-distance travel and were made aware of the small risk of tubal rupture and the need for emergency surgery.

In women with beta-HCG concentrations showing sustained rise on repeated measurements, surgical management was recommended. Expectant management was discontinued if women reported a significant increase in their abdominal

pain or if they opted for surgical management during the follow-up.

The study population included all women diagnosed with a TEP on ultrasound scan who were managed expectantly and whose beta-HCG concentrations had reduced to non-pregnant concentrations without the need for medical intervention. The first stage of follow-up involved monitoring of the serum beta-HCG concentrations at intervals of between 2 and 7 days, until they declined to non-pregnant concentrations (<20 IU/l) or until the urinary pregnancy test was negative. The maximum serum beta-HCG concentration (HCG-MAX) during this period was recorded, as well as the beta-HCG concentration at the first evaluation after the maximum concentration (HCG-SUB), and the daily beta-HCG change between HCG-MAX and HCG-SUB (HCG-TREND, % change/day) was calculated. The time expressed as the number of days taken for the serum beta-HCG to reduce to non-pregnant concentrations (tHCG) was also documented.

The second stage of the follow-up process included a TVUS 2 weeks after the beta-HCG had resolved to non-pregnant concentrations. Women with no evidence of ectopic trophoblastic tissue on ultrasound imaging were discharged from the clinic. In those women who had evidence of persistent TEP on the initial follow-up scan, further follow-up visits at 2-weekly intervals were arranged

until a complete resolution of pregnancy was confirmed. The number of days between the beta-HCG concentration reducing to non-pregnant concentrations and the ultrasound scan that confirmed resolution of the TEP (tUSS) was documented. The total number of days from the initial ultrasound diagnosis of TEP to the final ultrasound examination confirming resolution (tTOT) was also documented.

Statistical analysis of the data was performed using SPSS for Windows, Version 25 (IBM Corp., Armonk, NY, USA). In order to show a mean difference of 30 days between negative pregnancy test and complete physical resolution of pregnancy on ultrasound scan, with confidence level of 95% and 80% power, it was calculated that 170 women would need to be recruited.

The number and percentage in each category were calculated for categorical variables. The mean and SD were calculated for normally distributed continuous variables, with median and interquartile range calculated if not normally distributed. Analysis of variance was used to compare different ultrasound morphologies at the time of diagnosis and variables found to follow a normal distribution, whilst the Kruskal–Wallis test was used for non-normally distributed variables. Spearman's rank correlation was used to examine the association between the study variables and the time measurements

for resolution of TEP (tHCG, tUSS and tTOT). The level of significance was set at <0.05 throughout.

The study was registered with the Research Registry (Unique Identifying Number: 4867). Follow-up with TVUS in women diagnosed with TEP who opted for conservative management until physical resolution is confirmed is a part of standard clinical practice at the study centre. In view of this, the study did not require formal ethics approval given that patient identifiable data was not accessible to anyone outside the clinical care team.

RESULTS

During the study period, 14,944 women attended the EPU with suspected early pregnancy complications. A total of 718/14,944 (4.8%, 95% CI 4.5–5.2) were diagnosed with a TEP.

The flow chart of women in this study is shown in FIGURE 1. A total of 206 women had successful expectant management of TEP defined by decline of beta-HCG to non-pregnant concentrations. They were all invited to attend for further follow-up TVUS to document complete physical resolution of TEP. There were 29/206 (14.1%) women who did not complete follow-up: six attended for one or more visits, whilst 23 did not attend for any follow-up after decline of beta-HCG to non-pregnant concentrations. The study population included a total of 177
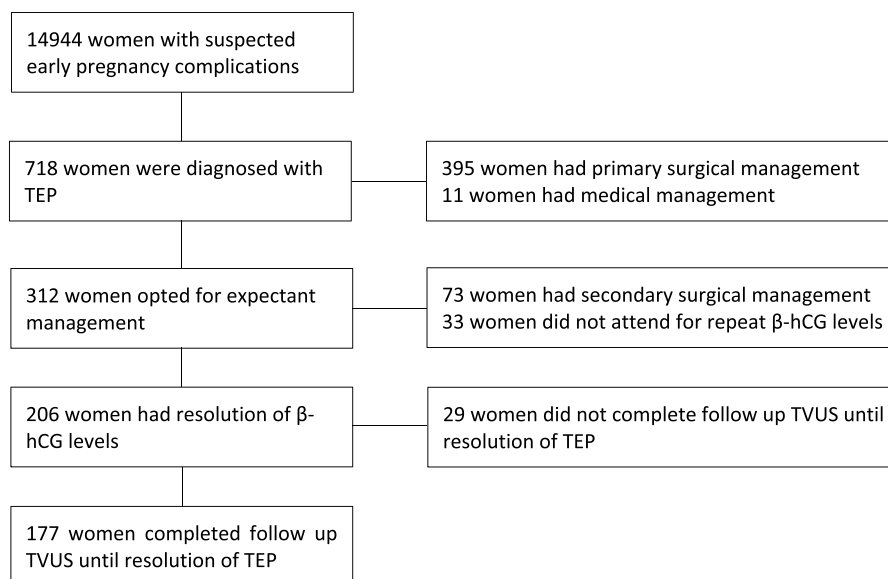

FIGURE 1 Flow chart of participants through the study. TEP = tubal ectopic pregnancy; TVUS = transvaginal ultrasound scan.

TABLE 1 ULTRASOUND MORPHOLOGICAL TYPE AT TIME OF DIAGNOSIS OF TEP FOR CASES MANAGED EXPECTANTLY (N = 177)

Morphological type	n (%, 95% CI)
Type 5	107 (60.5, 52.8–67.7)
Type 4	57 (32.2, 25.4–39.6)
Type 3	13 (7.3, 4.0–12.2)

TEP = tubal ectopic pregnancy.

women who attended the follow-up until complete physical resolution of the TEP was confirmed on TVUS.

The average age was 32.7 years (SD 5.4 years) and 120/177 (67.8%, 95% CI 60.4–74.6) women were nulliparous. Most women [165/177 (93.2%, 95% CI 88.5–96.4)] had conceived spontaneously and 22/177 (12.4%, 95% CI 8.0–18.2) had a history of a previous TEP. The mean gestational age at the time of diagnosis was 6 weeks and 2 days (SD 1 week and 3 days). One hundred and ten (62.2%, 95% CI 54.6–69.3) women who were subsequently diagnosed with a TEP and managed expectantly presented with pain and bleeding, whilst 43 (24.3%, 95% CI 18.2–31.3) presented with bleeding only, 15 (8.5%, 95% CI 4.8–13.6) with pain only, whilst 9 (5.1%, 95% CI 2.4–9.4) were asymptomatic and presented due to a previous history of ectopic pregnancy or miscarriage.

A total of 145/177 (81.9%, 95% CI 75.4–87.3) women were diagnosed with a TEP on their first scan whilst the remaining patients had an initial inconclusive TVUS and were diagnosed with a TEP on follow-up examinations.

The morphological types of TEP at the first diagnostic TVUS are shown in **TABLE 1**. The mean diameter of the TEP was 12.1 mm (SD 4.1 mm). Evidence of haematosalpinx was found in 9/177 (5.1%, 95% CI 2.4–9.4) women.

The median serum beta-HCG and progesterone concentrations on the initial blood tests were 198 mIU/l (IQR 80–480) and 8.2 nmol/l (IQR 3.5–27.2), respectively. In 130/177 (73.4%, 95% CI 66.3–79.8) women the initial beta-HCG concentration represented the maximum concentration, with the remainder having an increased beta-HCG concentration on follow-up blood tests before later resolving. The median overall maximum beta-HCG concentration was 218 mIU/l (IQR 92–516).

The median tHCG was 14 days (**TABLE 2**). There was a significant difference ($P = 0.004$) between the three morphological types of TEP, with tHCG being 9 days (69.2%) longer in morphological type 3 compared with type 5.

It was found that 112/177 (63.3%, 95% CI 55.7–70.4) women had resolution of the TEP on the first follow-up TVUS, which was performed at a median of 14 (IQR 14–15) days after the beta-HCG had declined to non-pregnant concentrations. In women who continued to have a visible TEP on the first TVUS, the mean diameter had reduced by a median of 32.0% (IQR 12–56) in comparison to the initial scan. The median tUSS was 15 days with no significant difference between the three morphological types of TEP (**TABLE 2**). There were no cases where the TEP did not fully resolve during the period of follow-up.

A Kaplan–Meier plot demonstrating the tUSS is shown in **FIGURE 2**; 90% and 95% of TEP had resolved 57 and 78 days after the serum beta-HCG concentration had declined to non-pregnant concentrations, respectively. In 8/177 (4.5%, 95% CI 2.0–8.7), physical resolution took longer than 78 days. There was a significant positive correlation between tUSS and tHCG ($r = 0.21$, $P = 0.006$), but not with any other variable (**TABLE 3**).

Ten out of 177 (5.6%, 95% CI 2.7–10.1) women had unscheduled attendances to the clinic after the beta-HCG concentrations had resolved to non-pregnant concentrations and before the TEP had resolved from the TVUS; one woman attended with bleeding and nine with pelvic pain. A small unilateral haematosalpinx was found on TVUS in one woman, with a new haemorrhagic corpus luteum cyst found in another. In the remaining eight women, no cause for their symptoms was identified. None of these women required surgical treatment.

At the TVUS that confirmed complete resolution of the TEP, 5/177 (2.8%, 95% CI 0.43–5.37) women had evidence of tubal pathology: four were found to have a hydrosalpinx and one a persistent haematosalpinx. Residual pain was reported by 4/177 (2.3%, 95% CI 0.6–5.7) women and 2/177 (1.1%, 95% CI 0.1–4.0) complained of persistent irregular bleeding. None of them required surgical intervention.

The median tTOT was 37 days (IQR 26–56) with 90% and 95% of TEP resolving 87 and 102 days after the initial diagnosis, respectively. There were no significant differences in tTOT between each morphological type of TEP (**TABLE 2**). It was shown that tTOT was positively correlated with the first beta-HCG measurement (beta-HCG-INIT;

TABLE 2 RESOLUTION TIMES FOR ALL PARTICIPANTS AND A COMPARISON BETWEEN THE DIFFERENT MORPHOLOGICAL TYPES OF TEP (N = 177).

	All patients (n = 177) Median (IQR)	Type 5 (n = 107) Median (IQR)	Type 4 (n = 57) Median (IQR)	Type 3 (n = 13) Median (IQR)	P-value
tHCG	14 (10, 22)	13 (10, 18)	16 (11, 26)	22 (19, 28)	0.004
tUSS	15 (14, 39)	15 (14, 37)	16 (14, 36)	18 (14, 67)	0.48
tTOT	37 (26, 56)	34 (25, 51)	40 (28, 57)	46 (36, 91)	0.12

IQR = interquartile range; TEP = tubal ectopic pregnancy; tTOT = total number of days from the ultrasound diagnosis of TEP to the ultrasound scan confirming its resolution; tUSS = number of days between the beta-HCG level reducing to non-pregnant levels and the scan that confirmed resolution of the TEP.
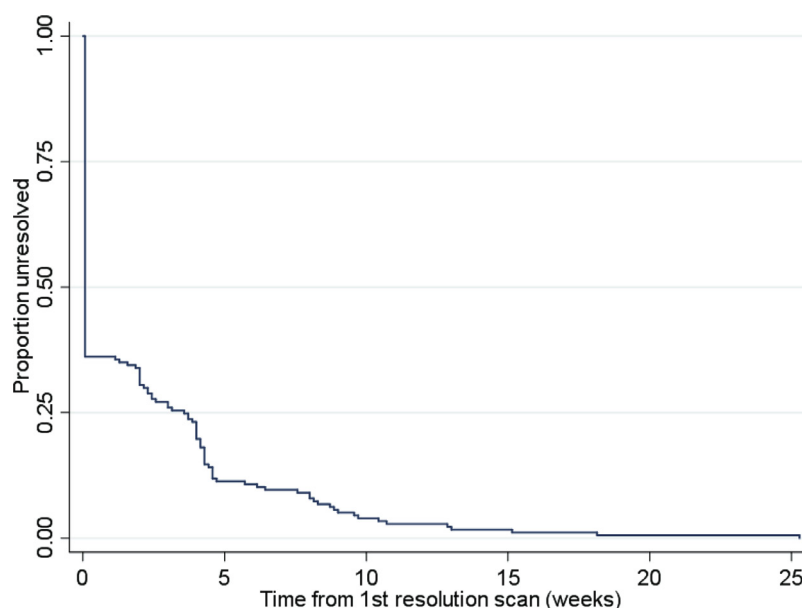
FIGURE 2 Kaplan–Meier plot showing the number of days between the beta-HCG concentration reducing to non-pregnant levels and the scan that confirmed resolution of the TEP (tUSS) (*n* = 177).

TABLE 3 ASSOCIATIONS BETWEEN TUSS AND OTHER STUDY VARIABLES (*N* = 177)

	Correlation coefficient	*P*-value
Maternal age	0.04	0.56
Gestational age	–0.13	0.11
First beta-HCG measurement	0.14	0.07
First progesterone measurement	–0.03	0.68
beta-HCG-MAX	0.12	0.10
beta-HCG-TREND	–0.13	0.10
tHCG	0.21	**0.006**
Mean diameter of TEP (at initial diagnosis)	0.11	0.15

beta-HCG-MAX, maximum serum beta-HCG level during the period of follow-up; beta-HCG-TREND, daily % change between beta-HCG-MAX and the first determination after this level; TEP = tubal ectopic pregnancy; tHCG = number of days taken for the serum beta-HCG to reduce to non-pregnant levels; tUSS = the number of days taken from the beta-HCG declining to non-pregnant levels and the physical resolution of TEP on follow-up ultrasound scan.

TABLE 4 ASSOCIATIONS BETWEEN TTOT AND OTHER STUDY VARIABLES (*N* = 177)

	Correlation coefficient	*P*-value
Maternal age	0.08	0.28
beta-HCG-INIT	0.31	**<0.001**
First progesterone measurement	0.08	0.29
beta-HCG-MAX	0.32	**<0.001**
beta-HCG-TREND	–0.32	**<0.001**
tHCG	0.62	**<0.001**
Mean TEP width at diagnosis	0.10	0.17

beta-HCG-INIT = first beta-HCG measurement; beta-HCG-MAX, maximum serum beta-HCG level during the period of follow-up; beta-HCG-TREND = daily % change between beta-HCG-MAX and the first determination after this level; TEP = tubal ectopic pregnancy; tHCG = number of days taken for the serum beta-HCG to reduce to non-pregnant levels; tTOT = total number of days from the ultrasound diagnosis of TEP to the ultrasound scan confirming resolution.

r = 0.31, *P* < 0.001) and beta-HCG-MAX measurements (*r* = 0.32, *P* < 0.001) and was negatively correlated with the beta-HCG-TREND (*r* = –0.32, *P* < 0.001). There was no correlation with maternal age, initial progesterone concentrations or the initial size of the TEP (TABLE 4).

There was a highly significant positive relationship between beta-HCG-INIT and tTOT (*P* < 0.001), where a 1-unit increase in beta-HCG-INIT on a logarithmic scale was equivalent to a 41% (95% CI 21–64) increase in tTOT (FIGURE 3).

At the time of analysis, 90/177 (50.8%, 95% CI 43.2–58.4) women had attended our unit with their subsequent pregnancies, with 4/90 (4.4%, 95% CI 1.2–11.0) having a repeat TEP, three in the ipsilateral and one in the contralateral Fallopian tube to the initial TEP.

DISCUSSION

This study has shown that in approximately two-thirds of women with TEP who are managed expectantly, trophoblastic tissue became non-detectable on TVUS within 14 days of the serum beta-HCG returning to non-pregnant concentrations. It was also found that in nearly 5% of women it took longer than 3 months for the physical resolution of pregnancy to be completed.

The strengths of this study were its prospective design, clearly defined
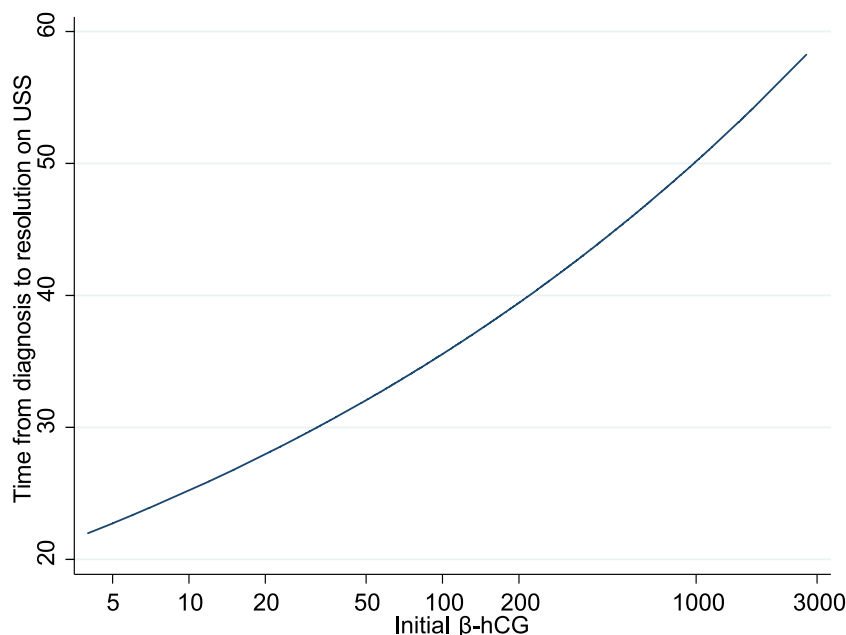
FIGURE 3 A graphical illustration of the relationship between beta-HCG-INIT and tTOT on a logarithmic scale. A statistically significant association is demonstrated between the two variables ($P < 0.001$). beta-HCG-INIT = first beta-HCG measurement at time of diagnosis of tubal ectopic pregnancy; tTOT = total number of days from the ultrasound diagnosis of tubal ectopic pregnancy to the ultrasound scan confirming resolution.

diagnostic criteria and immediate access to all ultrasound and biochemical measurements, which were stored on a dedicated clinical database. The study was conducted in a tertiary referral EPU and all ultrasound examinations were either carried out or directly supervised by expert ultrasound imaging operators using top of the range equipment. All TVUS images were digitally stored and reviewed prior to each follow-up visit to ensure consistency in the diagnosis and measurements. The weakness of the study is the relatively long interval between the follow-up visits, meaning there is a possibility that shorter resolution times would have been recorded if the visits had been organized on a more frequent basis. However, daily follow-up visits are too frequent to be implemented in routine practice and it was decided to approach the issues of TEP resolution from a practical clinical rather than pathophysiological perspective, with a focus on investigating the longest time to resolution. There was a relatively large 14% non-compliance rate with follow-up, which is another potential weakness of the study. The study EPU serves a cosmopolitan, highly mobile, inner city population, which could explain this relatively high proportion of women not attending for the full follow-up visit programme.

Previous studies of TEP undergoing successful expectant management reported median serum beta-HCG clearance times to non-pregnant concentrations of 18 and 19 days, which was longer than the 14 days recorded in this study (*Helmy et al., 2015*; *Mavrelos et al., 2015*). The maximum median beta-HCG readings (463 IU/l and 393 IU/l) and the mean sizes of TEP pregnancies (18 mm and 14 mm) in previous studies were higher compared with the findings in the current study (beta-HCG 218 IU/l and size 12 mm). All studies showed a significant positive correlation between the maximum recorded beta-HCG readings and its clearance time, which may explain the shorter median clearance time in the current study. The smaller TEP size in this study may reflect improved quality of ultrasound diagnosis driven by technological advances and increased experience of operators, facilitating detection of smaller TEP, which may have previously been classified as pregnancies of unknown location.

There have been no previous large studies looking at the physical resolution of TEP undergoing non-surgical management. Several case series have shown that physical resolution of interstitial pregnancies managed either expectantly or with methotrexate could take more than a year to complete (*Poon et al., 2014*; *Timor-Tritsch et al., 1992*). However, interstitial pregnancies, even when treated expectantly, tend to be much larger, often contain live embryos and have significantly higher beta-HCG concentrations compared with TEP. In women diagnosed with Caesarean scar ectopic pregnancies, reported median resolution rate with expectant management was 82 days (range 37–174) (*Harb et al., 2018*). Prolonged resolution times have also been reported in cases of cervical pregnancies (*Mangino et al., 2014*).

Information about the length of time required for a complete physical resolution of pregnancy is pivotal for counselling of women who are considering expectant management of TEP. Women should be informed of a very small but significant risk of complications such as intra-abdominal bleeding and tubal rupture, which may occur for some time after decline of beta-HCG concentrations to non-pregnant concentrations. The awareness that such a risk exists should help to increase the safety of expectant management protocols and ensure that the possibility of tubal rupture is not dismissed by clinicians because of a urine pregnancy test being negative.

In addition, the presence of retained, resolving trophoblastic tissue within the Fallopian tube could theoretically cause transient tubal obstruction, increasing the risk of a recurrent TEP should new conception occur before the primary TEP has resolved. In view of this, women could be advised to postpone trying for another pregnancy for 3 months as 95% of TEP would resolve by then. A 3-month follow-up scan could be offered to those women who are keen to try for another pregnancy as soon as possible. That would identify the small proportion in whom the resolution of TEP takes longer. However, this would only be important to women who are trying for a spontaneous conception and to those considering ovarian stimulation or intrauterine insemination. Women undergoing IVF could probably start treatment before physical resolution is completed as the presence of residual non-functional trophoblastic tissue is unlikely to decrease the chance of successful treatment. However, it would be helpful to inform fertility specialists that resolving TEP may be visible on the ultrasound scans carried out as a part of fertility treatment, to prevent offering women unnecessary interventions.

In summary, the results of this study provide women and clinicians, for the first time, with information about the length of time required for the completion of expectant management of TEP. Further work is needed to find out in what proportion of women presenting with acute pain following decline of beta-HCG concentrations to non-pregnant concentrations could their symptoms be attributed to residual tubal trophoblast. There is also a need to determine whether medical treatment with methotrexate could result in faster resolution of TEP compared with the expectant management.

ACKNOWLEDGEMENTS

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