Ultrasound Obstet Gynecol 2017
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17329

Single-dose systemic methotrexate *vs* expectant management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial

D. JURKOVIC*, M. MEMTSA*, E. SAWYER†, A. N. A. DONALDSON‡, A. JAMIL*, K. SCHRAMM†, Y. SANA†, M. OTIFY†, L. FARAHANI*, N. NUNES*, G. AMBLER§ and J. A. ROSS†

**Institute for Women's Health, University College Hospital, London, UK; †Early Pregnancy Unit, Department of Obstetrics and Gynaecology, King's College Hospital, London, UK; ‡Applied Mathematics & Statistics Department, State University of New York, Stony Brook, NY, USA; §Department of Statistical Science, University College London, London, UK*

KEYWORDS: expectant; methotrexate; placebo; randomized controlled trial; treatment; tubal ectopic pregnancy

ABSTRACT

Objective *Methotrexate is used routinely worldwide for the medical treatment of clinically stable women with a tubal ectopic pregnancy. This is despite the lack of robust evidence to show its superior effectiveness over expectant management. The aim of our multicenter randomized controlled trial was to compare success rates of methotrexate against placebo for the conservative treatment of tubal ectopic pregnancy.*

Methods *This study took place in two early-pregnancy units in the UK between August 2005 and June 2014. Inclusion criteria were clinically stable women with a conclusive ultrasound diagnosis of a tubal ectopic pregnancy, presenting with a low serum beta human chorionic gonadotropin (β-hCG) level of < 1500 IU/L. Women were assigned randomly to a single systemic injection of either 50 mg/m^2 methotrexate or placebo. The primary outcome was a binary indicator for success of conservative management, defined as resolution of clinical symptoms and decline of serum β-hCG to < 20 IU/L or a negative urine pregnancy test without the need for any additional medical intervention. An intention-to-treat analysis was followed.*

Results *We recruited a total of 80 women, 42 of whom were assigned to methotrexate and 38 to placebo. The arms of the study were matched in terms of age, ethnicity, obstetric history, pregnancy characteristics and serum levels of β-hCG and progesterone. The rates of success were similar for the two study arms: 83% with methotrexate and 76% with placebo. On univariate analysis, this difference was not statistically significant (χ^2 (1 degree of freedom) = 0.53; P = 0.47). On multivariate logistic regression, the serum level of β-hCG was the only covariate found to be significantly associated with outcome. The odds of failure increased by 0.15% for each unit increase in β-hCG (odds ratio, 1.0015 (95% CI, 1.0002–1.003); P = 0.02). In 14 women presenting with serum β-hCG of 1000–1500 IU/L, the success rate was 33% in those managed expectantly compared with 62% in those receiving methotrexate. This difference was not statistically significant and a larger sample size would be needed to give sufficient power to detect a difference in the subgroup of women with higher β-hCG. In women with successful conservative treatment, there was no significant difference in median β-hCG resolution times between study arms (17.5 (interquartile range (IQR), 14–28.0) days (n = 30) in the methotrexate group vs 14 (IQR, 7–29.5) days (n = 25) in the placebo group; P = 0.73).*

Conclusions *The results of our study do not support the routine use of methotrexate for the treatment of clinically stable women diagnosed with tubal ectopic pregnancy presenting with low serum β-hCG (< 1500 IU/L). Further work is required to identify a subgroup of women with tubal ectopic pregnancy and β-hCG ≥ 1500 IU/L in whom methotrexate may offer a safe and cost-effective alternative to surgery. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Ectopic pregnancy is a common condition that affects 1–2% of pregnant women worldwide. Although fatalities are rare in developed countries[1], the burden of disease is high owing to costs of diagnostic work-up and

Correspondence to: Mr D. Jurkovic, Gynaecology Diagnostic and Outpatient Treatment Unit, Lower Ground Floor, Elizabeth Garrett Anderson Wing, University College Hospital, 250 Euston Road, London, NW1 2BU, UK (e-mail: davor.jurkovic@nhs.net)

Accepted: 5 October 2016

Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

expensive treatment. A recent guideline from the UK National Institute for Health and Care Excellence on the diagnosis and management of early pregnancy complications stipulates that all women diagnosed with an ectopic pregnancy should be managed actively by either medical treatment with methotrexate or surgery[2]. Although clinically stable women who present with small ectopic pregnancies and low levels of serum beta human chorionic gonadotropin (β-hCG) are sometimes managed expectantly in clinical practice, there are limited data on the efficacy and safety of this approach. In a review by the Cochrane Collaboration, only two randomized trials comparing expectant with medical management were identified[3]. Women in the treatment arm of one trial were given an oral dose of methotrexate[4], while systemic prostaglandins were used in the other trial[5]; neither of these is used in standard clinical practice. A more recent systematic review and meta-analysis on the treatment of tubal ectopic pregnancies emphasized the need for more research in assessing the feasibility of expectant management in women presenting with serum β-hCG levels of < 1500 IU/L[6].

Several observational studies have shown a high success rate of expectant management in selected groups of women with small tubal ectopic pregnancies[7–9]. Expectant management follows the natural history of the condition and avoids the risks associated with surgical and medical management. This makes it attractive to pregnant women, and its uptake is high when offered as one of the available management options[10]. In the last 2 years, two randomized trials comparing expectant management with systemic methotrexate have been published[11,12]. One of these was a very small trial while the other included mainly women with a pregnancy of unknown location. This suggests that more robust evidence is needed to determine the role of expectant management in tubal ectopic pregnancy.

The aim of this placebo-controlled randomized trial was to assess whether medical treatment with methotrexate is more successful than expectant management in clinically stable women presenting with tubal ectopic pregnancy and a serum β-hCG level of < 1500 IU/L.

METHODS

Study design

This was a multicenter randomized controlled trial that was planned to be carried out in three UK teaching hospitals from August 2005 to June 2014.

Study population

All clinically stable women with a conclusive ultrasound diagnosis of a tubal ectopic pregnancy were eligible for the trial[13]. Additional inclusion criteria were the absence of both an embryonic heart beat and hemoperitoneum on the ultrasound scan, baseline serum β-hCG < 1500 IU/L, normal full blood count and liver and renal function tests and no history of hepatic, renal or pulmonary disease.

Ethical approval

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of good clinical practice and all of the applicable regulatory requirements including Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations. The trial protocol was reviewed and approved by the Royal Free Hospital Medical School Research Ethics Committee and by the Medicines and Healthcare Products Regulatory Agency (MHRA). The trial was registered as an International Standard Randomised Clinical Trial (ISRCTN95698259).

Study treatment

Women who consented to participate in the study were assigned randomly to methotrexate treatment or placebo. A computer-generated simple randomization list was used and the allocation sequence was kept at the King's College Hospital pharmacy, blinded to the recruiters and to local pharmacy staff. Upon receipt of the patient randomization request form from a local hospital pharmacy, a designated pharmacist at King's College Hospital referred to the sequence to identify the next eligible patient randomization number. Local pharmacies were then instructed to prepare trial medication as appropriate.

Women allocated to methotrexate treatment received a single gluteal intramuscular injection of 50 mg/m^2 methotrexate (Methotrexate injection PL 25215/0014; Hameln Pharma Plus GMBH, Hameln, Germany). Women allocated to placebo were given a gluteal intramuscular injection of 0.9% solution of sodium chloride (Sodium Chloride 0.9% injection PL 24598/0002; Fannin, Pincents Kiln Industrial Park, Reading, UK). Both placebo and methotrexate were labeled and distributed by Guy's and St Thomas' Pharmacy Manufacturing, London, UK. To maintain blinding for the study, the trial medication prepared by the pharmacy was kept in a sealed opaque bag. Syringes containing trial medication were kept out of the participant's view and medication was administered only by trained nurses or doctors who were independent from the trial. They were given clear instructions not to discuss with the women possible treatment allocation or any other aspect of the study. The administration of trial medication was documented and the prescription sheet was given to the investigator to keep with other trial documents.

All women were given trial medication within 24 h of their initial visit, which was labeled as day 1. They attended follow-up visits on days 4 and 7, during which a blood sample was taken to measure serum β-hCG levels. Full blood count, liver and renal function tests were also checked on day 7. A window of ± 1 day was considered acceptable for follow-up visits.

All women were advised against long-distance travel and were advised to refrain from sexual intercourse. They were provided with a 24-h contact number and were advised to return to hospital should they experience

Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

any significant increase in abdominal pain. The women were also advised to increase their fluid intake and avoid exposure to sunlight. They were informed of the common side-effects of methotrexate and advised to avoid alcohol, non-steroidal anti-inflammatory drugs and aspirin. The treatment was classified as unsuccessful and women were consequently offered surgery if serum β-hCG levels had increased by > 15% on two consecutive follow-up visits. Surgery was also advised for women who developed abdominal pain with evidence of hemoperitoneum on ultrasound. When β-hCG levels fell by > 15%, weekly blood tests were arranged until a level of < 20 IU/L was reached. In women with static serum β-hCG (within ± 15% of the previous reading), blood tests were arranged every 2 days to ensure that the levels were not increasing.

Outcome measures

The primary outcome of the study was a binary indicator of success of conservative management, defined in terms of the resolution of clinical symptoms and decline in level of serum β-hCG to < 20 IU/L or a negative urine pregnancy test without the need for any additional medical intervention. Secondary outcomes were the proportion of women suffering severe intra-abdominal bleeding requiring blood transfusion, number of emergency laparotomies performed, proportion of women experiencing significant pelvic pain or gastrointestinal side-effects and serum β-hCG resolution times.

Statistical analysis

We aimed to detect a reduction in surgical intervention rate from 40% to 12%. These were, respectively, contemporaneous surgical intervention rates in women managed expectantly and medically at the Early Pregnancy Unit of King's College Hospital. Using these figures, 70 patients were needed for the study, 35 in each arm, to guarantee a power of 80%.

A prespecified interim analysis using double triangle stopping boundary[14] was carried out when 34 women had been recruited, which showed a very small difference between the two treatments. The median unbiased estimate of the log odds ratio (OR) was 0.13 (95% CI, −1.96 to 2.2), which did not cross the stopping boundary, and a decision was made to continue with recruitment.

We performed the primary analysis by intention-to-treat and secondary analysis as per protocol, using the χ^2-test to assess the significance of the difference in success rates between the two treatment groups (active *vs* placebo). We used logistic regression to model the likelihood of success in terms of treatment and other covariates. A stepwise approach was followed, with multivariate models adjusting for those covariates that showed significance of $P < 0.25$ in the univariate models. Final statistical significance was judged as $P < 0.05$.

Two-sample univariate tests (Mann–Whitney *U*-test, *t*-tests or the appropriate χ^2-test) were planned to assess whether the treatments were balanced at baseline, and logistic regressions to model the likelihood of success or failure in terms of treatment and other covariates.

RESULTS

We enrolled a total of 80 women from two of the three centers; one center ultimately failed to recruit any patients. Forty-two women were allocated to a single dose of systemic methotrexate and 38 were allocated to placebo (Figure 1). Nine women declined the trial intervention after randomization (six in the methotrexate group and three in the placebo group) and all were managed expectantly. One woman in the methotrexate group did not attend any follow-up visits and was excluded from the analysis. Baseline characteristics of all women are presented in Table 1. The two groups were reasonably well-matched in terms of age, ethnicity, obstetric history, pregnancy characteristics and serum levels of β-hCG and progesterone.

Primary and secondary outcomes in all women recruited to the trial are shown in Table 2. Increasing abdominal pain and suspicion of intra-abdominal bleeding was the main reason for surgical intervention, followed by a rise in the level of serum β-hCG. No woman required emergency open surgery (laparotomy) and only one woman (in the placebo group) had a blood transfusion. The diagnosis of a tubal ectopic pregnancy was confirmed in all women who underwent surgery.

The success rate of management according to intention-to-treat was 83% with methotrexate and 76% with placebo. On univariate analysis, this difference was not statistically significant (χ^2 (1 degree of freedom) = 0.53; $P = 0.47$). On univariate logistic regression, none of the following covariates was found to have a significant association with outcome: maternal age ($P = 0.24$), smoking status ($P = 0.70$), parity ($P = 0.36$), previous miscarriage ($P = 0.58$), ethnicity ($P = 0.44$), previous ectopic pregnancy ($P = 0.94$), side of ectopic pregnancy ($P = 0.86$) or baseline progesterone level ($P = 0.21$).

On multivariate logistic regression, β-hCG was the only covariate that retained significance. The odds of failure increased by 0.15% for each unit increase in β-hCG (OR, 1.0015 (95% CI, 1.0002–1.003); $P = 0.02$). Likewise, the risk of failure increased by 0.12% for each unit increase in β-hCG (relative risk (RR), 1.0012 (95% CI, 1.000–1.002); $P = 0.01$). Moreover, the failure rate was significantly higher in the 14 women presenting with a baseline serum β-hCG of 1000–1500 IU/L (OR, 6.2 (95% CI, 1.76–22); $P = 0.01$; RR, 3.6 (95% CI, 1.6–8); $P = 0.002$). This effect was similar in both treatment groups (failure rate: 67% with placebo *vs* 38% with methotrexate; χ^2 (1 degree of freedom) = 1.02; $P = 0.31$). After adjusting for the effect of baseline β-hCG, no significant difference was found between the treatment groups in terms of the likelihood of failure (OR, 0.59 (95% CI, 0.19–1.9); $P = 0.37$ and RR, 0.69 (95% CI, 0.31–1.6); $P = 0.70$), for methotrexate relative to placebo.

Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

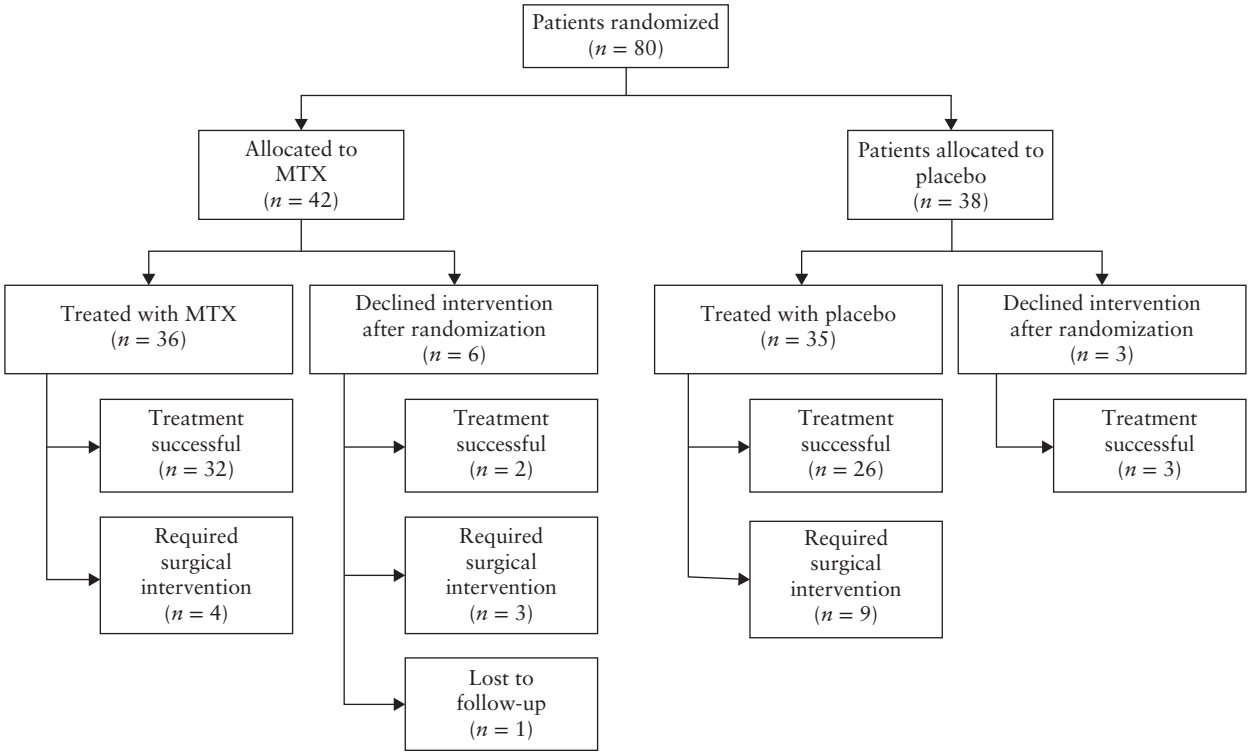

Figure 1 Flowchart of participants with ectopic pregnancy randomized to treatment with single dose of methotrexate (MTX) or placebo. Treatment was considered successful if clinical symptoms resolved and levels of serum beta human chorionic gonadotropin declined below 20 IU/L or urine pregnancy test was negative.

Table 1 Baseline characteristics of 80 women with ectopic pregnancy (EP) and serum beta human chorionic gonadotropin (β-hCG) < 1500 IU/L who were randomized to treatment with single dose of methotrexate or placebo

Characteristic	*Methotrexate* (n = *42*)	*Placebo* (n = *38*)	P
Maternal age (years)	29 ± 6.9	30 ± 6.7	0.45*
Ethnicity			
White	17 (40)	25 (66)	0.02†
Black	16 (38)	9 (24)	0.17†
Other/mixed	9 (21)	4 (11)	0.19†
Primigravid	22 (52)	21 (55)	0.80†
Parity	0 (0–1)	0 (0–1)	0.84‡
Previous miscarriage	10 (24)	9 (24)	0.59†
Previous EP	3 (7)	4 (11)	0.48†
Smoker	14 (33)	15 (39)	0.57†
GA (weeks)	6.9 ± 1.6	7.0 ± 2.1	0.62*
Diameter of EP (mm)	11.4 ± 6.9	13.0 ± 7.2	0.31*
US morphology of EP			0.04†
Gestational sac	23 (55)	12 (32)	
Inhomogeneous solid mass	19 (45)	26 (68)	
Baseline serum β-hCG (IU/L)	465 (238–914)	405 (189–784)	0.34‡
Baseline serum progesterone (nmol/L)	18 (8–28)	14 (7–28)	0.37‡

Data are given as mean ± SD, *n* (%) or median (interquartile range). Groups compared using *two-sample *t*-test, †χ^2-test or ‡Mann–Whitney *U*-test. GA, gestational age; US, ultrasound.

Table 2 Primary and secondary outcomes in women with ectopic pregnancy (EP) and serum beta human chorionic gonadotropin (β-hCG) < 1500 IU/L who were randomized to treatment with single dose of methotrexate or placebo

Outcome	*Methotrexate* (n = *41*)	*Placebo* (n = *38*)	P*
Uneventful decline in β-hCG	34 (83 (72–95))	29 (76 (61–87))	0.47
Indication for surgery			
Abdominal pain and evidence of blood in pelvis on US	6	2	
Abdominal pain only	0	2	
Rising β-hCG	1	5	
Blood transfusion	0	1	0.29

Data are given as *n* (% (95% CI)) or *n*. One woman in methotrexate group did not attend any follow-up visits and was excluded from analysis. *Groups compared using χ^2-test, without Yates correction, or two-tailed *t*-test. US, ultrasound.

In women with successful conservative management, there was no significant difference in median resolution time of β-hCG between the trial arms (17.5 (interquartile range (IQR), 14–28.0) days ($n = 30$) in the methotrexate group *vs* 14 (IQR, 7–29.5) days ($n = 25$) in the placebo group; $P = 0.73$).

The rates of success according to the actual protocol followed were 89% for methotrexate and 74% for placebo. The difference in success rate between the groups was not statistically significant ($\chi^2 = 2.4$; $P = 0.12$). The

Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

RR for failure in the methotrexate group relative to placebo was 0.40 (95% CI, 0.13–1.18).

DISCUSSION

Our study showed that medical treatment with methotrexate did not contribute significantly to the success of conservative management of unruptured tubal ectopic pregnancy presenting with low baseline serum β-hCG levels of < 1500 IU/L. There were no significant differences in the secondary outcomes of interest such as rates of emergency laparotomy and blood transfusion. Our sample size calculation assumed a 28% better success rate in the methotrexate arm than in the placebo arm. The proportion of patients requiring surgical intervention was lower than the proportion upon which we based our power calculation. This was mainly owing to higher than expected spontaneous resolution rates of ectopic pregnancy in the placebo arm. Our study was conceived over a decade ago and the estimated success rate of expectant management was based on data from the literature that was available at the time, which showed a wide range of resolution rates of between 7% and 66%[9,15] compared with the average rate of 88% when systemic methotrexate was used[16]. More recent studies have reported higher success rates of expectant management of between 59% and 92%[11,12], which are similar to our findings.

The strengths of our study are the clear and clinically relevant inclusion criteria, robust procedures used to minimize the risk of bias and a high rate of follow-up. The main limitation is the long period of time required to complete the study, which was partially due to administrative delays caused by the change of the chief investigator and the need to initiate treatment at a new site. Recruitment in one of the centers was unsuccessful because the local principal investigator left the hospital. In addition, we found that the majority of women eligible for inclusion in the study had a clear preference for one of the available treatment options and were reluctant to accept that management of their ectopic pregnancy should be decided by chance.

In the methotrexate arm, 6/42 (14%) women declined intervention after randomization compared with 3/38 (8%) in the placebo group. We carried out intention-to-treat analysis and, in view of the relatively small sample size, this moderately high drop-out rate reduces the power of the study. The intervention rate in the placebo arm of the trial was lower than anticipated, which increases the risk of Type II error.

In 14 women presenting with a baseline serum β-hCG level of 1000–1500 IU/L, the success rate in those managed expectantly was 33%, compared with 62% in those receiving methotrexate. This difference was not statistically significant and a larger sample size would be needed to give sufficient power to detect a difference in this subgroup of women.

Our overall findings are similar to those of previously published randomized trials comparing methotrexate with placebo in women diagnosed with tubal ectopic pregnancy. In the study by Korhonen *et al.*[4], women in the treatment arm were prescribed a very low dose of oral methotrexate while the systemic parenteral route was used in the other two trials[11,12]. In two out of these three trials, the researchers included only ectopic pregnancies presenting with serum β-hCG levels of < 2000 IU/L. In the study by Korhonen *et al.*, the inclusion criteria allowed for randomization of women presenting with ectopic pregnancy and β-hCG levels of < 5000 IU/L[4]. Despite this more liberal inclusion criterion, median baseline β-hCG levels in this study were slightly lower than in the other trials.

Two studies included only women with a tubal ectopic pregnancy that was positively identified on ultrasound[4,12]. In the study by Van Mello *et al.*[11], only 20% of women were diagnosed with ectopic pregnancy on ultrasound, while the remaining 80% had a pregnancy of unknown location, most of which are likely to represent failed intrauterine pregnancies. However, all women had plateauing serum β-hCG levels, which many clinicians feel compelled to treat. The study by Silva *et al.*[12] differs from the other studies as they included only women with ectopic pregnancy and falling serum β-hCG levels. This could explain the higher success rates in both arms of their trial compared with the other studies.

Methotrexate is often given to women with an ectopic pregnancy or those with a pregnancy of unknown location in order to shorten the length of follow-up and expedite the clearance of serum β-hCG. In our study, we found no significant difference between the two arms of the study in the length of time required for serum β-hCG to return to prepregnancy levels. The other three previous trials[4,11,12] reported similar findings, and it is safe to conclude that the administration of methotrexate does not result in faster resolution of tubal ectopic pregnancy managed conservatively.

All these findings call for reassessment of the role of methotrexate as the primary treatment of tubal ectopic pregnancy. There is a possibility that its future use may be limited to the treatment of women with non-tubal ectopic pregnancies and those with residual ectopic trophoblast after salpingotomy.

In conclusion, the results of our trial show that medical treatment with methotrexate of tubal ectopic pregnancy presenting with low serum β-hCG levels is not significantly better than is treatment with placebo, and its use in this group of women seems to offer no measurable health benefits. However, the relative observed rate of surgical intervention was 30% lower with methotrexate than with placebo (17% *vs* 24%), and a larger study is required to determine whether a reduction of this magnitude is statistically significant. In addition, further work may identify a subgroup of women with tubal ectopic pregnancy and β-hCG ≥ 1500 IU/L in whom methotrexate may offer a safe and cost-effective alternative to surgery.

Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

REFERENCES

1. Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ (Eds.); on behalf of MBRRACE-UK. *Saving Lives, Improving Mothers' Care – Surveillance of maternal deaths in the UK 2011–13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–13*. National Perinatal Epidemiology Unit: University of Oxford, Oxford, 2015.
2. National Institute for Health and Care Excellence. *Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage*. CG154. 2012. http://publications.nice.org.uk/ectopic-pregnancy-and-miscarriage-cg154.
3. Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. *Cochrane Database Syst Rev* 2007; **1**: CD000324.
4. Korhonen J, Stenman U, Ylöstalo P. Low-dose oral methotrexate with expectant management of ectopic pregnancy. *Obstet Gynecol* 1996; **88**: 775–778.
5. Egarter C, Kiss H, Husslein P. Prostaglandin versus expectant management in early tubal pregnancy. *Prostaglandins Leukot Essent Fatty Acids* 1991; **42**: 177–179.
6. Mol F, Mol BWJ, Ankum WM, van der Veen, Hajenius PJ. Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis. *Hum Reprod* 2008; **14**: 309–319.
7. Cacciatore B, Korhonen J, Stenman U-H, Ylostalo P. Transvaginal sonography and serum hCG in monitoring of presumed ectopic pregnancies selected for expectant management. *Ultrasound Obstet Gynecol* 1995; **5**: 297–300.
8. Trio D, Strobelt N, Picciolo C, Lapinski RH, Ghidini A. Prognostic factors for successful expectant management of ectopic pregnancy. *Fertil Steril* 1995; **63**: 469–472.
9. Elson J, Tailor A, Banerjee S, Salim R, Hillaby K, Jurkovic D. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. *Ultrasound Obstet Gynecol* 2004; **23**: 552–556.
10. Mavrelos H, 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 Obstet Gynecol* 2013; **42**: 102–107.
11. Van Mello NM, Mol F, Verhoeve HR, Wely M, Adriaanse AH, Boss EA, Dijkman AB, Bayram N, Emanuel MH, Friederich J, van der Leeuw-Harmsen L, Lips JP, Van Kessel MA, Ankum WM, van der Veen F, Mol BW, Hajenius PJ. Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison. *Hum Reprod* 2013; **28**: 60–67.
12. Silva PM, Araujo Júnior E, Cecchino GN, Elito Júnior J, Camano L. Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial. *Arch Gynecol Obstet* 2015; **291**: 939–943.
13. Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, Bourne T. The accuracy of transvaginal sonography for the diagnosis of ectopic pregnancy prior to surgery. *Hum Reprod* 2005; **20**: 1404–1409.
14. Whitehead J. The design of a sequential trial using the boundaries approach. In *The Design and Analysis of Sequential Clinical Trials*. Wiley: Chichester, UK, 1997; 69–134.
15. Sauer MV, Gorrill MJ, Rodi IA, Yeko TR, Greenberg LH, Bustillo M. Nonsurgical management of unruptured ectopic pregnancy: an extended clinical trial. *Fertil Steril* 1987; **48**: 753–755.
16. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. *Obstet Gynecol* 2003; **101**: 778–784.

Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.