Table 4: Clinical evidence tables for expectant versus medical management

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Jurkovic, D., Memtsa, M., Sawyer, E., Donaldson, A. N., Jamil, A., Schramm, K., Sana, Y., Otify, M., Farahani, L., Nunes, N., Ambler, G., Ross, J. A., Single-dose systemic methotrexate vs expectant management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial, Ultrasound in Obstetrics & Gynecology, 49, 171-176, 2017
Ref Id
659875

Country/ies where the study was carried out
UK.

Study type
RCT.

Aim of the study
To assess the effectiveness of methotrexate compared to placebo.

Study dates
August 2005 to Jun 2014.

Source of funding
Not reported.</td>
<td>Sample size
N=80 at randomisation
(N=38 randomised to placebo and N=42 randomised to methotrexate).

Characteristics
<table>
<tr><th></th><th>Placebo (N=38)</th><th>Methotrexate (N=38)</th></tr>
<tr><td>Maternal age, mean years (SD)</td><td>30 (6.7)</td><td>29 (6.9)</td></tr>
<tr><td>Gestational age, mean weeks (SD)</td><td>7 (2.1)</td><td>6.9 (1.6)</td></tr>
<tr><td>Primigravid, n (%)</td><td>21 (55)</td><td>22 (52)</td></tr>
<tr><td>Parity, median (IQR)</td><td>0 (0-1)</td><td>0 (0-1)</td></tr>
<tr><td>Previous miscarriage, n (%)</td><td>9 (24)</td><td>10 (24)</td></tr>
<tr><td>Previous ectopic pregnancy, n (%)</td><td>4 (11)</td><td>3 (7)</td></tr>
<tr><td>Serum hCG (IU/L) at baseline, median (IQR)</td><td>405 (189-784)</td><td>465 (238-914)</td></tr>
</table>
</td>
<td>Interventions
Placebo: single intramuscular injection of 0.9% sodium chloride
Methotrexate: single intramuscular injection, 50 mg/m2
Medication was given within 24 h of the initial visit.
Follow-up visits occurred on day 4, when serum hCG levels were measured and day 7, when hCG levels and liver and renal function tests were checked.
Women were advised to avoid sexual intercourse, alcohol, aspirin, non-steroidal anti-inflammatory drugs, and UV exposure.
Women were advised to increase their fluid intake and informed of the</td>
<td>Details
Computer-generated randomisation was performed. Trial investigators and patients were blinded to treatment allocation. The arms of the study were matched in terms of age, ethnicity, obstetric history, pregnancy characteristics and serum levels of hCG and progesterone. Trial medication was kept in a sealed opaque bag and distributed by the same provider. The medication was administered by personnel not related to the trial.
Analysis was ITT; it was estimated that 35 patients in each arm would be</td>
<td>Results
Resolution of ectopic pregnancy (defined as resolution of clinical symptoms and decline in hCG concentration <20 IU/L or a negative pregnancy test without the need for additional medical intervention)
Placebo group: 29/38
MTX group: 34/41

Additional treatment needed (surgery)
Placebo group: 9/38
MTX group: 7/41</td>
<td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk (computer-generated randomisation was performed)
Allocation concealment: low risk (patients and investigators were unaware of treatment allocation, randomisation list retained by third party)
Blinding of participants and personnel: low risk (double blind)
Blinding of outcome assessment: unclear risk (not mentioned whether the outcome assessors were blinded)
Blinding (performance bias and detection bias): low risk (see details above)
Incomplete outcome data: low risk (low drop-out rate [N=1])
Selective reporting: low risk (outcomes reported match with those in the study protocol http://www.isrctn.com/ISRCTN95698259)

Other information</td>
</tr>
</table>

	Serum progesterone (nmol/L) at baseline, median (IQR) 14 (7-28) 18 (8-28) US findings: gestational sac, n (%) 12 (32) 23 (55) US findings: inhomogenous solid mass, n (%) 26 (68) 19 (45) Size at presentation (mm), mean (SD) 13 (7.2) 11.4 (6.9) **Inclusion criteria** Haemodynamically stable women with a tubal ectopic pregnancy diagnosed through ultrasound; no previous history of hepatic, renal or pulmonary disease; absence of embryonic heart beat or haemoperitoneum on the US scan; normal full blood count and liver and renal function tests; and serum hCG< 1500 IU/L at baseline. **Exclusion criteria** Not reported.	common side effects of MTX.	needed to guarantee a power of 80% to detect a reduction in surgical intervention rates from 40% to 12%. Treatment was classified as unsuccessful if women were offered surgery (hCG levels had increased by >15% on 2 consecutive visits or women had abdominal pain with evidence of haemoperitoneum on US).		
Full citation Korhonen,J., Stenman,U.H., Ylostalo,P., Low-dose oral methotrexate with expectant management of ectopic pregnancy, Obstetrics and Gynecology, 88, 775-778, 1996 Ref Id 65331 **Country/ies where the study was carried out**	**Sample size** N=60 (N=30 randomised to placebo and N=30 randomised to methotrexate). Characteristics Placebo (N=30) Methotrexate (N=30) Maternal age, mean, years (SD) 31.7 (4.4) 31.8 (5.2) Gestational age, mean, days (SD) 49.1 (8.3) 52.3 (10.2)	**Interventions** Placebo: placebo tablets PO x 5 days Methotrexate: 2.5 mg/day PO x 5 days Follow-up visits occurred on days 2, where hCG levels were measured (if these had increased more than 30 to 50%, women were	**Details** Randomisation was performed with a table of random numbers. The trial was double blind, conducted in a single centre. It was estimated that N=58 had 80% power to detect a	**Results** Resolution of ectopic pregnancy (defined as decline in hCG concentration <5 IU/L) Placebo group: 23/30 MTX group: 23/30 Additional treatment needed (laparoscopy) Placebo group: 7/30 MTX group: 7/30	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: low risk (table of random numbers was used) Allocation concealment: low risk (codes with the allocations were opened at the end of the treatment)

Finland **Study type** RCT. **Aim of the study** To assess the recovery times and need for surgery in women with ectopic pregnancy. **Study dates** Not reported. **Source of funding** Not reported.	<table><tr><td>Gravidity, median (IQR)</td><td>2 (1-6)</td><td>2 (1-6)</td></tr><tr><td>Parity, median (IQR)</td><td>0.5 (0-3)</td><td>0.5 (0-3)</td></tr></table> **Inclusion criteria** Women with an ectopic pregnancy (<40 mm) and serum hCG<5000 IU/l, absent or mild abdominal pain. **Exclusion criteria** Women with an increase of serum hCG >50% in 2 days.	asked to return for transvaginal sonography), at 4 to 6 days, and 11 to 13 days, when serum hCG levels, serum glutamic oxaloacetate transaminase, red blood cell count, white blood cell count, and platelet counts were determined and transvaginal sonography was determined. Thereafter, expectant management was continued with individual monitoring at 1-3 week intervals. Women were informed about the common side effects of MTX, advised to avoid alcohol intake during the first 5 days, and limit sexual intercourse to a minimum.	difference of 30% between arms. Treatment was classified as unsuccessful if women were offered laparoscopy (hCG levels increased or plateaued, or women developed abdominal pain, intra-abdominal haemorrhage, or if an adnexal mass was visible by transvaginal sonography).		Blinding of participants and personnel: low risk (double blind) Blinding of outcome assessment: low risk (double blind) Blinding (performance bias and detection bias): low risk (see details above) Incomplete outcome data: low risk (low drop-out rate [N=2; reasons were provided]) Selective reporting: high risk (protocol does not appear to have been published) **Other information** Intervention (oral methotrexate) does not reflect current practice in the UK, where IM methotrexate is administered.
Full citation Silva, P. M., Araujo Junior, E., Cecchino, G. N., Elito Junior, J., Camano, L., Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial, Archives of	**Sample size** N=23 (N=13 randomised to placebo and N=10 randomised to MTX). **Characteristics** <table><tr><td></td><td>Placebo (N=13)</td><td>Methotrexate (N=10)</td></tr></table>	**Interventions** Placebo: single intramuscular injection of saline solution Methotrexate: single intramuscular injection, 50 mg/m2	**Details** Women were randomised and trial investigators and patients blinded to treatment allocation.	**Results** Resolution of ectopic pregnancy (defined as negative titres of hCG concentrations, <5mIU/mL) Placebo group: 12/13 MTX group: 9/10	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: unclear risk

Gynecology & Obstetrics, 291, 939-43, 2015 Ref Id 660110 **Country/ies where the study was carried out** Brazil **Study type** RCT **Aim of the study** To assess the effectiveness of MTX versus placebo in women with tubal ectopic pregnancy. **Study dates** September 2011 to January 2013. **Source of funding** Not reported.	<table><tr><td>Maternal age, mean, years (SD)</td><td>28 (6.8)</td><td>27.8 (4.8)</td></tr><tr><td>Number of pregnancies, mean (SD)</td><td>2.2 (1)</td><td>1.9 (1)</td></tr><tr><td>Parity, mean (SD)</td><td>0.8 (0.8)</td><td>0.6 (0.7)</td></tr><tr><td>Previous ectopic pregnancy, n (%)</td><td>1 (7)</td><td>1 (10)</td></tr><tr><td>Serum hCG (IU/l) at baseline, mean (SD)</td><td>794 (868)</td><td>883 (729)</td></tr><tr><td>Size at presentation (mm), mean (SD)</td><td>25.8(9.7)</td><td>28.3 (8.2)</td></tr></table> **Inclusion criteria** Haemodynamically stable women with a tubal ectopic pregnancy visible on transvaginal ultrasound; tubal mass< 0.5 cm; serum hCG <2000 IU/L at baseline; and declining titres of hCG 48h prior to treatment. **Exclusion criteria** Pregnancies of unknown location; non-tubal ectopic pregnancy; embryonic cardiac activity; signs of tubal rupture and women for whom MTX was contraindicated.	Follow-up visits occurred on day 4, where serum hCG levels were measured, and on day 7, where blood type, Rhesus factors, complete blood count, aspartate aminotransferase, alanine aminotransferase, urea and creatinine were checked.	Treatment was classified as unsuccessful if hCG titres did not fall by at least 15% between the 4th and 7th days after treatment.	Additional treatment needed (surgery) Placebo group: 1/13 MTX group: 1/10 Tubal rupture Placebo group: 0/13 MTX group: 0/10	(randomisation methods have not been reported) Allocation concealment: unclear risk (no details have been provided) Blinding of participants and personnel: low risk (double blinded) Blinding of outcome assessment: unclear risk (not mentioned whether the outcome assessors were blinded) Blinding (performance bias and detection bias): low risk (see details above) Incomplete outcome data: low risk (no drop outs have been reported) Selective reporting: high risk (protocol does not appear to have been published) **Other information**
Full citation van Mello, N. M., Mol, F., Hajenius, P. J., Ankum, W. M., Mol, B. W., van der Veen, F., van Wely, M., Randomized comparison of health-related quality of life in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 192, 1-5, 2015	**Sample size** See van Mello 2012 **Characteristics** See van Mello 2012 **Inclusion criteria** See van Mello 2012 **Exclusion criteria** See van Mello 2012	**Interventions** See van Mello 2012	**Details** See van Mello 2012	**Results** See van Mello 2012	**Limitations** See van Mello 2012 **Other information**

<table>
<tr>
<td>Ref Id
660241

Country/ies where the study was carried out
See van Mello 2012

Study type
See van Mello 2012

Aim of the study
See van Mello 2012

Study dates
See van Mello 2012

Source of funding
See van Mello 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full citation
van Mello, N. M., Mol, F., Verhoeve, H. R., van Wely, M., Adriaanse, A. H., Boss, E. A., Dijkman, A. B., Bayram, N., Emanuel, M. H., Friederich, J., van der Leeuw-Harmsen, L., Lips, J. P., Van Kessel, M. A., Ankum, W. M., van der Veen, F., Mol, B. W., Hajenius, P. J., Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison, Human Reproduction, 28, 60-7, 2012
Ref Id
377301

Country/ies where the study was carried out
The Netherlands

Study type</td>
<td>Sample size
N=73 (N=32 randomised to expectant management and N=41 randomised to MTX).

Characteristics
<table>
<tr><th></th><th>Expectant management (N=32)</th><th>Methotrexate (N=41)</th></tr>
<tr><td>Maternal age, mean, years (SD)</td><td>33.1 (5.6)</td><td>32.9 (5.7)</td></tr>
<tr><td>Gestational age, mean, weeks (SD)</td><td>7.7 (2.6)</td><td>6.7 (2)</td></tr>
<tr><td>Primigravid, n (%)</td><td>13 (41)</td><td>12 (29)</td></tr>
<tr><td>Parity, mean (SD)</td><td>0.5 (0.8)</td><td>0.7 (0.9)</td></tr>
</table>
</td>
<td>Interventions
Expectant management: did not receive any specific intervention
Methotrexate: single intramuscular injection, 1 mg/kg body weight; maximum 100 mg

MTX was given within 24 h of their initial visit. Follow-up visits occurred weekly and on day 7, where serum hCG serum concentrations and progesterone were measured. At day 7, in the MTX group, liver and renal function were</td>
<td>Details
A web-based block randomisation program stratified by hospital and serum hCG concentration (<1000 versus 1000 to 2000 IU/l). For 80% power to detect a 30% difference in treatment success at the 5% level, 72 women were required for the study.
Treatment was classified as unsuccessful in the MTX group if more than 4 MTX injections were required (surgical</td>
<td>Results
Resolution of ectopic pregnancy
Expectant management group: 19/32
MTX group: 31/41

Rupture rate
Expectant management: 0/32
MTX group: 0/41

Further treatment needed (further doses of MTX/commence MTX treatment/ salpingectomy)
Expectant management: 13/32
MTX group: 10/41</td>
<td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk (web-based block randomisation)
Allocation concealment: low risk (patients and investigators were unaware of allocation system)
Blinding of participants and personnel: high risk (not blinded)
Blinding of outcome assessment: high risk (not blinded)
Blinding (performance bias and detection bias): high risk (see details above)
Incomplete outcome data: low risk
Selective reporting: low risk (outcomes reported match with</td>
</tr>
</table>

RCT

Aim of the study
To assess whether expectant management is an alternative to MTX in women with low and plateauing hCG concentrations.

Study dates
April 2007 to January 2012.

Source of funding
Supported by a grant from the Netherlands Organization for Health Research and Development.

Previous miscarriage, mean (SD)	0.6 (1)	0.5 (1.3)
Previous ectopic pregnancy, n (%)	2 (6)	5 (13)
Serum hCG (IU/L) at baseline, mean (SD)	708 (376)	535 (500)
Serum progesterone (nmol/L) at baseline, mean (SD)	10 (37)	8 (21)
US findings: ectopic mass, n (%)	7 (21.8)	8 (19.5)
US findings: PUL, n (%)	25 (78.1)	33 (80.4)

Inclusion criteria
Haemodynamically stable women with either a tubal ectopic pregnancy visible through transvaginal sonography (an ectopic ring, or an ectopic mass and/or fluid in the pouch of Douglas) and plateauing serum hCG concentrations < 1500 IU/L at baseline
or
pregnancy of unknown location and a plateauing serum hCG concentration <2000 IU/l

A plateauing hCG level was defined as a <50% rise, or a fall between day 0 (first suspicion of an ectopic pregnancy) and day 4.

Exclusion criteria

checked and full blood count was carried out. In those given MTX, repeated doses were given (maximum of 3) if serum hCG concentrations did not fall by at least 15% in the weekly follow up.
Women who received MTX were advised to avoid sexual intercourse. They were also informed about the side effects of alcohol, aspirin, antibiotics, and non-steroidal anti-inflammatory drugs. Women were advised to increase their fluid intake, use appropriate buccal hygiene, avoid UV exposure and informed of the common side effects of MTX.

intervention was indicated).
Treatment was unsuccessful in the expectant management group if women became haemodynamically unstable or had clinical signs of tubal rupture (surgical intervention was indicated).

Health related quality of life outcomes (data from van Mello 2015)
Mean (SD) difference between baseline and 4 week scores. Higher scores indicate a lower quality of life.
SF-36 Physical component scale
Expectant management: 4 (6.3)
MTX group: 3 (6.3)
SF-36 Mental component scale
Expectant management: 9 (8.4)
MTX group: 10 (9.1)
RSCL physical symptoms
Expectant management: -7 (5.6)
MTX group: -6 (9.1)
HADS depression
Expectant management: -1.2 (2.4)
MTX group:-2.3 (3)
HADS anxiety
Expectant management: -3.1 (2.7)
MTX group: -3.5 (3.4)

those in the study protocol http://www.biomedcentral.com/1472-6874/8/10)

Other information

	Women < 18 years old; women in whom MTX was contraindicated; women with a viable ectopic pregnancy; signs of tubal rupture and/or active intra-abdominal bleeding.				