Single dose systemic methotrexate versus expectant management for treatment of tubal ectopic pregnancy: A placebo-controlled randomised trial

Jurkovic D*, Memtsa M*, Sawyer E†, Donaldson ANA‡ Jamil A*, Schramm K†, Sana Y†, Otify M†, Farahani L†*, Nunes N*, Ambler G§, Ross JA†

*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

Correspondence:

Mr Davor Jurkovic

Gynaecology Diagnostic and Outpatient Treatment Unit

Lower Ground Floor

Elizabeth Garrett Anderson Wing

University College Hospital

250 Euston Road

London, NW1 2BU

e-mail: davor.jurkovic@nhs.net

Short tittle: Treatment of ectopics

Key words: Tubal ectopic pregnancy, Treatment, Methotrexate, Expectant, Randomised controlled trial, Placebo

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.17329

Abstract

Objective: Methotrexate is routinely used worldwide for medical treatment of clinically stable women with tubal ectopic pregnancies. This is despite the lack of robust evidence to show its superior effectiveness over expectant management. The aim of our multicentre randomised trial study was to compare the success rates of methotrexate with placebo for the conservative treatment of tubal ectopic pregnancies.

Methods: The study was multicentre; it took place in three UK early pregnancy units between January 2006 and June 2014. Inclusion criteria were clinically stable women with a conclusive ultrasound diagnosis of a tubal ectopic pregnancy presenting with low serum β-hCG <1500IU/l. Women were randomly assigned to single systemic injection of methotrexate 50mg/m^2 or placebo. The primary outcome of the study was a binary indicator for success of conservative management, defined as resolution of clinical symptoms and decline of serum β-hCG to <20IU/l or 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 to methotrexate and 38 to placebo. The two arms of the study were balanced in terms of age, ethnicity, obstetric histories, pregnancy characteristics and serum β-hCG and progesterone. The proportions of successes were similar: 83% with methotrexate and 76% with placebo. On univariate analysis, this difference was not statistically significant ($\chi 2(1df) = 0.53$; P=0.23).

On multivariate logistic regression, β-hCG was the only covariate which was significantly associated with outcome. The odds of failure increased by 0.15% for each unit increase in β-hCG (OR=1.0015; 95% CI 1.0002 to 1.003; P=0.02). In 14 women presenting with serum hCG 1000-1500IU/l the success of expectant management was

33% compared to 62% in the methotrexate arm. Although this result was not statistically significant a larger sample size would give us greater power to detect a difference in this subgroup of women,

In women with successful conservative management there was no significant difference in median resolution times between methotrexate and placebo arms [17.5 days (IQR 14 - 28.0) (n=30)] vs [14 days (IQR 7 - 29.5) (n=25)] (P= 0.73)

Conclusion: The results of our study do not support routine use of methotrexate for the treatment of clinically stable women diagnosed with tubal ectopic pregnancies presenting with low serum hCG <1500IU/l. Further work is required to identify a subgroup of women with tubal ectopic pregnancies and hCG≥1500IU/l in whom methotrexate may offer a safe and cost-effective alternative to surgery.

Introduction

Ectopic pregnancy is a common condition which affects 1% to 2% of pregnant women worldwide. Although fatalities are rare with ectopic pregnancies in developed countries[1], the burden of disease is high owing to costs of diagnostic work up and expensive treatment. A recent NICE guideline on the diagnosis and management of early pregnancy complications stipulates that all women diagnosed with ectopic pregnancies should be managed actively either using medical treatment with methotrexate or surgery[2]. Although clinically stable women who present with small ectopics and low serum β-hCG levels are sometimes managed expectantly in clinical practice, there is limited data on the efficacy and safety of this approach. In a Cochrane Collaboration's review only two randomised trials comparing expectant with medical management were identified[3]. Women in the treatment arm of the first trial were given an oral dose of methotrexate[4], whilst systemic prostaglandins were used in the second 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 emphasised the need for more research to be done in assessing the feasibility of expectant management in women presenting with serum β-hCG levels <1500IU/l[6].

Several observational studies showed a high success of expectant management in selected groups of women with small tubal ectopic pregnancies[7-9]. Expectant management follows natural history of the condition and it 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 two years, two randomised trials comparing expectant management with systemic

methotrexate have been published[11,12]. One of these was very small whilst the other mainly included women with pregnancies of unknown location. This suggests that more robust evidence is needed to determine the role of expectant management in tubal ectopic pregnancies.

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

Methods

Study design

This was a multicentre randomized controlled trial which was carried out in three UK teaching hospitals form August 2005 to June 2014.

Study population

All clinically stable women with a conclusive ultrasound diagnosis of a tubal ectopic pregnancy[13] were eligible for the trial. The other inclusion criteria were the absence of embryonic heart rate and haemoperitoneum on ultrasound scan, initial serum β-hCG <1500IU/l, normal full blood count, 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 randomly assigned 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 or to local pharmacies staff. Upon receipt of the Patient Randomisation 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 methotrexate 50mg/m^2 (Methotrexate injection PL 25215/0014; Hameln Pharma Plus GMBH, Langes Feld 13, 31789 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, Calcot, Reading). Both placebo and methotrexate were labelled and distributed by Guy's and St Thomas' Pharmacy Manufacturing, London, UK. To maintain blinding for the study, the trial medication prepared by pharmacy was kept in a sealed opaque bag. Syringes containing trial medication were kept out of women's view and the medication was administered only by trained nurses or doctors who were

independent from the trial. They were given clear instructions not to discuss with 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 hours of the initial visit which was labelled as Day 1. They attended for follow up visits on days 4 and 7 when 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 visit window of +/- 1 day was considered acceptable for follow up visits.

All women were advised against long distance travel and they were advised to refrain from sexual intercourse. They were provided with a 24 hour contact number and advised to return to hospital should they experience any significant increase in abdominal pain. Women were also advised to increase their fluid intake and avoid exposure to sunlight. They were also informed of 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 offered surgery if serum β-hCG levels increased by >15% on two consecutive visits. Surgery was also advised in women who developed abdominal pain with evidence of haemoperitoneum on ultrasound scan. When β-hCG fell by >15%, weekly blood tests were arranged until it reached a level <20IU/L. In women with static serum β-hCG (within ± 15% of the previous reading) blood tests were arranged every two 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 of serum β-hCG to <20IU/l or negative urine pregnancy test without the need for any additional medical intervention. The secondary outcomes were the proportion of women suffering severe intra-abdominal bleeding requiring blood transfusion, number of emergency laparotomies, proportion of women experiencing significant pelvic pain or gastro-intestinal side effects and the serum β -hCG resolution times.

Statistical methodology

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

A pre-specified 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 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 per protocol. We used $\chi 2$ tests to assess the significance of the difference in proportions of success between the two treatment groups (active vs. placebo). We used logistic regression to model the likelihood of success in terms of treatment and other co-variates. A stepwise approach was followed, with multivariate models adjusting for

those covariates that showed significance below 25% in the univariate models. Final statistical significance was judged at the 5% level.

The analysis approach was on an intention to treat for the primary outcome. Two-sample univariate tests (Mann-Whitney, t-tests or the appropriate χ^2 tests) were planned to assess if 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 recruited a total of 80 women 42 of whom were allocated to single dose systemic methotrexate and 38 to placebo. (Fig. 1) Nine women declined trial intervention after randomisation: six in the methotrexate and three in the placebo group. They were all managed expectantly. One women in the methotrexate did not attend for any follow up visits and she was excluded from the analysis. Baseline characteristics of all women are presented in Table 1 which shows that the two groups were reasonable well balanced in terms of age, ethnicity, obstetric histories, pregnancy characteristics and serum 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 rise in 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 tubal ectopic pregnancy was confirmed in all women who underwent surgery.

The proportion of successes by intention to treat was 83% with methotrexate and 76% with placebo. On univariate analysis, this difference was not statistically significant ($\chi 2(1df) = 0.53$; P=0.23). On univariate logistic regressions, neither of the following covariates were found to have a significant association with outcome: maternal age (P=0.24), smoking status (P=0.70), parity (P= 0.36), previous miscarriages (P= 0.58), ethnicity (P=0.44), previous ectopic (P=0.94), side of ectopic (P=0.86) or baseline progesterone (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 to 1.003; P=0.02). Likewise, the risk of failure increased by 0.12% for each unit increase in β-hCG (OR=1.0012; 95% CI 1.000 to 1.002; P=0.01). Moreover, the failure rate was significantly higher in the 14 women presenting with initial serum β-hCG >1000IU/l (OR=6.2; 95% CI 1.76 to 22; P=0.01) and (RR=3.6; 95% CI 1.6 to 8; P=0.002). This effect was similar in both treatment groups, as indicated by a non-significant interaction (P=0.50). 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 in terms of odds ratios (OR=0.59; 95 % CI 0.19 to 1.9; P=0.37) or, in terms of relative risks (RR=0.69; 95 % CI 0.31 to 1.6; P=0.70), for methotrexate relative to placebo.

In women with successful conservative management there was no significant difference in median resolution times between methotrexate and placebo arms [17.5 days (IQR14 - 28.0)(n=30)] vs [14 days (IQR 7 - 29.5) (n=25)] (P=0.73).

The proportion of successes analysing per protocol were methotrexate 89% and placebo 74%. The difference between methotrexate vs placebo was not statistically significant

($\chi 2$=2.4; P=0.12). The relative risk for failure in the methotrexate group relative to placebo was 0.40 (95 % CI 0.13 to 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 pregnancies presenting with low initial serum hCG levels <1500 IU/l. There were no significant differences in the secondary outcomes of interest such emergency laparotomy and blood transfusion rates either. Our sample size calculation assumed 28% better treatment success rate in the methotrexate compared to the placebo arm. The proportions of patients requiring surgical intervention were lower than the proportion upon which we based our power calculation. This was mainly due to higher than expected spontaneous resolution rates of ectopic pregnancy in the placebo arm. Our study was conceived a while ago and the estimated success rate of expectant management was based on the data from the literature available at the time which showed a wide range of resolution rates between 7% and 66%[9,15] compared to the average rate of 88% when systemic methotrexate was used[16]. More recent studies reported higher success rates of expectant management between 59% and 92%[11,12] which is similar to our findings.

The strengths of our study are: clear and clinically relevant inclusion criteria, robust procedures used to minimise the risk of bias and high rate of follow up. The main limitation is the long length 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 for a new site initiation. The recruitment in one of the centres was poor which caused

further delays. 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 the management of their ectopic pregnancy should be decided by chance.

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

In 14 women presenting with serum hCG 1000-1500IU/l the success of expectant management was 33% compared to 62% in the methotrexate arm. Although this result was not statistically significant a larger sample size would give us greater power to detect a difference in this subgroup of women,

Our overall findings; however, are similar to the previously published randomised studies comparing methotrexate with placebo in women diagnosed with tubal ectopic pregnancies. (Table 3) In the study by Korhonen et al.[4] women in the treatment arm were prescribed a very low dose of oral methotrexate whilst systemic parenteral route was used in the other three trails. In three out of four trials the researches only included ectopic pregnancies presenting with serum β-hCG levels <2000IU/l. In the remaining study the inclusion criteria allowed randomisation of women presenting with ectopic and β-hCG levels <5000IU/l[4]. Despite the inclusion criteria being more liberal the median initial β-hCG levels in that particular study were slightly lower compared to other trials.

Three studies only included women with tubal ectopic pregnancies which were positively identified on ultrasound scan. In a study by van Mello et al.[11] only 20% of women were diagnosed with ectopic pregnancies on ultrasound, whilst the remaining 80% of women had pregnancies of unknown location, most of which are likely to represent failed intrauterine pregnancies. They all had plateauing serum β-hCG levels; however, which many clinicians feel compelled to treat.

Study by Silva et al.[12] is different form the other three as they only included women with ectopic pregnancies and failing serum β-hCG levels. This could explain higher success rate in both arms of their trial compared to the other studies.

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

All these findings call for a 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 pregnancies presenting with low serum hCG levels is not significantly better than placebo and its use in this group of women seems to offers no measurable health benefits. However, the actual observed reduction in failure rate with methotrexate

was nearly 30% and a larger study is required to detect a reduction of this magnitude as statistically significant. In addition, further work may identify a subgroup of women with tubal ectopic pregnancies and hCG≥1500 IU/l in whom methotrexate may offer a safe and cost-effective alternative to surgery.

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. Oxford: National Perinatal Epidemiology Unit, University of 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 BWJ, Bossuyt PMM, Ankum WM, Van der Veen F. Interventions for tubal ectopic pregnancy. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD000324. DOI: 10.1002/14651858.CD000324.pub2.

4. Korhonen J, Stenman U, Ylostalo P. Low-dose oral methotrexate with expectant management of ectopic pregnancy. Obstet Gynecol 1996;88:775-8.

5. Egarter C, KissH,Husslein P. Prostaglandin versus expectant management in early tubal pregnancy. Prostaglandins Leukotrienes & Essential Fatty Acids 1991;42:177–9.

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;14:309-19.

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;23:552-6.

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 :60–7.

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;291:939-43.

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, 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

Figure captions

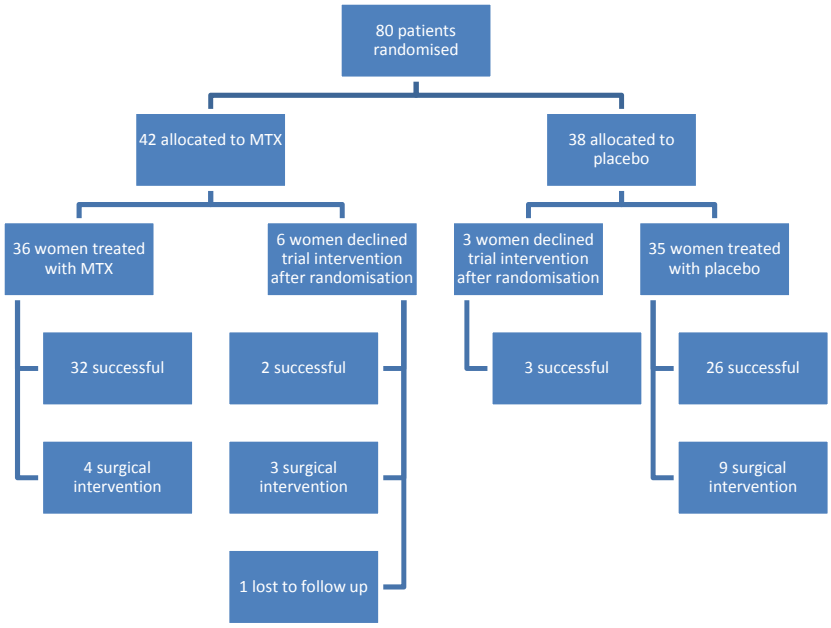

Fig. 1 Trial profile.

Table 1:
Baseline characteristics of women with an ectopic pregnancy and serum hCG < 1500 IU/l who were included in the trial.

Covariate	Single dose MTX (n=42)	Placebo (n=38)	P-values [test]
Maternal age (years): mean(SD)	29(6.9)	30(6.7)	0.45[2]
Ethnicity white: n(%)	17 (40)	25 (66)	0.02[1]
Ethnicity black: n(%)	16 (38)	9 (24)	0.17[1]
Ethnicity other/mixed: n(%)	9 (21)	4 (11)	0.19[1]
Primigravida: n(%)	22 (52)	21 (55)	0.80[1]
Parity: Quartiles	0-0-1	0-0-1	0.84 [3]
Previous miscarriage: n(%)	10 (24)	9 (24)	0.59[1]
Previous ectopic: n(%)	3 (7)	4 (10)	0.48[1]

Smoker: n(%)	14 (33)	15 (39)	0.57[1]
Gestational age (weeks): mean(SD)	6.9 (1.6)	7.0 (2.1)	0.62[2]
Ectopic pregn. diameter (mm): mean(SD)	11.4 (6.9)	13.0 (7.2)	0.31[2]
Ultrasound morphology of ectopic pregnancy			
Gestational sac: n(%)	23 (55)	12 (32)	0.04[1]
Inhomogenous solid mass: n(%)	19 (45)	26 (68)	
Baseline serum hCG (IU/l): Quartiles	238-465-914	189-405-784	0.34[3]
Baseline Serum Progesterone (nmol/l): Quartiles	8 - 18- 28	7-14-28	0.37[3]

[1] Chi-sq; [2] two-sample t [3] Mann-Whitney

Table 2:
Primary and secondary outcomes of women with an ectopic pregnancy and hCG < 1500 IU/l in a randomised double blind trial of methotrexate versus placebo

Outcome	Single dose MTX (n=41)	Placebo (n=38)	P*
Uneventful decline in hCG (%)(95%CI)	34 (83)(72-95)	29 (76)(61-87)	0.61
Surgical intervention	7 (17) (6-29)	9 (24)(13-39)	0.43
Indication for surgery:			
Abdominal pain & evidence of blood in pelvis on USS	6	2	
Abdominal pain alone	0	2	
Rising hCG	1	5	
Blood transfusion	0	1	0.29

* X^2 without Yates correction and two tailed p value