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Heparin improves the lining of the womb's preparation for pregnancy

Submission date
11/09/2012

Recruitment status
No longer recruiting

Registration date
16/10/2012

Overall study status
Completed

Last Edited
23/09/2016

Condition category
Pregnancy and Childbirth

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

Plain English summary of protocol

Background and study aims
Every year in England and Wales there are 700,000 births and thus hundreds of thousands of delighted parents. However, many couples are not so fortunate; in the same period of time: 15% of couples experience sub-fertility; 25% (500,000) of conceptions fail to implant; 15% (300,000) of pregnancies end in early miscarriage; 2% of couples suffer recurrent miscarriages (three or more losses). We have shown that failure of the lining of the womb (endometrium) to prepare adequately for pregnancy a process known as decidualisation is an underlying factor in these clinical problems. During decidualisation, the endometrial lining becomes transformed into a secretory lining in preparation for accepting the embryo. Decidualisation is a characteristic of the endometrium of the pregnant uterus. Decidualisation is a process that occurs in early pregnancy. It is an adaption of the uterus to enable implantation of the embryo. The blood thinning agent, Heparin, has been used in an attempt to improve reproductive success. However, heparin has always been given by daily sub-cutaneous injections causing bruising, pain and occasionally bleeding. These injections are given for weeks. Heparin also has the ability to increase activity of growth factors in the endometrium thereby improving decidualisation and increase successful implantation of the pregnancy. We would like administer Heparin as a single dose by flushing it directly into the womb prior to pregnancy, during the window of implantation (5-7 days after ovulation). We wish to study whether this new method of administration enhances decidualisation and minimises the adverse effects of heparin.

Who can participate?
Women 18 years or older but younger than 45 years who are able to give informed consent and had previous unsuccessful in vitro fertility (IVF) treatment (no live birth after transfer of two good quality embryos) or had recurrent miscarriages (3 or more miscarriages) in the past.

What does the study involve?
Patient will be recruited with informed written consent. The patient will have a minimum of 24 hours to review the patient information sheet and consent form. If the patient consents, she will be asked to use barrier contraception for the month in which the study occurs. These patients will be asked to attend 5 to 7 days after ovulation (as assessed by a home ovulation kit) and they will be randomized (after a negative pregnancy test) to either receive locally administered low molecular weight heparin (intervention group) OR locally administered saline (control group).

After administration, they will mobilize and after four hours, bloods for Anti-Xa (assessing systemic heparin activity) will be taken. The patient will then go home with a side effect diary. 24 hours later the patient will re-attend and an endometrial biopsy (sampling of lining of the womb) will be taken together with a full blood count and liver function tests. All of these procedures will performed in outpatient and you will go home afterwards. A telephone consultation will follow 14 days later to ask about period heaviness and duration. Participant questionnaire and side effects diaries will be sent by pre-paid envelope back to principal investigator.

What are the possible benefits and risks of participating?
There is no immediate medical benefit to you from taking part, however, the information that we gain from this study may help us to treat women in the future. We do not expect any commercially significant results to be gained from this research. It is possible that the action of taking an endometrial biopsy may help the endometrium to respond correctly to an implanting embryo, however, the medical evidence for this is currently limited and there is no guarantee that the biopsy may help. You will be informed of the results by letter and you will be invited to a patient information evenings at the end of study. Women who are pregnant cannot take part in this study and who could possibly be pregnant. Sampling the lining of the womb (endometrial biopsy) may be uncomfortable or slightly painful, but leaves no long term effects because your womb lining regenerates every month. There is a very small risk of bleeding with the use of heparin which is a blood thinning agent. For this reason, we will take a blood test 4 and 24 hours after administration. If you have any bruises which appear suddenly, please call us immediately as this might indicate a problem with bleeding. We have an antidote against the blood thinning agent which will reverse its effect. There is a very small risk of infection but we will perform pelvic swabs prior to any intervention in the study if not done recently.

Where is the study run from?
The study will be conducted at University of Warwick. The patients will be seen in outpatients at Centre of Reproductive Medicine at University Hospitals Coventry and Warwickshire NHS Trust.

When is study starting and how long is it expected to run for?
The proposed date of starting the study is 1st January 2013. However, this depends upon ethical and MHRA approval. Duration of the study will be 12 months from the ethics approval to collect samples from patients. A further 12 months will be required to analyse the data.

Who is funding the study?
Biomedical Research Unit, University Hospitals Coventry and Warwickshire NHS Trust

Who is the main contact?
Professor Siobhan Quenby
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2012-003682-18

Protocol serial number
HEP001QUEN

Study information

Scientific Title
Endome-trial flushing of low molecular weight heparin improves decidualisation a prospective randomised control pilot study

Study objectives
To assess the effects of local low molecular weight heparin administration on endometrial decidualisation in a non-conception menstrual cycle.

Added 25/09/2013: study participation was completed in July 2013. All 40 participants were recruited and the study is not recruiting any more participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee West Midlands - Edgbaston, 05/11/2012, ref: 12/WM/0347

Study design
Prospective randomized pilot study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Previous at least one unsuccessful IVF treatment, Recurrent Miscarriages

Interventions
Patient will be recruited with informed written consent. The patient will have a minimum of 24 hours to review the patient information sheet and consent form. If the patient consents, she will be asked to use barrier contraception for the month in which the study occurs.These patients will be asked to attend 5 to 7 days after ovulation (as assessed by a home ovulation kit) and they will be randomized (after a negative pregnancy test) to either receive locally administered low molecular weight heparin (intervention group) OR locally administered saline (control group). After administration, they will mobilize and after four hours, bloods for Anti-Xa (assessing systemic heparin activity) will be taken. The patient will
then go home with a side effect diary. 24 hours later the patient will re-attend and an endometrial biopsy will be taken together with a full blood count and liver function tests.

A telephone consultation will follow 14 days later to ask about period heaviness and duration. Participant questionnaire and side effects diaries will be sent by pre-paid envelope back to principal investigator.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
Measurement of effective decidualisation will include the density of uterine natural killer cell by immunohistochemistry

Key secondary outcome(s))
1. To assess the effect of locally administered heparin on other markers of decidualisation including endometrial stromal cell culture, genome wide expression profile, induction of other decidualisation protein markers including prolactin, Prokinectin, IGFBPs (insulin Like Growth Factor Binding Proteins), HBEGF (Heparin Binding Epidermal Growth Factor)
2. To identify any potential side effects of local endometrial administration of heparin
3. To assess patient acceptability of this method of administration

Completion date
31/12/2013

Eligibility

Key inclusion criteria
1. Women attending the Centre for Reproductive Medicine, University Hospitals of Coventry and Warwickshire NHS Trust, Coventry who had previous one unsuccessful IVF treatment (defined as failure to achieve live birth after transfer of two good quality embryos)
2. Women with recurrent miscarriages (defined as 3 or more unexplained miscarriages)
3. Women 18 years of age or older but younger than 45 years old
4. Able and willing to give informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Key exclusion criteria
1. Women who had unprotected sexual intercourse during the month when endometrial flushing is planned
2. Women having a vaginal infection, these women will be eligible for inclusion once treatment of the infection has been completed
3. Pregnancy
4. Breast feeding
5. Women with weight of < 45 kg (due to higher risk of bleeding)
6. Women with bleeding disorders
7. Women with severe hypertension
8. Women with Known Renal or Liver Diseases
9. Women who had recent stroke
10. Women taking Warfarin for any medical condition
11. Women taking systemic steroids, systemic salicylates, acetylsalicylic acid, NSAIDS including Ketorolac, dextran and clopidogrel or any immunosuppressant medications
12. Women with Diabetes Mellitus (due to potential risk of hyperkalaemia)
13. Women with hypersensitivity to Heparin, Pork, Beef or other Animal products
14. Women with Peptic Ulcers
15. Women undergoing Tubal Patency testing, Hysteroscopy or Laparoscopy at the time when endometrial flushing is planned

Date of first enrolment
01/01/2013

Date of final enrolment
31/12/2013

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Clinical Sciences Research Laboratory
Coventry

United Kingdom
CV2 2DX

Sponsor information

Organisation
University of Warwick (UK)

ROR
https://ror.org/01a77tt86

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
University Hospitals Coventry and Warwickshire NHS Trust - Biomedical Research Unit (UK)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes