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Duration of luteal support with progesterone pessaries to improve the success rates in assisted conception

Submission date
03/02/2012

Recruitment status
No longer recruiting

Registration date
26/03/2012

Overall study status
Completed

Last Edited
19/05/2022

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
Progesterone is the most important hormone that plays a key role in pregnancy. It is normally produced by an ovarian cyst until the 9th week of pregnancy, at which point the placenta becomes the main producer of progesterone for the remainder of the pregnancy. During in vitro fertilisation (IVF) the body has a reduced capacity to produce enough progesterone. Supplementation with progesterone after the embryo has been transferred into the uterus significantly improves pregnancy rates. Progesterone can be given using pessaries, vaginal creams or gels and also by injection with similar beneficial effects. However, it has yet to be seen whether the duration of progesterone support influences the pregnancy outcome. Common sense dictates that additional progesterone would be beneficial up until the time when the placenta is mature enough to take over this role. The aim of this study is to find out whether additional progesterone up until 12 weeks of pregnancy significantly improves pregnancy outcomes for IVF patients.

Who can participate?
Women undergoing IVF who are confirmed to be pregnant.

What does the study involve?
All participants receive 2 weeks of progesterone treatment after their embryo transfer. Participants are then randomly allocated to be treated with one of two forms of pessary, either one with the active ingredient progesterone or a placebo (no active ingredient), for a further 8 weeks after getting pregnant. Patients attend pregnancy scans at 7 and 12 weeks of pregnancy. Live birth rates are recorded and all babies born from the study are examined by a neonatologist.

What are the possible benefits and risks of participating?
There are no known risks associated with the medication.

Where is the study run from?
Hewitt Centre for Reproductive Medicine, Liverpool Women's NHS Foundation Trust Hospital, Liverpool, UK.

When is the study starting and how long is it expected to run for?
November 2008 to May 2012.

Who is funding the study?
Main funding has been provided by The Moulton Charitable Foundation, with further funding provided by Actavis Pharmaceuticals UK Ltd, who have also provided the medication free of charge.

Who is the main contact?
Mr Rafet Gazvani
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2006-000599-33

Protocol serial number
EudraCT 2006-000599-33

Study information

Scientific Title
Duration of Luteal Support with progesterone pessaries to improve the success rates in assisted conception: a randomised controlled trial

Acronym
DOLS

Study objectives

Infertilty effects 1 in 6 couples in the UK, and is a trend that is increasing. Success with in vitro fertilisation (IVF) continues to improve but has generally reached a plateau, with success rates of around 30-40%. Approximately 25% of pregnancies following IVF do not continue. This places a massive burden on individuals and health care systems in dealing with resultant miscarriage, treatment failure and repeat treatment cycles.

We aim to conduct a prospective randomised controlled double blind study to investigate the effect of the duration of luteal support with progesterone in IVF cycles. Following 2 weeks of standard treatment and a positive biochemical pregnancy test, this randomised controlled trial will allocate women to a supplementary 8 weeks of treatment of vaginal progesterone or 8 weeks of placebo. Further studies would be required to investigate whether additional supplementation with progesterone is beneficial in early pregnancy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
National Research Ethics Service, North West Research Ethics Committee, NHS North West Manchester, 17/11/2006, ref: 06/MRE08/17

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

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Infertilty

Interventions
Patients will be randomised to two groups of treatments:
Group A: Active drug. Cyclogest, Actavis UK PL00142/05/08. One pessary (400mg) vaginally or rectally twice daily for 8 weeks following positive pregnancy test.
Group B: Placebo. Provided by Actavis UK. One pessary, vaginally or rectally twice daily for 8 weeks following positive pregnancy test.

Both drugs appear similar with no identifying markings on the drug or packaging.

Patients will attend for pregnancy scans at 7 and 12 weeks of pregnancy at which point active trial participation is complete. Live birth rates are recorded and all babies born from the trial will be examined by a neotatologist.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Cyclogest

Primary outcome(s)
The proportion of all randomised women that continue successfully to a viable pregnancy (at least one fetus with FHR >100 beats minute) on transabdominal / transvaginal ultrasound at 10 weeks post embryo transfer / 12 weeks gestation (i.e. at the end of 8 weeks supplementary trial treatment).

The following clinical estimates are available. The success rate at the biochemical testing stage is approximately 32.5%. Currently without further progesterone supplementation, 80% of these women will carry on successfully with a viable pregnancy (25.8% of clinical pregnancy rate) whilst 20% of these women will miscarry. We anticipate that an increase of 10% from the biochemical to the clinical pregnancy rate would be clinically important and therefore justify an additional 8 weeks of supplementation with progesterone, in other words, a reduction of 10% in the miscarriage rate.

Key secondary outcome(s))
1. Viable pregnancy (at least one fetus with FHR>100 beats per minute) on transvaginal ultrasound at 5 weeks post embryo transfer / 7 weeks gestation (i.e. at the end of 3 weeks supplementary trial treatment).
2. Relationship of serum markers (Estradiol, progesterone, Inhibin A, Inhibin B, Actavin A. free B-HCG and PAPP-A) taken at 5 and 10 weeks post embryo transfer with treatment allocation, primary outcome and secondary outcomes
3. A pelvic Doppler will be performed to determine if the blood velocity in the uterine artery is different in the two groups. This will be performed at 5 and 10 weeks post embryo transfer.
4. Side effects: A visual analogue score relating to the following side effects will be completed at both 5 weeks and 10 weeks post embryo transfer; nausea, bloating, vaginal discharge and vaginal irritation.
5. Antenatal Downs Screening Outcomes - Antenatal Downs screening results for all patients will be monitored, including individual serum quantification for double, triple, quadruple screening and nuchal translucency.
6. Neonatal outcomes - Outcome data regarding the child will be collected at delivery (Table 6). A standard neonatal examination will be conducted. Women will be asked to inform the study team of the outcome of the routine neonatal examination. Excessive androgenisation would be an important adverse outcome of supplementary progesterone and this would be detected by routine neonatal examination. Long term follow-up of the child may also be conducted as a separate study. Women will be asked to whether they consent to being contacted in future about long-term follow-up studies.
Some neonatal and other pregnancy outcomes will be captured in Trusts that do not recruit to this trial. We will identify a local contact and R&D contact in each Trust in order to obtain the necessary approvals. At each site that will contribute data to the outcomes clinicians will be following their routine clinical practice. Consent to participate in the study will not be sought at sites that contribute to data collection about outcomes and study medication will not be administered at these sites. Thus, the sites that contribute to data collection about outcomes will be exempt from site-specific assessment as part of approval by the Research Ethics Committee.
7. Compliance data - Patient compliance with using pessaries is recorded at each visit. A secondary analysis may look at the effect of compliance on the primary outcome.

Completion date

26/05/2012

Eligibility

Key inclusion criteria
All patients undergoing IVF will be considered for the DOLS Trial
1. Biochemical pregnancy confirmed by urinary pregnancy test. If positive then they will be eligible to enter the trial
2. Progesterone treatment (2 weeks) completed up to the day of the pregnancy test
3. Patients treated at Hewitt centre only
4. Only those patients who have been treated with the long stimulation protocol
5. Only patients having used Menopur for controlled ovarian stimulation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Key exclusion criteria
1. All women who are undergoing frozen embryo transfer
2. Any women not willing to take part will be excluded
3. All diabetic, epileptic and hypertensive patients on treatment
4. Poorly controlled asthmatics having had more than one hospital admission in the last year
5. Patients with renal and cardiac dysfunction (Under the care of nephrologist and cardiologist respectively)
6. Breast Cancer patients
7. Severe liver impairment/jaundice
8. Previous history of thromboembolism
9. Transport centre patients, ie egg collection at Chester or Leighton
10. Patients previously recruited to the DOLS Trial
11. Patients who have not had a "long cycle" of IVF

Date of first enrolment
28/11/2008

Date of final enrolment
26/05/2012

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Hewitt Centre for Reproductive Medicine
Liverpool
United Kingdom
L8 7SS

Sponsor information

Organisation
Liverpool Women's NHS Foundation Trust (UK)

ROR
https://ror.org/04q5r0746

Funder(s)

Funder type
Charity

Funder Name
The Moulton Charitable Foundation (UK)

Funder Name
Actavis (UK)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to the regulatory applications submitted and subsequently approved, together with the consent obtained from participants, did not allow for the sharing of datasets generated from the study.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	26/07/2012		Yes	No
Basic results		22/04/2022	19/05/2022	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes