ISRCTN10360127 https://doi.org/10.1186/ISRCTN10360127

Effects of estrogen supplementation for patients with thin endometrial lining receiving oral clomiphene citrate

Submission date	Recruitment status	[X] Prospectively registered
26/01/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
28/01/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
04/02/2021	Urological and Genital Diseases	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Subfertility is defined as the inability to conceive after 1 year of regular unprotected intercourse. It can be treated with fertility treatments such as intrauterine insemination (IUI) or timed sexual intercourse (TSI). This study aims to find out whether estrogen supplementation improves the thickness of the endometrial lining (the lining of the uterus) in patients with thin lining as a result of clomiphene citrate, which is used for ovulation induction (release of an egg from the ovary) in fertility treatment. Oral estradiol supplements have been used in fertility treatment for a long time but the duration of use may vary according to the clinician's preference as there are no standard protocols with regards to the duration of use.

Who can participate?
Women with primary or secondary subfertility planned for intrauterine insemination (IUI) or timed sexual intercourse (TSI)

What does the study involve?
Participants are randomly allocated to take no treatment or to take oral estradiol valerate 8 mg once a day for 4 days. Participants will be required to visit the reproductive medicine unit for serial transvaginal sonogram (ultrasound) assessment of endometrial thickness.

What are the possible benefits and risks of participating?
Oral estradiol is a safe drug used in fertility treatment and there have been no reported cases of serious side effects from this drug besides occasional nausea or vomiting that a small number may experience. Oral estradiol supplementation may improve the endometrial thickness and therefore may improve pregnancy rates.

Where is the study run from?
University Malaya Medical Centre (Malaysia)

When is the study starting and how long is it expected to run for?
December 2019 to December 2022

Who is funding the study?
University Malaya Medical Centre (Malaysia)

Who is the main contact?
Dr Rajeev Kumar Rajaratnam
rajeev.kumar@ummc.edu.my

Contact information

Type(s)
Public

Contact name
Dr Rajeev Kumar Rajaratnam

Contact details
Department of Obstetrics & Gynaecology
University Malaya Medical Centre
Jalan Universiti
Lembah Pantai
Kuala Lumpur
Malaysia
59100
+60 (0)133962212
rajeev.kumar@ummc.edu.my

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
MREC ID NO: 20191227-8112

Study information

Scientific Title
Estrogen supplementation for thin endometrium in patients undergoing ovulation induction with clomiphene citrate: a randomized controlled trial

Acronym
ESTE

Study objectives

Estrogen supplementation increases endometrial thickness among patients with thin endometrium who were on clomiphene citrate for ovulation induction.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/04/2020, Medical Research Ethics Committee, University Malaya Medical Centre (Lembah Pantai, 59100 Kuala Lumpur, Malaysia; +60 (0)3-79493209/2251; rosmawatib@ummc.edu.my), ref: 20191227-8112

Study design
Multicentre randomized control 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 to request a participant information sheet

Health condition(s) or problem(s) studied
Primary or secondary subfertility

Interventions
Patients diagnosed with either primary or secondary subfertility undergoing ovulation induction with clomiphene citrate in preparation for IUI (intrauterine insemination) or TSI (timed sexual intercourse) will be randomly allocated to receive either oral estradiol valerate 8 mg OD for 4 days or a control group (no treatment). Those eligible will be approached by the attending clinician and the research investigator. An explanation will be given regarding the study and its flow. They will be given sufficient time to consider their participation in the trial. Written, informed consent will be obtained by the attending clinician from patients agreeing to participate in the study. A patient information sheet will be provided to outline the study, procedures performed for assessment and treatment given. There will be a sealed opaque envelope containing the randomization ticket that will be opened in front of the patient.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Estradiol valerate (Progynova)

Primary outcome measure
Endometrial thickness measured using transvaginal sonogram at initial visit (baseline), between days 8-10 of the current cycle and 4 days later

Secondary outcome measures
1. Pregnancy rate measured using the urinary pregnancy test or serum B-HCG when the patient misses her period the subsequent month
2. Miscarriage rate measured using the transabdominal/transvaginal sonogram and clinical assessment if the patient experiences early pregnancy complications such as bleeding or passing out of products of conception
3. Nausea and vomiting assessed where the patient records having any of these symptoms during her visit 4 days after being randomised

Overall study start date
29/12/2019

Completion date
31/12/2022

Eligibility

Key inclusion criteria
Women diagnosed with primary or secondary subfertility undergoing ovulation induction using clomiphene citrate in preparation for intrauterine insemination (IUI) or timed sexual intercourse (TSI)

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
124

Key exclusion criteria
1. Planned IVF
2. Diagnosed with an endometrial polyp
3. Using GnRH Agonist
4. Systemic diseases (e.g. autoimmune, cardiac, liver, thyroid disease or malignancy)

Date of first enrolment
31/01/2021

Date of final enrolment
31/05/2022

Locations

Countries of recruitment
Malaysia

Study participating centre
University Malaya Medical Centre
Lembah Pantai
Kuala Lumpur
Malaysia
59100

Study participating centre
Hospital Tengku Ampuan Rahimah Klang
Jalan Langat, Klang
Selangor
Malaysia
41200

Sponsor information

Organisation
University Malaya Medical Centre

Sponsor details
Department of Obstetrics & Gynaecology
University Malaya Medical Centre
Jalan Universiti
Lembah Pantai
Kuala Lumpur
Malaysia
59100
+60 (0)3-79494422
cic_staff@um.edu.my

Sponsor type
Hospital/treatment centre

Website
http://www.ummc.edu.my/#

ROR
https://ror.org/00vkrxq08

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
University Malaya Medical Centre

Results and Publications

Publication and dissemination plan
To publish in local and international journals

Intention to publish date
15/01/2023

Individual participant data (IPD) sharing plan
All data obtained will be kept private and confidential within the Reproductive Medicine Unit. Data will be charted in a data collection form as well as into the clinical notes during which the patient undergoes ovulation induction. Patients consent will be obtained with regards to the use and storage of the data on the online electronic medical record system as well as the clinical notes. Data will be tabulated and stored by the primary investigator as soft copy material. The treating physicians, primary investigator and the embryologist of the reproductive medicine unit will have access to the data for tabulation and storage purpose. All data will be kept confidential and only investigators and treating clinicians will have access. All records will be stored for 2 years after completion of 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 file			04/02/2021	No	No