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A randomised controlled trial looking at whether adding a drug called mifepristone to standard medical treatment (with a drug called methotrexate) reduces the need for emergency surgery for tubal ectopic pregnancy in women clinically suitable for medical management of tubal ectopic pregnancy

Submission date
14/10/2025

Recruitment status
Recruiting

Registration date
23/12/2025

Overall study status
Ongoing

Last Edited
09/04/2026

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Ectopic pregnancy (EP) affects 1 in 80 pregnancies. Ectopic pregnancy is the leading cause of death for women in the first 3 months of pregnancy. It occurs when a pregnancy grows in an abnormal location outside the womb, usually within a Fallopian tube. These pregnancies cannot develop normally. As they grow, there is a risk that the tube will burst ('ruptured' ectopic pregnancy) causing life-threatening, internal bleeding. Historically, the only treatment was an operation to remove the affected Fallopian tube together with the ectopic pregnancy. Nowadays around 40% of women can be diagnosed early (before signs of 'rupture'), and the ectopic pregnancy can be treated medically with an injection, called methotrexate, which avoids a hospital stay. Some very early ectopic pregnancies with low and reducing hormone levels may resolve without treatment.

In some women, methotrexate is suboptimal. Methotrexate can take several weeks to work, involve multiple hospital visits, and does not work for every EP. One in seven (1 in 7) women will need a second injection and just under a third will ultimately need surgery to treat the EP. There is a need to improve non-surgical treatment of EP, which could reduce the need for emergency surgery, repeat doses and time to full physical recovery.

A drug called mifepristone, which is used for miscarriage treatment, could improve the success of methotrexate treatment by acting against a key pregnancy hormone - progesterone. Mifepristone is taken by mouth as a once-off medication and has few side effects. Previous research has shown that mifepristone might improve the effect of methotrexate treatment, but

it has never been formally tested in a large enough, high-quality research study. We plan to do a large clinical trial to test whether adding mifepristone (taken as a once-off treatment) at the same time as standard Methotrexate treatment versus taking methotrexate with a placebo (dummy drug) improves the treatment success for tubal EP. Successful treatment will be determined if the treatment works to treat the EP without the need for surgery.

Who can participate?
328 women with a tubal EP from 40 UK hospitals, who are eligible for methotrexate and who have opted for methotrexate, will be invited to take part in our trial. Participants will have an equal chance of getting either mifepristone tablets or placebo tablets at the same time as their first methotrexate injection.

What does the study involve?
To understand how mifepristone might work, we will collect blood samples and check how the levels of two key hormones - progesterone and human chorionic gonadotrophin (known as hCG), change before, during and after treatment (taken before treatment starts then on days 1,4 ,7 and 11 which is usual care after methotrexate to have hCG testing at these times, progesterone will be an additional analysis on the same blood sample i.e. no additional samples needed). We will compare the need for emergency surgery, the time for pregnancy hormones in blood tests to reduce to non-pregnant levels, the number of hospital visits and number of women who require a second injection of the methotrexate, as well as safety and acceptability of treatment in both groups.

What are the possible benefits and risk of taking part?
The information we get from this study may help us improve the treatment for women who experience a tubal Ectopic Pregnancy in the future.

Although most people tolerate mifepristone well, some people may develop some side effects. If you do encounter any side effects these will be monitored, recorded and managed closely by your hospital care team. Other than these potential side, we do not believe there are any other possible disadvantages to taking part in AMETHYST.

Where is the study run from?
University of Aberdeen (UK)

When is the study starting and how long is it expected to run for?
October 2025 to July 2028

Who is funding the study?
The study is funded by the National Institute of Health and Care Research (the research arm of the NHS) and co-sponsored by the University of Aberdeen and NHS Grampian.

Who is the main contact?
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This study is being led by Dr Andrea Woolner from the University of Aberdeen, a.woolner@abdn.ac.uk

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Additional identifiers

Integrated Research Application System (IRAS)
1010254

Protocol number
3-049-25

Study information

Scientific Title
AMETHYST: A multicentre, double-blind, placebo-controlled randomised trial comparing a combination of mifepristone and methotrexate versus methotrexate and placebo as a medical treatment for tubal ectopic pregnancy

Acronym
AMETHYST

Study objectives
Primary objective:
To compare a combination of methotrexate and mifepristone with methotrexate and placebo for the outcome of the need for surgical intervention for tubal ectopic pregnancy.

Secondary objectives:
To compare methotrexate and mifepristone with methotrexate and placebo for women with

tubal ectopic pregnancy for the outcomes of:
1. The need for a second methotrexate injection
2. The number of days to resolution of the EP (return of serum hCG to <15 IU/L i.e. non-pregnant levels)
3. The number of hospital visits related to their ectopic pregnancy/ treatment (until resolution of ectopic pregnancy or surgery to treat their tubal ectopic pregnancy or end of 12 week follow up period)
4. Safety
5. Patient acceptability and satisfaction at 7 days & 12 weeks
6. Return of menstrual cycle by 12 weeks (end of study period)

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 23/12/2025, West of Scotland REC 1 (West of Scotland Research Ethics Service, Admin Building, Level 2, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G120XH, United Kingdom; -; ggc.wosrec1@nhs.scot), ref: 25/WS/0168

Primary study design
Interventional

Study design
Interventional double-blind randomized parallel-group placebo-controlled trial

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Ectopic pregnancy

Interventions
Randomisation to AMETHYST takes place after fully informed consent is received by a locally delegated member of staff. Randomisation is double blinded, computer-generated randomisation in a 1:1 ratio to mifepristone or placebo, minimised on centre, baseline hCG levels and ectopic size.

The intervention is 600 mg mifepristone when used alongside standard medical treatment for tubal ectopic pregnancy (methotrexate) compared to placebo when used alongside standard medical treatment for tubal ectopic pregnancy (methotrexate). For the purposes of the study, methotrexate is defined as the non-investigational medicinal product (NIMP).

Participants will take a single dose of 600 mg mifepristone (or identical placebo), with no dose adjustment. The dose will be taken orally as three individual capsules. The mifepristone and placebo will be administered by clinical staff (doctors, nurses or midwives), ideally within the same appointment that the methotrexate is administered, or as soon as possible on the same day (within 12 hours maximum).

All participants will be followed up for 12 weeks (post IMP/ Placebo administration). The trial follow-up is at days 1, 4, 7, 11 and thereafter weekly (up to 12 weeks) until hCG levels drop to non-pregnant levels. This mirrors Standard of Care, where women are asked to attend for these

routine follow-up visits to monitor the success of methotrexate and identify the need for any further treatment.

Patient acceptability and satisfaction will be assessed via questionnaire at 7 days and 12 weeks after randomisation. The 12-week questionnaire will also ask about return of menstrual cycle since the ectopic pregnancy.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Mifepristone Linepharma 200 mg tablets

Primary outcome(s)
Rate of surgery to treat tubal ectopic pregnancy (removal of Fallopian tube [salpingectomy] /incision of Fallopian tube to remove ectopic pregnancy (salpingostomy) by laparoscopy /laparotomy) measured using patient records at 12 weeks

Key secondary outcome(s)
1. Second dose (injection) of methotrexate required measured using patient records within 12 weeks
2. Number of days to resolution of tubal ectopic pregnancy (return of hCG to <15IU/l, i.e. non pregnant levels) from treatment start to 12 weeks measured using patient records
3. The number of hospital visits related to their ectopic pregnancy/ treatment (until resolution of ectopic pregnancy to <15IU/l, or surgery to treat their tubal ectopic pregnancy or end of 12 week follow up period) measured using patient records
4. Safety (measured by recorded Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions as classified and reported by the clinical team) up to 12 weeks
5. Patient acceptability and satisfaction measured by patient questionnaire at 7 days and 12 weeks
6. Return of menstrual cycle by 12 weeks (end of study period) measured by patient questionnaire

Mechanistic outcomes:
7. Serum progesterone and hCG levels (baseline and post-treatment) including trajectory and rate of decline to non-pregnant levels (measured via standard care blood sample) t baseline and 12 weeks

Completion date
31/08/2028

Eligibility

Key inclusion criteria
1. Women aged 16 years and older
2. Ultrasound diagnosis of likely tubal ectopic pregnancy defined as extrauterine gestational sac with yolk sac and/or embryo, without cardiac activity or extrauterine sac-like structure or

inhomogeneous adnexal mass with no evidence of normally sited intrauterine pregnancy on ultrasound scan; includes interstitial ectopic pregnancy within diagnosis of tubal ectopic pregnancy
3. Minimum of two hCG measurements, taken at least two days apart, with a plateau or suboptimal rising pattern according to clinical judgment
4. Deemed suitable by clinical team for methotrexate treatment
5. Where the woman wishes to opt for methotrexate treatment
6. Methotrexate treatment planned to be administered within 24 hours of decision to proceed with methotrexate treatment
7. A pre-treatment serum hCG of 1000 to 5000 IU/L*
8. Where an individual woman's initial pre-treatment serum hCG level(s) is
8.1. Clinically stable (Early Warning Score as per local policy of no more than 2)
8.2. Haemoglobin at baseline between 100 and 165 g/L
8.3. Able to attend outpatient follow up as per local clinical protocol for methotrexate treatment

*hCG testing is a routine part of standard of care and diagnostic process in confirming an ectopic pregnancy. Sites will take pre-treatment hCG as per their usual clinical process and this result will be recorded for the purposes of the trial. The most recent hCG will be used as the baseline hCG for analysis purposes, but we will also ask sites to provide all pre-treatment hCGs to the study team in the baseline CRF so that the trajectory of pre-treatment hCGs can also be analysed alongside post-treatment results. None of the hCG blood tests are required specifically for the purposes of the trial – we will collect only results taken as part of standard of care, but for eligibility purposes pre-treatment levels of 1000-5000 IU/L are mandated. This is to avoid recruitment of women whose ectopic pregnancy may already be resolving i.e. sequentially reducing low level hCGs where NICE guidance suggests expectant management can be offered. This is vital in an efficacy trial to ensure women with ectopic pregnancies where methotrexate is appropriate in line with NICE guidance is offered.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 Years

Upper age limit
100 Years

Sex
Female

Total final enrolment
0

Key exclusion criteria

1. Evidence of normally sited (intrauterine) pregnancy
2. Breastfeeding
3. Immediate pre-treatment hCG
4. Women with any hCG measurement >5000 IU/L
5. Women eligible for and opt for expectant management
6. Clinically unstable (any component of Early Warning Score of 3 or more)
7. Women with a pregnancy of unknown location
8. Women with uterine ectopic pregnancy (such as caesarean scar or intramural)
9. Women with non-tubal extrauterine ectopic pregnancy (such as abdominal or ovarian ectopic pregnancy)
10. Women with heterotopic pregnancy
11. Women with ectopic pregnancy mass on ultrasound of greater than or equal to 3.5cm (see ESHRE guidelines on how to measure ectopic pregnancy mass)
12. Women with ectopic pregnancy mass with visible fetal pole heart pulsation [live ectopic pregnancy]
13. Evidence of ruptured ectopic pregnancy including evidence of significant free fluid on ultrasound (see ESHRE guidelines), or severe abdominal pain or where clinician deems unsuitable for medical management
14. Significantly abnormal liver/ renal/ haematological indices** including pre-existing blood dyscrasia as per usual clinical care in deciding if appropriate to offer methotrexate as per local policies
15. Active pulmonary disease
16. Severe, acute or chronic infections and immunodeficiency syndrome
17. Inherited porphyria
18. Significant gastrointestinal medical illnesses including chronic liver disease and gastric /peptic ulcer disease as per usual clinical care in deciding if appropriate to offer methotrexate as per local policies
19. Known allergy to methotrexate (the NIMP) or mifepristone (IMP)
20. Adrenal insufficiency
21. Known serious conditions being treated with systemic corticosteroids
22. Severe uncontrolled asthma
23. Women lacking capacity to consent
24. Participating in any active intervention phase or other clinical trial of an investigational medicinal product
25. Any contraindication for mifepristone treatment (excluding tubal ectopic pregnancy) or methotrexate treatment that is listed in the relevant SmPC
26. Women taking strong CYP3A4 inhibitors or strong CYP3A4 inducers such as those listed in the British National Formulary (BNF: https://bnf.nice.org.uk/interactions/mifepristone/)

**It is standard care to obtain full blood count, liver function tests and renal function (often known as urea and electrolytes) prior to methotrexate treatment (the NIMP). These are not required before clinical treatment with mifepristone. Because all trial participants will receive the NIMP as part of standard of care this is included as an exclusion criteria. It is acceptable to use a sample taken per standard of care for this purpose within the last 4 weeks.

Date of first enrolment
01/04/2026

Date of final enrolment
31/08/2028

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
-
-
England
-

Sponsor information

Organisation
University of Aberdeen

ROR
https://ror.org/016476m91

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during the current study will be available upon reasonable request upon completion of the study. A request to access the datasets generated during the study should be directed in the first instance to datasharing@abdn.ac.uk The dataset will be available in fully anonymised electronic form, at an individual level, and in accordance with participant consent. Applicants will be asked to complete a data request form, which will be reviewed by a Data Sharing Committee which includes the Chief Investigator. Applications will be assessed on a case-by-case basis by bona fide researchers. We are obligated to ensure that optimal use is made of the data that is collected for research, and we recognise the value of sharing individual-level data. The interests of research participants, researchers and other stakeholders will be considered when considering each application.

IPD sharing plan summary

Available on request