ISRCTN67795930 https://doi.org/10.1186/ISRCTN67795930

A trial designed to treat women with a diagnosis of ectopic pregnancy with a combination of methotrexate (standard treatment) and gefitinib (trial agent)

Submission date
15/09/2016

Recruitment status
No longer recruiting

Registration date
15/09/2016

Overall study status
Completed

Last Edited
06/11/2023

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Plain English summary as of 23/11/2018:
Background and study aims
An ectopic pregnancy occurs when a fertilised egg attaches itself somewhere other than inside the womb, usually in one of the fallopian tubes (the tubes connecting the ovaries and womb, which a mature egg travels down during ovulation). Sadly, there is no chance of this pregnancy surviving and if it is allowed to continue it could potentially be life-threatening to the mother. If an ectopic pregnancy is detected early enough, it can be treated with a single dose of a drug called methotrexate which stops the pregnancy developing. In some cases this single dose of methotrexate is not successful and a further dose of methotrexate is required or surgery may be needed. A more effective treatment is therefore needed to reduce the requirement for repeat doses of methotrexate or surgery. Previous studies using a drug called gefitinib (a drug used in lung cancer patients) in addition to methotrexate have shown promising results, as it appears to have a blocking effect on the cells found in an ectopic pregnancy. These studies were in a small number of women and so a larger study is needed to prove the effectiveness of this treatment. The aim of this study is to find out whether treatment using methotrexate and gefitinib is more effective than methotrexate alone.

Who can participate?
Women aged between 18 and 50 who are being treated for an ectopic pregnancy.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive an injection of methotrexate and then take tablets containing gefitinib once a day for seven days. Those in the second group receive an injection of methotrexate and then take tablets containing a placebo (dummy drug) once a day for seven days. Participants in both groups are then monitored until the resolution of the ectopic pregnancy defined by a serum hCG level of ≤15 IU/l or surgical removal of the ectopic pregnancy.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Royal Infirmary of Edinburgh (lead site) and 70 other centres throughout the England, Scotland and Wales (UK)

When is the study starting and how long is it expected to run for?
April 2016 to December 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Mrs Ann Doust
gem3@ed.ac.uk

Previous plan English summary:
Background and study aims
An ectopic pregnancy occurs when a fertilised egg attaches itself somewhere other than inside the womb, usually in one of the fallopian tubes (the tubes connecting the ovaries and womb, which a mature egg travels down during ovulation). Sadly, there is no chance of this pregnancy surviving and if it is allowed to continue it could potentially be life-threatening to the mother. If an ectopic pregnancy is detected early enough, it can be treated with a single dose of a drug called methotrexate which stops the pregnancy developing. In some cases this single dose of methotrexate is not successful and a further dose of methotrexate is required or surgery may be needed. A more effective treatment is therefore needed to reduce the requirement for repeat doses of methotrexate or surgery. Previous studies using a drug called gefitinib (a drug used in lung cancer patients) in addition to methotrexate have shown promising results, as it appears to have a blocking effect on the cells found in an ectopic pregnancy. These studies were in a small number of women and so a larger study is needed to prove the effectiveness of this treatment. The aim of this study is to find out whether treatment using methotrexate and gefitinib is more effective than methotrexate alone.

Who can participate?
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What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive an injection of methotrexate and then take tablets containing gefitinib once a day for seven days. Those in the second group receive an injection of methotrexate and then take tablets containing a placebo (dummy drug) once a day for seven days. Participants in both groups are then monitored for three months in order to find out whether they required any additional treatment (surgery or further methotrexate).

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Royal Infirmary of Edinburgh (lead site) and 49 other centres throughout the England, Scotland and Wales (UK)

When is the study starting and how long is it expected to run for?
April 2016 to December 2018

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Ms Kirandeep Sunner
gem3@trials.bham.ac.uk

Study website
https://www.ed.ac.uk/centre-reproductive-health/gem3

Contact information

Type(s)
Scientific

Contact name
Mrs Ann Doust

Contact details
GEM3 Trial Management Team
The University of Edinburgh
Room S7128
2nd Floor Simpson Centre
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh
United Kingdom
EH16 4SA
+44 131 242 9492
gem3@ed.ac.uk

Additional identifiers

EudraCT/CTIS number
2015-005013-76

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
AC15004

Study information

Scientific Title

A multi-centre, double-blind, placebo-controlled, randomised trial of combination methotrexate and gefitinib versus methotrexate alone to treat tubal ectopic pregnancies (GEM3)

Acronym
GEM3

Study objectives
Study hypothesis as of 23/11/2018:
A combination of intramuscular methotrexate and oral gefitinib, an EGFR anatagonist, is more effective in preventing the need for surgery in the treatment of ectopic pregnancy than methotrexate alone.

Previous study hypothesis:
Combination of intramuscular methotrexate and oral gefitinib, an EGFR antagonist, is a more effective treatment for ectopic pregnancy than methotrexate alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scottish A Research Ethics Committee, 29/02/2016, ref: 16/SS/0014

Study design
Multi-centre double-blind randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

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

Interventions
Participants will be randomly allocated to one of two study arms using a computer-based algorithm to avoid chance imbalances in stratification variables.

Arm 1: Participants are administered 50 mg/m2 methotrexate as intramuscular injection and take a single tablet containing 250 mg gefitinib daily for 7 days.

Arm 2: Participants are administered 50 mg/m2 methotrexate as intramuscular injection and take a single tablet containing a placebo daily for 7 days.

Participants will be monitored as per local standards care for an ectopic pregnancy post randomisation so they will have their routine blood tested which includes checking safety bloods and measurement of hCG levels. In addition to this the trial requires participants to have an additional safety blood to ensure that the treatment is not causing any untoward effects. Once the hCG level has dropped to 15iu/L the research team will call the participant 3 months after resolution to complete the 3 month questionnaire.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Gefitinib, methotrexate

Primary outcome measure
Primary outcome measure as of 23/11/2018:
Surgical intervention for treatment of the index EP (salpingectomy/salpingostomy by laparoscopy/laparotomy) is measured using patient notes at each visit until resolution of EP.

Previous primary outcome measure:
Need for surgical intervention for treatment of ectopic pregnancy is determined through interviews with patients at clinic appointments and at the 3 month follow up telephone call.

Secondary outcome measures
Secondary outcome measures as of 23/11/2018:
1. The need for a second dose of MTX is measured using medical notes at each visit.
2. Number of days to resolution of tEP is measured using blood test at baseline and then at resolution is defined by serum hCG levels falling to non-pregnancy levels (hCG ≤15 IU/L), which corresponds to a negative urinary pregnancy test using the most sensitive assays.
3. Number of treatment-associated hospital visits until resolution or emergency 'rescue' surgery is measured using patient interviews at each hospital visit.
4. Return to menses, assessed 3 months post-resolution by telephone interview.
5. Safety and tolerability: women will be assessed clinically (at each contact as per local policies) and biochemically (haematological, renal, and liver function tests between days 14–21 post-treatment) and these will be repeated if deemed clinically significant.
6. Acceptability of treatment: assessed 3 months post-resolution by participant-reported Likert scores via a telephone interview

Previous secondary outcome measures:
1. Need for additional methotrexate treatment is determined through interviews with patients at clinic appointments
2. Time to hCG resolution (days) from randomisation to hCG level of ≤15 iu/L calculated from the day of diagnosis to the day the hCG dropped to 15iu/L, is determined through blood testing at baseline and throughout the trial based on local trust policy
3. Number of treatment-associated hospital visits until resolution or scheduled/emergency surgery is determined through medical record review at 3 months

4. Safety/tolerability is assessed through blood testing undertaken within 3 days of randomisation and 14-21 days post randomisation and patient interviews at clinic visits 14-21 days post randomisation
5. Acceptability of treatment is assessed using the Likert score after 3 months through a follow up telephone call at 3 months
6. Return to menses is assessed after 3 months post resolution of the ectopic pregnancy through a follow up telephone call at 3 months

Overall study start date
01/04/2016

Completion date
01/03/2022

Eligibility

Key inclusion criteria
1. Clinical decision made for treatment of tubal EP with MTX
2. Able to understand all information (written and oral) presented (using an interpreter if necessary) and provide signed consent
3. Women 18-50 years at time of randomisation
4. Diagnosis of either:
4.1. Definite tubal EP (extrauterine gestational sac with yolk sac and/or embryo, without cardiac activity on USS) or
4.2. Clinical decision of probable tubal EP (extrauterine sac-like structure or inhomogeneous adnexal mass on USS with a background of sub optimally rising serum hCG concentrations (on at least 2 different days)
5. Pre-treatment serum hCG level of 1000–5000 iu/L (within 1 calendar day of treatment)
6. Clinically stable
7. Haemoglobin between 100 and 165 g/L within 3 calendar days of treatment
8. Able to comply with treatment and willing to participate in follow up

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
Female

Target number of participants
338

Total final enrolment
328

Key exclusion criteria
1. Women with a Ppregnancy of unknown location (PUL)
2. Evidence of intrauterine pregnancy
3. Breastfeeding
4. Hypersensitivity to gefitinib
5. Women with mean EP mass on ultrasound greater than 3.5cm (mean dimensions)
6. Women with evidence of intrauterine pregnancy
7. Evidence of significant intra-abdominal bleed on ultrasound USS defined by echogenic free fluid above the uterine fundus or surrounding ovary within 1 calendar day of treatment
8. Significant abdominal pain, guarding/rigidity
9. Clinically significant abnormal liver/renal/haematological indices noted within 3 calendar days of treatment
10. Galactose intolerance
11. Significant pre-existing dermatological disease eg severe psoriasis/eczema
12. Significant pulmonary disease eg severe/uncontrolled asthma
13. Significant gastrointestinal medical illness eg Crohn's disease/ulcerative colitis
14. Participating in any other clinical trial of an investigational medicinal product
15. Previous participation in GEM3
16. Women of Japanese ethnicity

Date of first enrolment
02/11/2016

Date of final enrolment
06/10/2021

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Royal Infirmary of Edinburgh
NHS Lothian
51 Little France Crescent
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
Princess Royal Maternity Hospital
NHS Greater Glasgow and Clyde
Glasgow
United Kingdom
G31 2ER

Study participating centre
Crosshouse Hospital
NHS Ayrshire and Arran
Kilmarnock
United Kingdom
KA2 0BE

Study participating centre
Ninewells Hospital
NHS Tayside
Dundee
United Kingdom
DD2 1SG

Study participating centre
West Suffolk Hospital
West Suffolk NHS Foundation Trust
Bury St Edmunds
United Kingdom
IP33 2QZ

Study participating centre
Burnley General Hospital
East Lancashire Hospitals NHS Trust
Burnley
United Kingdom
BB10 2PQ

Study participating centre
James Cook Hospital
South Tees Hospital NHS Foundation Trust

South Tees
United Kingdom
TS4 3BW

Study participating centre
Chesterfield Royal Hospital
Chesterfield Royal NHS Foundation Trust
Chesterfield
United Kingdom
S44 5BL

Study participating centre
Norfolk and Norwich University Hospital
Norfolk and Norwich University Hospital NHS Trust
Norwich
United Kingdom
NR4 7UY

Study participating centre
Countess of Chester Hospital
The Countess of Chester Hospital NHS Foundation Trust
Chester
United Kingdom
CH2 1UL

Study participating centre
St Mary's Hospital
Central Manchester University Hospital NHS Foundation Trust
Manchester
United Kingdom
M13 9WL

Study participating centre
Heartlands Hospital
Heart of England NHS Foundation Trust
Birmingham
United Kingdom
B9 5SS

Study participating centre
Stoke Mandeville Hospital
Buckinghamshire Healthcare NHS Trust
Aylesbury
United Kingdom
HP21 8AL

Study participating centre
Forth Valley Hospital
NHS Forth Valley
Larbert
United Kingdom
FK5 4WR

Study participating centre
Addenbrookes Hospital
Cambridge University Hospital NHS Foundation Trust
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
University Hospital Wishaw
NHS Lanarkshire
Wishaw
United Kingdom
ML2 0DP

Study participating centre
Princess Alexandra Hospital
The Princess Alexandra Hospital NHS Trust
Harlow
United Kingdom
CM20 1QX

Study participating centre
New Cross Hospital
The Royal Wolverhampton NHS Trust
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
East Surrey Hospital
Surrey and Sussex NHS Trust
Redhill
United Kingdom
RH1 5RH

Study participating centre
Frimley Park Hospital
Frimley Park Hospital NHS Trust
Camberley
United Kingdom
GU16 7UJ

Study participating centre
Warrington Hospital
Warrington and Halton Hospitals NHS Foundation Trust
Warrington
United Kingdom
WA5 1QG

Study participating centre
University Hospital Coventry
University Hospitals Coventry and Warwickshire NHS Trust
Coventry
United Kingdom
CV2 2DX

Study participating centre
Victoria Hospital
NHS Fife
Kirkcaldy
United Kingdom
KY1 2SD

Study participating centre
Royal Stoke Hospital
University Hospitals North Midlands NHS Trust

Stoke-on-Trent
United Kingdom
ST4 6QG

Study participating centre
Hinchingbrooke Hospital
North West Anglia NHS Foundation Trust
Huntingdon
United Kingdom
PE29 6NT

Study participating centre
St Thomas' Hospital
Guys and St Thomas' NHS Foundation Trust
London
United Kingdom
SE1 7EH

Study participating centre
The Queen's Medical Centre
Nottingham University NHS Trust
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Darent Valley Hospital
Dartford and Gravesham NHS Trust
Dartford
United Kingdom
DA2 8DA

Study participating centre
St Michael's Hospital
University Hospitals Bristol NHS Foundation Trust
Bristol
United Kingdom
BS2 8EG

Study participating centre
West Middlesex Hospital
Chelsea and Westminster Hospitals NHS Foundation Trust
Isleworth
United Kingdom
TW7 6AF

Study participating centre
Leighton Hospital
Mid Cheshire Hospitals NHS Foundation Trust
Crewe
United Kingdom
CW1 4QJ

Study participating centre
St Helier Hospital
Epsom and St Helier University Hospitals NHS Trust
Carshalton
United Kingdom
SM5 1AA

Study participating centre
Peterborough City Hospital
North West Anglia Foundation Trust
Peterborough
United Kingdom
PE3 9GZ

Study participating centre
King's College Hospital
King's College Hospital NHS Foundation Trust
London
United Kingdom
SE5 9RS

Study participating centre
Raigmore Hospital
NHS Highland
Inverness
United Kingdom
IV2 3UJ

Study participating centre
Hillingdon Hospital
Hillingdon Hospitals NHS Foundation Trust
Uxbridge
United Kingdom
UB8 3NN

Study participating centre
Birmingham Women's Hospital
Birmingham Women's and Children's NHS Foundation Trust
Birmingham
United Kingdom
B15 2TG

Study participating centre
Sunderland Royal Hospital
City Hospitals Sunderland NHS Trust
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Southend Hospital
Southend University Hospital NHS Foundation Trust
Southend
United Kingdom
SS0 0RY

Study participating centre
University College London Hospital
University College London Hospital NHS Foundation Trust
London
United Kingdom
NW1 2BU

Study participating centre
Darlington Memorial Hospital
County Durham and Darlington NHS Foundation Trust

Darlington
United Kingdom
DL3 6HX

Study participating centre
University Hospital of Durham
County Durham and Darlington NHS Foundation Trust
Durham
United Kingdom
DH1 5TW

Study participating centre
Scunthorpe General Hospital
Northern Lincolnshire and Goole Hospitals NHS Foundation Trust
Scunthorpe
United Kingdom
DN15 7BH

Study participating centre
Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield
United Kingdom
S10 2JF

Study participating centre
Queen's Hospital Romford
Barking, Havering and Redbridge University Hospitals NHS Trust
Romford
United Kingdom
RM7 0AG

Study participating centre
Worcestershire Royal Hospital
Worcester Acute Hospital NHS Trust
Worcester
United Kingdom
WR5 1DD

Study participating centre
Gloucestershire Royal Hospital
Gloucestershire Hospitals NHS Foundation Trust
Gloucester
United Kingdom
GL1 3NN

Study participating centre
Whiston Hospital
St Helen's and Knowsley Teaching Hospital NHS Trust
Whiston
United Kingdom
L35 5DR

Study participating centre
Furness General Hospital
University Hospital of Morecombe Bay NHS Foundation Trus
Barrow-in-Furness
United Kingdom
LA14 4LF

Study participating centre
Queen's Hospital
University Hospitals of Derby and Burton NHS Foundation Trust
Burton
United Kingdom
DE13 0RB

Study participating centre
Queen Charlotte and Chelsea Hospital
Imperial College Healthcare NHS Trust
London
United Kingdom
W12 0HS

Study participating centre
Southmead Hospital
North Bristol NHS Trust
Bristol
United Kingdom
BS10 5NB

Study participating centre
Homerton Hospital
Homerton University NHS Foundation Trust
London
United Kingdom
E9 6SR

Study participating centre
Epsom General Hospital
Epsom and St Helier University Hospitals NHS Trust
Epsom
United Kingdom
KT18 7EG

Study participating centre
Warwick Hospital
South Warwickshire NHS Foundation Trust
Warwick
United Kingdom
CV34 5BW

Study participating centre
Rotherham General Hospital
The Rotherham NHS Foundation Trust
Rotherham
United Kingdom
S60 2UD

Study participating centre
Basildon University Hospital
Basildon and Thurrock University Hospitals NHS Foundation Trust
Basildon
United Kingdom
SS16 5NL

Study participating centre
Royal Free Hospital
Royal Free London NHS Foundation Trust

London
United Kingdom
NW3 2QG

Study participating centre
Cardiff Royal Infirmary
Cardiff and Vale University Health Board
Cardiff
United Kingdom
CF24 0JT

Study participating centre
Tameside Hospital
Tameside and Glossop Integrated Care NHS Foundation Trust
Ashton-under-Lyme
United Kingdom
OL6 9RW

Study participating centre
Wrexham Maelor Hospital
Betsi Cadwaladr University Health Board
Wrexham
United Kingdom
LL13 7TD

Study participating centre
St Peter's Hospital
Ashford and St Peter's Hospitals NHS Foundation Trust
Chertsey
United Kingdom
KT16 0PZ

Study participating centre
Doncaster Royal Infirmary
Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust
Doncaster
United Kingdom
DN2 5LT

Sponsor information

Organisation
University of Edinburgh and NHS Lothian ACCORD

Sponsor details
The Queens Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ
+44 121 415 91111
accord@nhslothian.scot.nhs.uk

Sponsor type
University/education

Website
http://www.accord.ed.ac.uk

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Government

Funder Name
National Institute for Health 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

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
01/08/2022

Individual participant data (IPD) sharing plan
Anonymous data will be made available to other researchers upon request, for example for individual patient data meta-analysis, if the aim is to answer further resolved questions in a scientifically rigorous study design. Please contact Ann Doust (ann.doust@ed.ac.uk).

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data is used. #datasaveslives. You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

(added 06/11/2023): BCTU operate a controlled-access model where we vet access requests (approved by CI), this ensures the data is delivered to only those who can demonstrate they have the plan and expertise to handle it appropriately.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	20/11/2018		Yes	No
Results article		01/02/2023	06/02/2023	Yes	No
Results article	Secondary analysis	13/05/2023	15/05/2023	Yes	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan	version 2.0	23/02/2022	06/11/2023	No	No