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Comparing intrauterine insemination and in vitro fertilisation for unexplained infertility: a study on effectiveness and costs

Submission date
22/05/2023

Recruitment status
Recruiting

Registration date
12/01/2024

Overall study status
Ongoing

Last Edited
15/07/2025

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
Unexplained infertility affects a significant number of couples, causing emotional distress and leading them to consider costly and intensive treatments like in vitro fertilization (IVF). IVF involves hormone injections to stimulate egg production, followed by egg retrieval, fertilization in a lab, and embryo transfer. However, IVF carries risks such as infection and ovarian hyperstimulation syndrome. Intrauterine insemination (IUI), a simpler procedure with lower hormone doses, directly introduces sperm into the womb to increase the chances of fertilization. Current UK guidelines recommend IVF for unexplained infertility, but recent research suggests that three cycles of IUI may offer similar success rates and be more cost-effective. To investigate this further, a randomized controlled trial is planned, where couples will be randomly assigned to receive either three cycles of IUI or proceed directly to an IVF cycle. Couples assigned to IUI can still opt for IVF if unsuccessful. The study will assess patient outcomes such as quality of life, work disruption, and emotional/physical burden, alongside evaluating cost-effectiveness.
The research has been developed in collaboration with fertility patient treatment co-design groups, commissioners, and laypeople. Patient voices have been incorporated through questionnaires, focus groups, and the involvement of a patient co-applicant and infertility counselor. The study aims to recruit a diverse patient population and intends to share the results with healthcare professionals, policymakers, patient support groups, and the general public through various channels, including medical journals, scientific meetings, and accessible online resources.

Who can participate?
Couples with a diagnosis of unexplained infertility, referred to fertility centres for assisted conception, will be considered for the UNiTY trial. Both members of the couple must be aged over 18 years, and the female member must be aged under 40 years.

What does the study involve?
By taking part in this trial, you will either have your standard single IVF treatment, unchanged and as suggested by your care team, or up to three IUI treatments. Neither you nor your doctor or nurse will be able to choose which treatment you receive. Your treatment will be decided by a

computer at the UNITY Trial Office. The computer will allocate the treatment randomly. You will have an equal chance of receiving either 3 cycles of IUI or 1 cycle of IVF. This method of research is called a “randomised controlled trial”.

What are the possible benefits and risks of participating?
IVF is routinely performed in the UK, and IUI is well established and is routinely performed in many countries around the world. There are no other trial-specific risks beyond those such as multiple births that were explained in the information that you had before treatment. You will sign routine local treatment consent forms as would any couple beginning fertility treatment.
If you are allocated to the IUI treatment you will get up to three cycles of IUI before progressing on to your originally suggested IVF treatment.
If you are allocated to the IVF treatment, being part of the study will not change your chances of having a baby.
In either case, you will be taking part in research which may change how we routinely treat couples like yourselves with unexplained infertility.

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

When is the study starting and how long is it expected to run for?
April 2023 to August 2028

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

Who is the main contact?
Prof. Jackson Kirkman-Brown, j.kirkmanbrown@bham.ac.uk

Study website
https://www.spermeggembryo.com/UNiTY

Contact information

Type(s)
Principal Investigator

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Prof Jackson Kirkman-Brown

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
314070

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 314070, NIHR135258, CPMS 60300, RG_22-146

Study information

Scientific Title
A randomised controlled trial evaluating the clinical and cost-effectiveness of intrauterine insemination (IUI) versus in vitro fertilisation (IVF) for unexplained infertility

Acronym
UNiTY

Study objectives
To evaluate the clinical effectiveness by analysing the birth rate after treatment with up to three cycles of intrauterine insemination (IUI), compared to one cycle of in vitro fertilisation (IVF) for couples with unexplained infertility

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 12/02/2024, East Midlands - Derby Research Ethics Committee (2 Redman Place, Stratford, London, EC20 1JQ, United Kingdom; +44 207 104 8236; derby.rec@hra.nhs.uk), ref: 24/EM/0003

Study design
Parallel open multicentre non-inferiority randomized controlled trial with integrated economic healthcare science and bioethics evaluations and an internal pilot phase with embedded qualitative process evaluation

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Unexplained infertility

Interventions
Couples who enter the trial will be randomised to receive either three cycles of letrozole stimulated Intra Uterine Insemination (IUI) or one cycle of In-Vitro Fertilisation (IVF) with standard ovarian stimulation and first fresh or frozen embryo transfer.

Couples will be randomised in a 1:1 ratio. A minimisation algorithm will ensure balance for the following variables:
1. Woman's ethnicity (Asian, Black, Mixed, Other and White)
2. Woman's Body Mass Index (BMI) (19.0 - <24.90, 25.0 - 29.9, 30.0 - 34.9 kg/m²)
3. Woman's age (18.0 - <34.95, 35.0 - 37.9, >38.0 - 38.9 years)
4. Randomising centre

Both interventions will be delivered in the fertility clinic the couples are attending. Data will be collected on adverse events and pregnancy rates throughout the study. Both partners will complete questionnaires to evaluate satisfaction with treatment, quality of life and resource use at 8, 18 and 24 months post-trial entry. Sperm samples given by study participants will be included in the healthcare science sub-study; which aims to assess the standardisation of semen

quality assessment at different sites (NB participation in this sub-study is not optional). Additionally, both partners and healthcare providers will be given the opportunity to discuss their experiences of study participation in the qualitative patient evaluation.

The pilot study will run for the first 9 months of the trial; patients taking part in the pilot will follow the pathway described above.

Intervention Type
Mixed

Primary outcome measure
The live birth of a baby at ≥34 weeks gestation, conceived within 240 days of randomisation (approximately 8 months). In line with the evaluation of treatment policy, initial or subsequent pregnancies may be included within this timeframe. This outcome will be assessed at 18 months post-randomisation.

Secondary outcome measures
Measured using patient records unless otherwise noted:

The following outcomes will be assessed at two timepoints: 18 months post-randomisation to allow for pregnancy outcomes to be obtained and concern pregnancies conceived within 240 days (approximately 8 months) of randomisation; and 24 months post-randomisation to allow for pregnancy outcomes to be obtained and concern pregnancies conceived within 420 days (approximately 14 months) of randomisation.

Pregnancy outcomes:
1. Singleton live birth ≥37 weeks
2. TTP leading to a live birth defined as time from randomisation to pregnancy in days (censored at 240 days)
3. Cycle cancellation and reason (failure to respond/over-response)
4. Biochemical pregnancy
5. Clinical pregnancy
6. Ongoing pregnancy at 12 weeks (range 11 to 14 weeks)
7. Multiple pregnancy
8. Ectopic pregnancy
9. Miscarriage (defined as delivery before 24 weeks of gestation)
10. Stillbirth (defined as intrauterine death ≥24 weeks)
11. Termination
12. Number of embryos remaining (IVF group)

Outcomes in live births ≥24 weeks:
1. Gestational age at delivery
2. Gestation<28 weeks
3. Gestation<32 weeks
4. Gestation<37 weeks
5. Birthweight, grams
6. Small for gestational age (<10th centile)
7. Mode of birth (unassisted vaginal, instrumental vaginal, elective caesarean section, emergency caesarean section)
8. APGAR<7 out of 10 at 1 minute
9. APGAR<7 out of 10 at 5 minutes

10. APGAR<7 out of 10 at 10 minutes
11. Survival at 28 days (or discharge from hospital whichever is sooner)

Complications:
The following outcomes will be assessed for the first IVF treatment within 420 days post-randomisation.
1. Maternal in IVF only
1.1. Ovarian hyperstimulation syndrome – severe/critical OHSS
1.2. Pelvic infection
1.3. Bleeding post oocyte retrieval
2. Admission to High Dependency Unit (HDU)/ Intensive Therapy Unit (ITU)

The following outcomes will be assessed at 28 days post birth (or woman's discharge date from hospital whichever is sooner).
3. Antenatal
3.1. Antepartum haemorrhage
3.2. Pregnancy-induced hypertension
3.3. Pre-eclampsia
3.4. Obstetric cholestasis
3.5. Preterm pre-labour rupture of membranes
3.6. Gestational diabetes
4. Intrapartum
4.1. Chorioamnionitis
4.2. Intrauterine growth restriction
4.3. Macrosomia
5. Post-partum
5.1. Haemorrhage

The following outcomes will be assessed at 28 days post birth (or baby's discharge date from the hospital, whichever is sooner).
6. Neonatal
6.1. Congenital or chromosomal abnormalities
6.2. Admission to hospital
6.3. Early infection (as assessed by the treating clinician)
6.4. Retinopathy of prematurity
6.5. Necrotising enterocolitis
6.6. Intraventricular haemorrhage
6.7. Respiratory distress syndrome
6.8. Ventilation or oxygen support

Patient-reported outcomes:
1. Health-related quality of life (using the EQ-5D-5L questionnaire overall score and thermometer scale) measured at 8 and 18 months post-randomisation
2. Satisfaction with treatment and care provision (using the CSQ-8) post-treatment

Overall study start date
01/04/2023

Completion date
31/08/2028

Eligibility

Key inclusion criteria
Couples with a diagnosis of unexplained infertility, referred to fertility centres for assisted conception, will be considered for the UNiTY trial.
Unexplained fertility for the purpose of this trial is defined as the absence of the following fertility explanations after complete investigations:
1. Female infertility
1.1. Tubal disease
1.2. Deep endometriosis +/- ovarian endometriosis
1.3. Significant uterine abnormality requiring surgery (including cavity distorting fibroids, fibroids >5 cm or multiple fibroids)
1.4. Uterine septum with history of previous pregnancy loss
2. Male infertility
2.1. Total progressively motile sperm count less than 10M
2.2. Normal sperm morphology of 2% or less

Participant type(s)
Service user

Age group
Adult

Lower age limit
18 Years

Upper age limit
39 Years

Sex
Both

Target number of participants
942 couples

Key exclusion criteria
1. Female partner is 39 years or older on the date of randomisation
2. Either partner is under 18 years old
3. Female partner's BMI is <19.0 or >34.9 kg/m²
4. Either or both partners have a diagnosis of an ongoing sexually transmitted infection
5. If self-funded, couple unable to pay for IVF
6. Either partner is unable to give informed consent
7. Either partner is unable to complete trial follow-up
8. Couple has had two or more consecutive IVF treatment failures

If couples do not meet the requirements for NHS-funded IVF in their area, but do meet the trial eligibility criteria, they can proceed as self-funded participants.

The female age limit for NHS-funded IVF treatment is 40 years. In order for couples to have multiple cycles of IUI followed by IVF before turning 40 years of age, and without jeopardising

their funding, women will need to be <39 years of age on the date of randomisation. Research teams will discuss this with all couples during screening, particularly those in which the woman is older, to be sure they understand the possibility of losing NHS funding.

Date of first enrolment
01/09/2024

Date of final enrolment
30/06/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Birmingham Women's Fertility Centre
Mindelsohn Way
Birmingham
United Kingdom
B15 2GH

Study participating centre
University College London Hospitals NHS Foundation Trust
Reproductive Medicine Unit
Elizabeth Garrett Anderson Wing
Clinic 1
Lower Ground floor
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
Centre for Reproductive Medicine, University Hospitals Coventry and Warwickshire NHS Trust
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Study participating centre

Jessop Fertility (Sheffield)
Tree Root Walk
Broomhall
Sheffield
United Kingdom
S10 2SF

Study participating centre
Guy's and St Thomas' NHS Foundation Trust
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Leicester Fertility Centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Liverpool Womens Hospital
Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
Manchester University Hospital NHS Ft (hq)
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
The Shrewsbury and Telford Hospital NHS Trust
Mytton Oak Road

Shrewsbury
United Kingdom
SY3 8XQ

Study participating centre
Chelsea & Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
West Middlesex University Hospital
Twickenham Road
Isleworth
United Kingdom
TW7 6AF

Study participating centre
Cambridge Ivf
New Kefford House
Maris Lane
Trumpington
Cambridge
United Kingdom
CB2 9LG

Study participating centre
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United Kingdom
NE9 6SX

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Sponsor type
University/education

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

On completion of the trial, the data will be analysed and a Final Study Report prepared. Results of this trial will be submitted for publication in a peer reviewed journal. The publication policy will be governed by the Trial Steering Committee

Intention to publish date
31/03/2029

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the UNiTY trial team: unity@trials.bham.ac.uk. Requests for data generated during this study will be considered by BCTU. Data will typically be available within 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data). Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the Chief Investigator and, where appropriate (or in absence of the Chief Investigator) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent Trial Steering Committee (TSC). A formal Data Sharing Agreement (DSA) may be required between respective organisations once
the release of the data is approved and before data can be released. Data will be fully anonymised unless the DSA covers the transfer of patient-identifiable information, provided consent has been obtained for this transfer. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	17/01/2024	09/07/2024	No	No