# RESEARCH PROPOSAL FOR MASTER OF MEDICINE (OBSTETRICS AND GYNAECOLOGY)

**DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY UNIVERSITY MALAYA**

**Study Title**

Estrogen Supplementation For Thin Endometrium In Patients Undergoing Ovulation Induction With Clomiphene Citrate

(ESTE STUDY)

Study Duration : 30/1/2021-31/5/2022

# Study Investigator(s)

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 Sponsor: University Malaya Medical Centre

 (Self Sponsored)

1. **Introduction and Literature Review**

Clomiphene has been reported to induce ovulation in 60-85% of patients and achieves a pregnancy rate of 15-50% per woman *(Clark & Markaverich et al)*

It exerts an intrinsic negative influence on the synchronization of glandular development and stromal maturity of the endometrium. This gives rise to a low glandular density and a decrease in the number of vacuolated cells *(Ashraf & Firoozeh)*

Anti estrogenic effects of clomiphene on the endometrium (thinning of the endometrium) is likely to be the cause of suboptimal pregnancy rates inspite of good ovulation rates.

Several studies show that a thin endometrium is correlated to lower pregnancy rates

*(Al- Ghamdi et al)*

In order to counter the anti estrogenic effect of clomiphene , many trials provided estrogen supplementation early in the proliferative phase of the clomiphene stimulated cyles *(Kruger,Yagel Swasti et al)*

In humans, a minimum of 5 days of estrogen is required to build a sufficiently thick endometrium that is optimal for implantation *(Michalas , Kurita et al)*

Clinical trials concluded that the endometrial thickness ranged between 6-17 mm (mean 9.7 +/- 2.1mm). ET of more than 8 mm increases the chance of chemical and clinical pregnancy rate *(Satirapod et al 2014; Moini et al 2015)*

A recent metanalysis conducted involving 23 studies (3846 women). They compared the use clomiphene, letrozole and gonadotrophins. The chance of conception decreased when ET≤ 7mm

(OR: 0.38; 95% CI 0.09-1.5) compared to ET ≥7mm *(Kasius et al).*

**1a. Research Question**

Can exogenous estrogen supplementation accelerate the thickness of endometrium within a short duration?

1. **Objectives**

**2a. Primary Objective**

To improve endometrial thickness at trigger within a short duration using exogenous estrogen supplementation.

 **2b. Secondary Objective**

Improve pregnancy rates among patients with thin endometrium due to the effect of clomiphene citrate.

1. **Hypothesis**

Estrogen supplementation increases endometrial thickness within a short duration in patients receiving clomiphene citrate.

1. **Study Design**

This will be a multicenter, randomized controlled trial.

1. **Study Setting**

Reproductive Medicine Unit University Malaya Medical Centre and Hospital Tengku Ampuan Rahimah Klang, Selangor.

1. **Study Population**

Women attending the Reproductive Medicine Unit diagnosed with primary or secondary infertility undergoing ovulation induction using clomiphene citrate in preparation for IUI or TSI will be offered to participate in this study.

1. **Eligibility Criteria**

7a. Inclusion Criteria:

Age 18-35

Planned for IUI/TSI

BMI 30 Kg/m2 and below

ET< 8 mm after one week of clomiphene citrate

7b. Exclusion Criteria:

 Planned for IVF

 Endometrial Polyp

 Use of GnRH Agonist

 Systemic Diseases (e.g. Autoimmune, cardiac, liver, thyroid disease or malignancy)

1. **Sample Size Calculation**

Based on literature review, clinical trials show the mean endometrial thickness is about 9.7 ± 2.1 mm to achieve better outcomes.

Total number of patients undergoing IUI & TSI in UMMC per year: 186

Number of cases with thin ET < 8mm : 82 (44 %)

Total number of patients undergoing IUI & TSI in HTAR per year: 230

Total number of patients with ET < 8mm : 100 (43.4%)

Total population (ET< 8mm) : 182

Data from clinical trial shows the mean ET 9.7 ± 2.1 mm

Recommended sample size based: 124

A sample size of 62 in treatment group and 62 in the placebo group is needed in order to reject the null hypothesis with a confidence interval of 95 % and margin of error 5 % and power of 80 %.

1. **Study Outcome**

**9a. Primary Outcome**

Sonographic evidence of increased endometrial thickness of more than 8mm at day of trigger.

**9b. Secondary Outcome**

Clinical pregnancy rates achieved from the particular particular cycle.

1. **Methodology**

Patients diagnosed with either primary or secondary subfertility undergoing ovulation induction with clomiphene citrate in preparation for IUI(Intrauterine Insemination) or TSI (Timed Sexual Intercouse) will be randomly allocated to receive either oral estradiol valereate 8mg OD for four days or in the control arm.

**10a. Recruitment of participants**

Patients that fulfil the eligibility criteria will be identified during their visit to the Reproductive Medicine Unit University Malaya Medical Centre and Hospital Tengku Ampuan Rahimah, Klang. Patients eligible will be approached by the attending clinician and the research investigator. Explanation will be given regarding the study and its flow. They will be allowed sufficient time to consider their participation in the study. 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.

**10b Randomisation**

Treatment allocation will be performed in accordance with a computer generated randomisation sequence with the use of numbered, opaque and sealed envelopes.

**10c. Study Procedure**

Patients who are diagnosed with primary or secondary subfertility and planned for IUI or TSI will be commenced on oral clomiphene citrate from Day 2- Day 6. They will be assessed on Day 10 for follicular tracking where a transvaginal USG (4-7 MHz) will be performed by a trained and certified sonographer. The endometrial thickness (ET) should be measured at the thickest part of the midsagital section in a well aligned uterus. Patients with ET ≥ 8 mm will be excluded from the study. Patients with ET < 8 mm will be recruited for the study. Patients may choose not to participate in the study. After obtaining informed consent, patients will be allocated to two groups; Those receiving oral estradiol valereate 8mg OD or control for four days. Both investigators and participants will be blinded in the study. Patients are not allowed to take any other hormonal preparation during the study period.

Oral estrogen may sometimes cause nausea and vomiting. If the patient experiences any of these symptoms, they will be advised to discontinue therapy and seek immediate medical attention. Patients will be advised to contact the investigator who will then advise if she should visit the Reproductive Medicine Unit or the emergency department of the respective medical centre. If they do not experience any effects during the duration of the medication intake, they will be assessed on Day 14 if they were to experience any undesired effects. Any adverse events will be reported by the investigator to the CRC/sponsor within 24 hours. These information will be documented in the patient file as well as the form to report adverse events. Treatment will be instated for any adverse event under the discretion of the investigator who will follow up the patient until the adverse event has resolved or until the condition has stabilised. Follow up will be continued throughout the cycle until the next menstrual period (Day 1 of subsequent cycle).

Patients will be required to have a transvaginal sonogram on day 10 and 14 of the cycle. If necessary, they will need to visit the doctor just prior to trigger. There are no potential adverse effects from this procedure.

The patients recruited will then be reassessed on day 14 (Follicular tracking and ET surveillance) and those with ET > 8 mm will be subjected for trigger with HCG (Human Chorionic Gonadotrophins). Participants may choose to withdraw from the study at any point if they wish to. The sponsor will financially compensate the time spent by the study staff, use of facilities, etc., for including patients in the study and they will not receive any reimbursement.

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| **VISIT** | **PROCEDURE** | **ACTION** | **DURATION** |
| 1(Week 1) | Screening and Assesment:-Diagnosed with Primary or Secondary Infertility -Fulfills Inclusion and exclusion criteria | Plan for Intrauterine Insemination (IUI) or Timed Sexual Intercourse (TSI)Briefing and explanation about the trialAdvised for Clomiphene Citrate on Day 2-6 of menstrual cycle. | Consultation : 45 minutes |
| 2(Week 4) | Day 10 of menstrual cycle:Transvaginal Sonogram:-Follicular tracking- Measurement of endometrial thickness (ET)  | Exclude those with ET of > 8mmSubject recruitment and enrolment:-Recruit subjects with ET < 8mm-Written Informed Consent-Allocation into 2 groups:-Randomisation | TVS: 5 to 10 minutesRecruitment, enrolment, consent & allocation : 15- 20 minutes |
| 3(Week 6) | Day 14 of menstrual cycle:Transvaginal Sonogram:-Follicular tracking-Measurement of ET | ET > 8mm : subjected for trigger with Human Chorionic Gonadotrophin (HCG)Advice on IUI/TSI | TVS: 5 to 10 minutesHCG administration: 5 to 10 minutes |
| 4(Week 6) | IUI | Procedure of IUI performed by Reproductive medicine SpecialistAdvise to monitor for pregnancy after 2 weeks | IUI Procedure: 15-30 minutes |
| 5(Week 8) | Pregnancy assessmentUPTSerum B-HcG  | Assessment to confirm if pregnancy has occured | UPT: Dipstick: 5 minutesLaboratory: 1 hourSerum B-HcG: 1 hour |

**10d Study Flowchart**

Follicular Tracking and measurement of ET on Day 14

EXCLUDED

Oral estradiol valereate 8 mg OD for 4 days

Control

ET ≥ 8 mm

ET < 8 mm

ET unchanged

ET increased

TRIGGER

Data Analysis

Monitor if pregnancy achieved

1. **Statistical Consideration & Data Analysis**

The statistical analysis will be carried out according to the intention to treat analysis. The primary endpoint will be the sonographic evidence of thickened endometrium of more than 8 mm and the secondary endpoint is the ability to achieve clinical pregnancy.

Statistical analysis will be performed using SPSS for windows. The Chi squared test or if necessary the Fishers exact test will be used to compare data. Statistical significance is set at p < 0.05. At Alpha = 0.05, the study power was 80%.

1. **Ethical Considerations**

This study will be performed in full conformance of the “Declaration of Helsinki”, Good Clinical Practise (GCP) and within the laws and regulation of Malaysia as per protocol by the local ethical committee- University Malaya, NMRR and MREC (Ministry of Health). To ensure participant's confidentiality investigators will comply to the Caldicott principles.

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. Data will be tabulated and stored by the primary investigator as a 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 where only investigators and treating clinicians will have access to. All records will be stored for 2 years after completion of study

All your information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. Permission from the Director General of Health, Malaysia will be obtained prior to publication. When publishing or presenting the study results, identity of patients will not be revealed. Individuals involved in this study, qualified monitors and auditors, the sponsor or its affiliates and governmental or regulatory authorities may inspect and copy medical records, where appropriate and necessary. Data from the study may be archived for the purpose of analysis, but the identity will not be revealed at any time.

1. **Outcome & Significance**

Anti estrogenic effects of clomiphene on the endometrium (thinning of the endometrium) is likely to be the cause of suboptimal pregnancy rates inspite of good ovulation rates in patient undergoing ovulation induction using clomiphene citrate. In order to counter the anti estrogenic effect of clomiphene, estrogen supplementation early in the proliferative phase of the clomiphene stimulated cyles improves the endometrial thickness which also improves clinical pregnancy rates thus yielding better success. There may or may not be any benefits directly however information obtained from this study will help improve management protocol for patients undergoing ovulation induction using clomiphene citrate. This study will provide added information to the available literature on the role of estrogen supplementation in patients with a thin endometrium undergoing ovulation induction with clomiphene citrate. Estradiol valereate is easily available and may improve outcome in patients planned for IUI and TSI.

**Referrences:**

1. The effect of ethinyl estradiol on endometrial thickness and uterine volume during ovulation induction by clomiphene citrate ;Yagel & Ben Chetrit -1992
2. Endometrial development was improved by transdermal estradiol in patients treated with clomiphene citrate ; Shimoya & Tomiyama- 1998
3. Use of ethinyl estradiol to reverse anti estrogenic effects of clomiphene citrate in patients undergoing IUI; a comparative randomized study ; Sandro, Hussein & Vittorio- 2000
4. High Dose phytoestrogens can reverse the antiestrogenic effects of clomiphene citrate on the endometrium of patients undergoing IUI ;Vittorio, Loerdana & Gian Carlo-2004
5. Adding phytoestrogens to clomiphene induction in unexplained fertility; Ahmad & Alaa- 2007
6. Effect of estradiol valereate on endometrium thickness during clomiphene citrate stimulated ovulation; Satirapod & Wingpraw- 2014
7. Adding the phytoestrogen Cimicifugae Racemosa to clomiphene induction cycles with timed intercourse in polycyctic ovary syndrome improves cycle outcomes and pregnancy rates; Ahmed & Safwat-2014