RESEARCH PROPOSAL FOR MASTER OF MEDICINE

(OBSTETRICS AND GYNAECOLOGY)

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

UNIVERSITI MALAYA

TITLE

COMPARISON OF ORAL DYDROGESTRONE WITH VAGINAL PROGESTRONE FOR LUTEAL PHASE SUPPORT IN FERTILIZATION VIA INTRAUTERINE INSEMINATION

Time frame: 1/7/2020- 1/3/2021

A Randomized Controlled Trial

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TITLE:

Comparison of oral dydrogestrone with vaginal progesterone for luteal phase support in IUI.A randomized clinical trial.

Introduction

Intrauterine insemination (IUI) is a form of treatment where sperm are inserted into the uterine cavity around the time of ovulation. IUI has been used in people with unexplained infertility, mild endometriosis, mild male factor infertility, disability (physical or psychological) preventing vaginal sexual intercourse, conditions that require specific consideration in relation to methods of conception (such as after sperm washing in a couple where the male is HIV positive) and as part of donor insemination.

IUI can be carried out in a natural cycle, without the use of drugs, or the ovaries may be stimulated with oral anti-oestrogens or gonadotrophins. In a Cochrane Database of Systematic Reviews 2016 of Intra-uterine insemination for unexplained subfertility by Veltman-Verhulst SM, Hughes E, Ayeleke RO, Cohlen BJ, noted a significant increase in live birth rate was found for women treated with IUI and OH compared to women treated with IUI in a natural cycle (OR 2.07, 95% CI 1.22 to 3.50). As for pregnancy rate outcome, the OR for clinical pregnancy per woman randomised was 2.14 (95% CI 1.26 to 3.61), which was significantly in favour of IUI combined with OH. 2 RCTs reported multiple pregnancy rates for those with unexplained subfertility. The highest multiple pregnancy was reported by Goverde 2000(29 % in the OH group compared to 4% in the natural group).These analysis included 4 RCTs comprised a total of 396 couples and included high quality trials.

Consequently, IUI has been performed generally combined with controlled ovarian hyperstimulation (COH), i.e., with Clomiphene citrate and/or Gonadoptroin. Ovulation induction with the change in endocrine metabolism has negative effect on the luteal phase function. The luteal phase is defined as the period between the ovulation and pregnancy occurrence or starting the new menstruation.Ovulation induction with growth of many follicles induces the hyeprestrogenemic state that cannot compensate with progesterone. Controlled ovarian hyper stimulation also results in multifollicular development with higher steroid serum concentrations, compared with natural cycles. It is assumed that supraphysiologic serum steroid concentrations might adversely

affect LH secretion via feedback mechanisms, which in turn results in premature luteolysis and defective progesterone secretion.

Currently, progesterone supplementation is the first line treatment of luteal phase deficiency. Progesterone induces a secretory transformation of the uterine glands, increases vascularity of the endometrial lining, and stabilizes the endometrium in preparation for embryo implantation. Also, progesterone potentially sustains the survival of the embryo by shifting the immune system toward production of non-inflammatory T-helper (Th) 2 cytokines.

In an updated systematic review and meta-analysis by Katherien A.Green et al 2017, included 11 RCTs , confirming that progesterone supplementation improves clinical pregnancy and live birth in gonadrotrophin OI-IUI cycles .There does not seem to be a benefit of exogenous progesterone in Clomiphrene Citrate OI-IUI cycles .There is insufficient evidence that progesterone support improves outcomes in OI-IUI cycles using Letrozole or CC plus gonadotrophins.In this updated systematic review and meta-analysis ,only published RCTs that compared exogenous vaginal progestrone during luteal phase after OI-IUI versus no progestrone were included.

Progesterone can be administered orally, vaginally, or through intramuscular(IM) injection. The anatomy of vagina with its rich vascular plexus provides an ideal environment for absorbing drugs. The rugae of the vaginal wall increase the total available surface area. Vaginal administration results in higher uterine concentrations, but is often uncomfortable in the presence of vaginal bleeding, or may be washed out if bleeding is severe. Vaginal route also associated with vaginal irritation, discharges, bleeding and interference with coitus. The main issues regarding intramuscular progesterone are pain caused by daily injections, inflammatory response and local abscess.

Oral dosing requires a higher concentration in order to compensate for "first-pass" liver metabolism, resulting in a bioavaibilty less than 10% but oral administration is the easiest route of administration, and generally the most acceptable route for the patient. Oral dydrgesterone is a synthetic progesterone with enhanced oral bioavability that could overcome these issues. On the other hand, dydrogesterone has the

immunologic effects and it is associated with higher rate of pregnancy and even lower pregnancy complications such as fetal distress and gestational hypertension. (Barbosa 2016).

In randomized controlled trial by Donya Khosrav et al 2015, demonstrated oral dydrogestrone is effective as vaginal progesterone for luteal-phase support in woman undergoing IUI cycles. Moreover, the mean serum progesterone levels and satisfaction rates in dydrogestrone group were higher than cyclogest group. This prospective, randomized, double blind consisted of 150 infertile women younger than 35years old undergoing ovarian stimulation for IUI cycles. They underwent ovarian stimulation with oral dydrogesterone (20 mg) as group A and vaginal cyclogest (400 mg) as group B in preparation for the IUI cycles. The results showed that the two drugs were equally effective infertility (p=0.58). 29.7% of patients, who received dydrogesterone, were pregnant and fertility rate was 25.7% in patients who received cyclogest .Abortion rate in two groups was not statistically different (p =0.056) although rate of abortion was higher in group B in comparison with A group. 9.1% of abortion rate in group A and 15.8 % in group B. Satisfaction rates were significantly higher in group A compared to group B (p<0.001). Satisfaction rates in patients who received dydrogestrone was 85.1% compared to 60.8% in those who received cyclogest

Base on meta-analyis and prospective randomized controlled studies for luteal phase support in intrauterine insemination cycles reviewed by Ismet Gun et al 2016,the usefulness of progestrone supplementation during the luteal phase in IVF/ICSI cycles for reproductive outcomes is notably accepted in Cochrane study. However the timing of initiation, duration, route and amount of administration still debated.

Therefore, the aim of this prospective study is to compare the effect of oral dydrogesterone with vaginal progesterone for the luteal phase support on the outcome of IUI cycles.

Study Objective

The aim of this prospective study is to compare the effect of oral dydrogesterone with vaginal progesterone for the luteal phase support on the outcome of IUI cycles.

Hypothesis

Oral dydrogestrone is non-inferior to vaginal progesterone for luteal phase support in woman undergoing IUI cycles.

Methodology

This is a randomized controlled trial, carried out in the reproductive unit in UMMC. All patients who will be undergoing IUI treatment and whom fulfill the inclusion criteria, will be recruited to participate for the study.

Inclusion Criteria

1. Infertile women aged less than 40 years' old.
2. Undergoing ovarian stimulation with Gondaotropins for IUI treatment.
3. Normal hormonal assay
4. Normal pelvis in transvaginal sonography

Exclusion criteria

1. Basal levels of FSH ≥ 10mlU/ml
2. Endometriosis stage 3, 4
3. Severe male factor infertility

Primary outcome

1. To determine clinical pregnancy rate outcome up to 12 weeks
2. To determine miscarriage rate

Secondary outcome

1. To determine patient satisfaction

Recruitment procedure

1. The patients will be identified by the researcher from the clinic's census book during IUI treatment and follow up.
2. Patient is will be assessed for eligibility before recruited into this study by using Eligibility Form.
3. The researcher will explain about the study protocol to the patients and obtain their informed consents.
4. The researcher will obtain their socio-demographic data from the patient directly and from their medical records.
5. Patients whom do not fulfill inclusion criteria will be excluded. Proforma will be filled up once patient recruited in the study.
6. Patients will be randomized into 2 groups, A and B. Randomisation will be using random number generator at Random.org in random one block.
7. The random allocation sequence will be placed in sealed numbered opaque envelopes for strict number order assignment to participants.
8. Randomisation is by opening the lowest remaining numbered sealed envelope.
9. Those in group A will receive oral Dydrogesterone 10mg BD and those in group B will receive vaginal micronized progesterone 200mg BD.
10. The decision to proceed with IUI is made by usual care provider.
11. Luteal phase support will be started after IUI with Dydrogesterone 10mg twice per day in group A versus vaginal micronized progesterone 200mg twice per day in group B.
12. Serum progesterone level is measured on the mid-luteal phase, 7 days after IUI Progesterone administration will continued for 2 weeks. Serum BHCG will be checked two weeks after IUI.If it is positive (>25) then the medication will be continued till 12 weeks of pregnancy.
13. Clinical pregnancy rates, abortion rates, and patient satisfaction in both groups will be compared.
14. Patient satisfaction will be obtained from patients based on questionnaire.

Sample size estimation

Sample size is calculated by using clinical pregnancy as the primary outcome based on randomized control trial by Donya Khosrav et al 2015.

Sample size estimation for RCT Oral versus Vaginal is calculated using application Stata V13.

To achieve power of 0.08 and alpha value: 0.05 and aiming proportion rate 0.5 for pregnancy outcome for oral Dydrogestrone, thus the total sample size is 140.Assume drop of will be 10%, thus final sample will be 160.

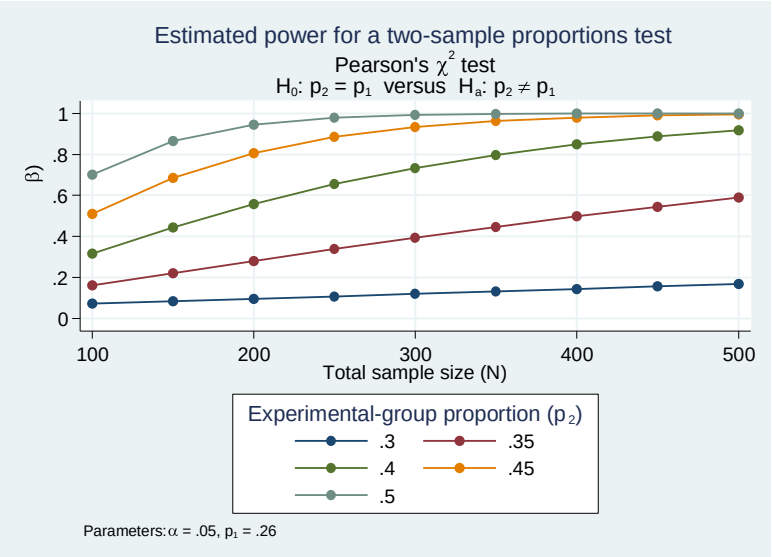
Method : Ref: Khosravi et al, 2015

Pregnancy rate:

Oral, P1=0.30

Vagina, P2=0.26

power two proportions 0.26 (0.30 0.35 0.40 0.45 0.50), test(chi2) n(100(50)500) graph



Patient's demographic data and treatment characteristics

Variable	Dydrogestrone group	Cyclogest group	P value
Age (years)			
Body mass index			
Ethnicity			
Comorbid			
Duration of infertility			

Type of infertility • Primary • Secondary			
Infertility diagnosis • Female factor • Male Factor • Unexplained subfertility			
Baseline LH			
Baseline FSH			

STATISTICAL ANALYSIS

Baseline characteristics

Pearson's X^2 test will be used to compare categorical variables. A value of p below 0.05 is considered to show statistical significance. For normally distributed data, mean with standard deviation will be used. Appropriate odd ratios (OR), significance tests and 95% confidence intervals (CI) will be obtained. However, if the data found to be non-normally distributed, the data will be normalized by transforming the data such as by logarithmic transformation before testing it with independent t-test or Mann-Whitney U test. All the results obtained will be presented accordingly.

Ethical consideration

For this study, approval shall be obtained from the University of Malaya Medical Center Clinical Research Ethics Committee before conducting the study. All eligible participants will be asked for written consent to the study procedures with information sheet explaining the trial. Information regarding the safety issues of intervention usage in this trial also will be provided in the information including the confidentiality of the data.

Proposed timetable to show plan of work

The study is planned to start from February 2020 for recruitment process and to be completed in February year 2021. The detail breakdown of work plan is as listed in the Gantt chart below

Appendix 1

Outcome form after luteal phase support in IUI cycle
Please mark x in the box for your answer

Date of recruitment:

1. Serial number: ☐☐☐
2. MRN: ☐☐☐☐☐

3. Ethnicity:

Malay : ☐
Chinese : ☐
Indian : ☐
Others : ☐

4. Age (in years):

☐☐

5. Date of birth:

☐☐ ☐☐ ☐☐☐☐

6. LMP:

☐☐ ☐☐ ☐☐☐☐

7. Co morbids:

_____

8. Duration of infertility:

_____

9. Type of infertility:

Primary : ☐
Secondary : ☐

10. Baseline LH:

_____

11. Baseline FSH:

_____

12. Semen Analysis:

_____

13. Baseline FSH:

_____

14. BHCG reading after 2 weeks on Progesterone:

_____

15. Clinical pregnancy after 12 weeks: Yes : ☐ No : ☐
16. Miscarriage: Yes : ☐ No : ☐

Appendix 2

Patient Satisfaction form
Please mark x in the box for your answer

Patient's Name:
Patient ID Number:

1. How would you describe the convenience of administering/ dosing the current progesterone preparation?

   Very convenient ☐
   Neither convenient or inconvenient ☐
   Very difficult ☐

2. How would you describe the ease and comfort of using the current progesterone preparation?

   Very convenient ☐
   Neither convenient or inconvenient ☐
   Very difficult ☐

3. How would you describe your overall experience with current progesterone preparation?

   Very comfortable ☐
   Neither comfortable or uncomfortable ☐
   Very uncomfortable ☐

4. Were you aware of any extra vaginal discharged whilst using the current progesterone preparation (applicable for vaginal progesterone)?

   Yes ☐
   No ☐

5. Did you have to clean yourself more often during the time you used the current progesterone preparation (applicable for vaginal progesterone)?

   Yes ☐
   No ☐

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