Clinical trial results:
Randomised double blind control trial of single dose methotrexate versus expectant management in women with tubal ectopic pregnancy

Summary

EudraCT number	2004-003753-56
Trial protocol	GB
Global end of trial date	25 March 2014

Results information

Result version number	v1 (current)
This version publication date	14 October 2018
First version publication date	14 October 2018
Summary attachment (see zip file)	FINAL STUDY REPORT (MTX in pregnancy Clinical Study Report 27APR15Final.docx)

Trial information

Trial identification

Sponsor protocol code	04WH19

Additional study identifiers

ISRCTN number	ISRCTN95698259
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Ms Jackie Ross, King's College Hospital NHS Foundation Trust, 0044 02032993168, jackie.ross1@nhs.net
Scientific contact	Ms Jackie Ross, King's College Hospital NHS Foundation Trust, 0044 02032993168, jackie.ross1@nhs.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2014
Global end of trial reached?	Yes
Global end of trial date	25 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of methotrexate as compared to placebo in the non-surgical management of tubal ectopic pregnancies

Protection of trial subjects:

Trial subjects will be questioned at each visit regarding symptoms and signs which may be related to the methotrexate, specifically abdominal pain, nausea, diarrhoea, dry eyes, stomatitis. Surgery will be advised if the hCG increases by more than 15% on two consecutive occasions, there is evidence of haematoperitoneum, or if the patient is in severe pain.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	31 August 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	80
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants are women presenting to the early pregnancy units with a definite ultrasound diagnosis of tubal ectopic pregnancy from two centres within the UK between 2005 and 2014.

Pre-assignment

Screening details:

The study will include women presenting to the early pregnancy units with a definite ultrasound diagnosis of tubal ectopic pregnancy.

Pre-assignment period milestones

Number of subjects started	80
Number of subjects completed	80

Period 1

Period 1 title	Whole Group (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Methotrexate

Arm description:

Participants randomized to receive methotrexate 50mg/m2 administered as an IM injection on one occasion.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Methotrexate 50mg/m2 administered as a single dose intramuscular injection,

Arm title	Placebo

Arm description:

Participants eligible for inclusion randomized to receive placebo administered as a single dose intramuscular injection

Arm type	Placebo
Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Normal saline administered as a single dose intramuscular injection

Number of subjects in period 1	Methotrexate	Placebo
Started	42	38
Completed	36	35
Not completed	6	3
Consent withdrawn by subject	6	3

Baseline characteristics

End points

End points reporting groups

Reporting group title	Methotrexate
Reporting group description:	
Participants randomized to receive methotrexate 50mg/m2 administered as an IM injection on one occasion.	
Reporting group title	Placebo
Reporting group description:	
Participants eligible for inclusion randomized to receive placebo administered as a single dose intramuscular injection	

Primary: Efficacy of systemic methotrexate as compared to placebo in the non-surgical management of tubal ectopic pregnancies.

End point title	Efficacy of systemic methotrexate as compared to placebo in the non-surgical management of tubal ectopic pregnancies.[1]
End point description:	
The primary outcome measure is the number of surgical procedures in each group	
End point type	Primary
End point timeframe:	
Within the duration of the trial - ie up to day 14 or when weekly Beta HCG level = 20 iU/L or lower.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see attached reports and publication for statistical results and analysis.

End point values	Methotrexate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: whole	36	35		

Attachments (see zip file)	Participant flow chart/4a. Patient flow chart.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

until 3 months post randomization and administration of active or placebo injection.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Methotrexate

Reporting group description:

Active intervention group

Reporting group title	Placebo group

Reporting group description: -

Serious adverse events	Methotrexate	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 36 (5.56%)	4 / 35 (11.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Ruptured ectopic pregnancy			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy	Additional description: Pregnancy reported within the 3 months post randomization and administration of IMP		
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Participants admitted to hospital overnight with abdominal pain.		
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Methotrexate	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 36 (22.22%)	4 / 35 (11.43%)	
Pregnancy, puerperium and perinatal conditions			
Abdominal pain			
subjects affected / exposed	8 / 36 (22.22%)	4 / 35 (11.43%)	
occurrences (all)	8	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2010	Clarification regarding extension to end of trial date detailed in the protocol.
17 August 2011	Amendment to allow each Pharmacy to use their own stock and brand of IMP/ placebo rather than have them supplied from a central location. Labels will remain the same except the name of the dispensing pharmacy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 February 2008	Changes in conduct or management of the trial Change or addition of principal investigator(s), co-ordinating investigator y Change/addition of site(s)	15 May 2008

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27731538