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Metformin and gonadotrophin-releasing hormone (GnRH) antagonist co-treatment in in-vitro fertilisation (IVF) for women with polycystic ovary syndrome (PCOS)

Submission date 07/04/2009	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 25/06/2009	**Overall study status** Completed	
Last Edited 12/07/2016	**Condition category** Nutritional, Metabolic, Endocrine	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
OG08/8802

Study information

Scientific Title
The use of metformin and gonadotrophin-releasing hormone antagonist for the treatment of women with polycystic ovary syndrome undergoing in-vitro fertilisation embryo transfer: a single centre prospective double-blind randomised placebo-controlled trial

Study objectives
To determine whether the use of metformin in conjunction with the short gonadotrophin-releasing hormone (GnRH) antagonist protocol for in-vitro fertilisation (IVF) treatment reduces the incidence of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome (PCOS).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Pending approval from the Leeds West Research Ethics Committee; date for review is the 8th May 2009

Study design
Single centre prospective double-blind randomised placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Polycystic ovary syndrome

Interventions
Participants in the trial will be randomised to receive either metformin or placebo in addition to routine medication for the short GnRH antagonist IVF treatment protocol.

Treatment arm: metformin -
Following a spontaneous or induced withdrawal bleed subjects will be seen on day 21 of their menstrual cycle prior to starting IVF treatment. Patients will be randomised to either metformin or placebo. One tablet (metformin 850 mg) would be taken 12-hourly from the day 21 appointment until the day of oocyte retrieval, approximately 21 days. Both patients and investigators will be blinded to whether they are taking placebo or metformin. The metformin will be packaged and labelled as such so that the patient is blinded to whether it is metformin or placebo but with sufficient information to inform how to take the medication. All medications for the treatment cycle, including metformin/placebo, will be dispensed following the day 21 appointment.

Stimulation with 100 IU recombinant follicle stimulating hormone (rFSH) (Puregon) would commence on the evening of day 2 of the cycle following confirmation by transvaginal ultrasound scanning (TVUSS) the endometrial thickness was less than 4 mm and that the ovaries were quiescent (no follicle greater than 10 mm). Women will be asked to return on day 6 of the cycle following 5 days of stimulation, orgalutran 0.25 milligrams will be started. Participants will then be reviewed on alternate days until the lead follicle is greater than 15 mm and daily thereafter. 5,000 units human chorionic gonadotrophin (hCG) will be administered 36 hours prior to oocyte retrieval when there were three or more follicles over 17 mm in diameter.

Oocyte retrieval would be performed under conscious sedation (midazolam and fentanyl) using the standard ultrasound guided transvaginal approach. Oocytes would be inseminated (IVF) or injected (intra-cytoplasmic sperm injection [ICSI]) within 4 hours of oocyte retrieval. Embryo replacement would be carried out 2 days following oocyte retrieval. Embryo transfer would be ultrasound guided using a Wallace embryo replacement catheter. The two best quality embryos would be selected for transfer. Luteal phase progestogen support with per vaginal cyclogest (400 mg) would be commenced and continue until the day of the pregnancy test.

A pregnancy test (serum hCG) would be carried out 14 days following oocyte retrieval. A positive pregnancy test would be recorded if serum hCG was found to be greater than 2 IU/l. A TVUSS would be arranged for all women with a positive pregnancy test at 4 weeks after the embryo transfer.

Treatment arm: placebo -
Following a spontaneous or induced withdrawal bleed subjects will be seen on day 21 of their menstrual cycle prior to starting IVF treatment. Patients will be randomised to either metformin or placebo. One tablet (placebo) would be taken 12-hourly from the day 21 appointment until the day of oocyte retrieval, approximately 21 days. Both patients and investigators will be blinded to whether they are taking placebo or metformin. The placebo will be packaged and labelled as such so that the patient is blinded to whether it is metformin or placebo but with sufficient information to inform how to take the medication. All medications for the treatment cycle, including metformin/placebo, will be dispensed following the day 21 appointment.

Stimulation with 100 IU rFSH (Puregon) would commence on the evening of day 2 of the cycle following confirmation by TVUSS the endometrial thickness was less than 4 mm and that the ovaries were quiescent (no follicle greater than 10 mm). Women will be asked to return on day 6 of the cycle following 5 days of stimulation, orgalutran 0.25 mg will be started. Participants will then be reviewed on alternate days until the lead follicle is greater than 15 mm and daily thereafter. 5,000 units human chorionic gonadotrophin (hCG) will be administered 36 hours prior to oocyte retrieval when there were three or more follicles over 17 mm in diameter.

Oocyte retrieval would be performed under conscious sedation (midazolam and fentanyl) using the standard ultrasound guided transvaginal approach. Oocytes would be inseminated (IVF) or injected (ICSI) within 4 hours of oocyte retrieval. Embryo replacement would be carried out 2 days following oocyte retrieval. Embryo transfer would be ultrasound guided using a Wallace embryo replacement catheter. The two best quality embryos would be selected for transfer. Luteal phase progestogen support with per vaginal cyclogest (400 mg) would be commenced and continue until the day of the pregnancy test.

A pregnancy test (serum hCG) would be carried out 14 days following oocyte retrieval. A positive pregnancy test would be recorded if serum hCG was found to be greater than 2 IU/l. A TVUSS would be arranged for all women with a positive pregnancy test at 4 weeks after the embryo transfer.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Metformin, gonadotrophin-releasing hormone (GnRH) antagonist

Primary outcome measure
Incidence of confirmed moderate and severe ovarian hyperstimulation syndrome (OHSS) requiring hospitalisation within 6 weeks of IVF treatment cycle. Aim to determine if metformin reduces incidence.

Secondary outcome measures
1. Stimulation based measures:
1.1. Incidence of mild OHSS
1.2. Duration of stimulation (days)
1.3. Total dose of FSH used (units)
1.4. Number of follicles greater than 10 mm
1.5. Number of cycles cancelled
2. Biochemistry based measures:
2.1. Oestradiol concentration on day of oocyte retrieval
2.2. Anti-Mullerian Hormone (AMH) on day of oocyte retrieval
2.3. Testosterone concentration on day of oocyte retrieval
2.4. Fasting insulin concentration on day of oocyte retrieval
2.5. Fasting glucose on day on oocyte retrieval
2.6. Serum VEGF concentration on day of oocyte retrieval
2.7. Full blood count (FBC) on day of oocyte retrieval, embryo transfer and day 3 post transfer
2.8. Urea, creatinine and electrolytes (U&E) on day of oocyte retrieval, embryo transfer and day 3 post transfer
2.9. Liver function tests (LFT) on day of oocyte retrieval, embryo transfer and day 3 post transfer
3. Embryology based measures:
3.1. Number of oocytes collected
3.2. Number of metaphase II oocytes for fertilisation
3.3. Number of embryos
3.4. Number of embryos available for freezing
3.5. Quality of embryos

4. Pregnancy outcomes:
4.1. Biochemical pregnancy rate (positive serum hCG)
4.2. Clinical pregnancy rate (pregnancy demonstrable on USS)
4.3. Live birth rate

Overall study start date
01/06/2009

Completion date
01/09/2010

Eligibility

Key inclusion criteria
1. Women with a known diagnosis of PCOS (as defined by the Rotterdam European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine [ESHRE /ASRM] sponsored PCOS consensus workshop group, 2004)
2. Women must have a normal serum follicular stimulating hormone (FSH) concentration (reference range 1 - 8.0 iU/L)
3. Women must be 20 - 39 years of age
4. Women must have a body mass index (BMI) less than or equal to 35 kg/m^2
5. Pre-treatment inclusion criteria to include:
5.1. Serum testosterone level less than 5.0 nmol/l
5.2. Normal prolactin level (reference range less than 600 mU/L)
5.3. Normal thyroid function test level (thyroid stimulating hormone [TSH] reference range 0.2 - 6.0 mIU/L)
5.4. Normal renal, liver and haematological indices

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
200

Key exclusion criteria
1. Women on other oral-antidiabetic agents or blood-glucose lowering preparations
2. Women taking phenprocoumon
3. Women taking antivirals such as didanosine, stavudine, tenofovir
4. Women taking cimetidine
5. Women taking ketofen
6. Women who have radiological examinations using contrast media within the preceding 48 hours

7. Women with renal or hepatic impairment
8. Women who have had a recent myocardial infarct
9. Women with known vitamin B12 deficiency

Date of first enrolment
01/06/2009

Date of final enrolment
01/09/2010

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Reproductive Medicine Unit
Leeds
United Kingdom
LS2 9NS

Sponsor information

Organisation
Leeds Teaching Hospitals NHS Trust (UK)

Sponsor details
Research and Development Directorate
The General Infirmary at Leeds
34 Hyde Terrace
Leeds
England
United Kingdom
LS9 6LN

Sponsor type
Hospital/treatment centre

Website
http://www.leedsteachinghospitals.com/

ROR
https://ror.org/00v4dac24

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Leeds General Infirmary (UK) - Reproductive Medicine Unit

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration