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Research Paper: Does Progesterone Suppository to Luteal Phase Support Have Any Effect on Pregnancy Rates in the Intrauterine Insemination Cycles?

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ABSTRACT

Objectives: Rate of infertility in overall is around 15-10%. Intra-Uterine Insemination (IUI) is one procedure for infertility treatment. Luteal phase support defect is a main factor in fail of pregnancy. Goal of this study was to evaluate the effect of luteal phase support with progesterone suppository in patients who undergoing IUI cycles.

Materials & Methods: 100 infertile couples who were undergoing IUI treatment included in this study. Ovulation induction was done for all patients. When IUI was done, patients were distributed into two groups. The study group (n=50) received progesterone suppository and control group (n=50) doesn't received any medicine. Then biochemical pregnancy rate, clinical pregnancy rate and abortion rate compared between two study groups.

Results: There were no differences in basic characteristics between two groups. Biochemical and clinical pregnancy were parallel in the study and control groups. There were no statistically significant increases in abortion rate between the study groups (P=0.49).

Conclusion: Luteal phase support by progesterone suppository does not improve the pregnancy rate of stimulated IUI cycles.

1. Introduction

Infertility defines according to the World Health Organization is when pregnancy does not occur in couple after a year sex without using any contraception. About 15% of the reproductive age population is infertile. Multiple factors are cause of infertility including couple age, oocyte quality, sperm parameters, infections and so on [1].

Intrauterine insemination is one of the most common techniques of infertility treatment. Based on various studies, the IUI success rate is about 11% and luteal phase defects is one of IUI failure cause [2].

After ovulation, the follicle into the corpus luteum, secretes this hormone. High levels of estrogen and progesterone secret of luteinizing cells to stimulation endometrial thickening.

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If pregnancy does not occur, the corpus luteum destroyed about 2 weeks after ovulation. The progesterone levels come down and stay stable to endometrial disappears and a new cycle of menstruation starts. The destruction of corpus luteum stops after fertilization of oocyte. 5 days after fertilization, the fertilized oocyte into the uterus and implantation in the endometrial site. After implantation, cells that will later become the placenta started HCG hormone secretion. This hormone stimulates the secretion of Luteinizing Hormone (LH) and continue progesterone secretion and finally the pregnancy continues [3, 4].

How to manage the luteal phase is still controversial and often experimental clinics based on the findings used a special protocol to manage luteal phase. Luteal phase hormone therapy depends on the treatment protocol. Because there was not one clinical method to support the luteal phase, we decided to study to evaluation the effects of luteal phase support with progesterone in cycles of ovulation induction and intrauterine insemination on pregnancy rates.

2. Materials and Methods

Study subjects

In this randomized prospective, observational study, 100 infertile patients referred to Yazd Research and clinical center for infertility, from April 2015 to August 2016, randomly selected. Our study was approved by the ethical committee of the Yazd, Shahid Sadoughi University of Medical Sciences.

All of the women who were 18–35 year old included in this study, and hysteron- salpingography were done for diagnosis and confirmed of openness of fallopian tubes. Patient with tubal factor, severe endometriosis, endocrine factor and hypothalamic amenorrhea and severe male factor (sperm count lower than 5 million per ml based on WHO 2012 classification) excluded from this study.

Ovulation stimulation protocol

All the patients were on IUI cycle. Standard protocol for all of patient were done, the protocol was that all women received 100 mg clomiphene citrate daily from the third to the seventh day of her menstrual cycle, on days 8, 9 and 10 ,150 IU Gonal-F (Serono Company 75 IU) were injected subcutaneously. Then, the patients underwent vaginal sonography on the 11th day and follicular count and size were recorded. Continuous treatment with gonadotropin was adjusted according to the count and size of follicle. The daily administration of gonadotropin was at least increase a 2 mm in the follicle size.

When at least one follicle reached 18 mm in diameter patients were given 10000 IU HCG and 34-36 hours after injection, IUI was performed for patients. In this step patients randomly were divided into two groups. Case group (n=50) received progesterone suppository 400 mg (Aburaihan Co., Tehran, Iran) and control group (n=50) received no medicine. Positive serum ßhCG test (chemical pregnancy), 14 days after embryo transfer and observation of gestational sac on transvaginal ultrasound examination (clinical pregnancy), were assessed 3 weeks after positive serum βhCG. The miscarriage rate was the number of miscarriages before 20 weeks gestation per number of women with a positive clinical pregnancy. Finally chemical and clinical pregnancy rate and abortion rate compared between tow study groups.

Statistical analysis

After collecting the necessary data were recorded in the computer system and was analyzed using Statistical Package for the Social Sciences 20.0 (SPSS, SPSS Inc., Chicago, Illinois). Continuous data were presented as mean±SD and assessed by independent Student's t-test. Enumeration data were compared by chi-square or fisher exact test. $P<0.05$ was considered significant.

All procedures performed in studies involving human participants were in accordance with the Ethics Committee of the Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This project was registered in (Iranian registry for clinical trial) IRCT by number: IRCT2015100424335N1.

3. Results

Baseline characteristics of the patients presented in Table 1. Mean age of patients was 28.30±3.40 in case and 27.62±3.51 in control group and this difference was not statistically significant. There was no significant difference in Infertility duration basal FSH (follicle-stimulating hormone) level, Anti-Mullerian Hormone (AMH), and LH level between two studied groups ($P>0.05$).

In 26% of the control and 42% of the case group, β-hCG test became positive. However, only 12 patients (24%) in the control and 16 patients (38%) in the case group achieved clinical pregnancy approved by ultrasound (Ta-

Table 1. Baseline characteristics of study patients in both groups

Variable	Case Group (n=50)	Control Group (n=50)	P
Age (years)	28.30±3.40	27.62±3.51	0.3
Infertility duration (years)	3.94±1.31	4.14±1.19	0.4
Baseline FSH (IU/L)	6.54±1.54	6.74±1.66	0.5
LH (IU/L)	7.50±1.51	7.00±1.70	0.1
AMH (ng/ml)	2.63±1.11	2.29±0.89	0.06

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FSH: Follicle-Stimulating Hormone; AMH: Anti-Mullerian Hormone; LH: Luteinizing Hormone; Continuous data presented as mean±SD with P-values obtained from independent samples T test; Enumeration data presented as N (%) with P-value obtained from chi-square or fisher exact tests. P<0.05 was considered statistically significant.

ble 2). Although, pregnancy happened in a higher number of women who received progesterone in comparison to the control group, this difference was not statistically significant. Although miscarriage rate was higher in case group than other group but it was not statistically significant difference between two groups (Table 2).

4. Discussion

During the luteal phase LH is in low level and it is possible these amounts are not necessary for stimulation of endometrium [5]. LH secretion in infertility treatment cycle may be was in low level 10 days after the treatment with GNRH agonist and unsatisfactory to luteal stage support [6]. The medical scientists believe that luteal phase support by any types of progesterone is necessary in ovulation induction of intrauterine insemination cycles and can elevate pregnancy rate and reduces abortion rate [7-9].

The different reports about progesterone administration to luteal phase support was the main goal for us to design this study for assessment the effects of suppository progesterone in the luteal phase support on pregnancy rate in patients who underwent infertility treatment by IUI method. Our result showed the prevalence of chemical pregnancy with the positive β-CG was higher in the group who received progesterone suppositories more than control group, although this increase was not statistically significant.

Chantilis et al. reported that β-HCG positivity rate and the pregnancy rate in the control group and a recipient of the suppository was not different [10]. In contrast of the report, Fanchin in 2001 showed that serum progesterone in patients who received progesterone suppositories was higher than control group and vaginal progesterone suppositories were easily use [11].

Gopinath (2014) in his study reported that luteal phase support by vaginal progesterone was not effective in ART cycles [8]. As well as, Ebrahimi and colleagues in a clinical trial concluded that the progesterone suppositories does not effect on improving IUI treatment [12]. In a retrospective study by Costello in 2004, they published no positive significant relation between the luteal phase support by progesterone in IUI cycles and increasing pregnancy rate [13].

Table 2. IUI outcomes of study patients in both groups

Variable	Case Group (n=50)	Control Group (n=50)	P
Chemical pregnancy	21(42%)	13(26%)	0.19
Clinical pregnancy	16(38%)	12(24%)	0.14
Miscarriage rate	9(18%)	4(8%)	0.23

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Enumeration data presented as N (%) with P-value obtained from chi-square or fisher exact tests. P<0.05 was considered statistically significant.

Montville and his colleagues in their study assessed the effect of progesterone on PCOS women and their results had shown that administering progesterone in these patients can be effective on pregnancy rate and the use of progesterone suppositories can be increased pregnancy rate in PCOS patients [14], the results of this study was in opposition of our study, and this different maybe was in patient selection. The results of the clinical trial in 2010 showed luteal phase support by vaginal progesterone in the women who had in the IUI cycle treatment was not approved pregnancy rate [15]. Aali et al. (2012) designed a study on 196 infertile patients who were in IUI cycle. They treated these patients by progesterone suppository and the results were compared with control group. Based on this study luteal phase support can increases progesterone level and extending the luteal phase in ovulation induction cycles with IUI. They reported luteal phase support had no positive effect on pregnancy rate [16].

In another study researchers considered the effect of vaginal progesterone on pregnancy rate and endometrium thickness. They found that the vaginal type of progesterone is better than another types [17]. In the study of Polyzos and colleagues, they compared vaginal suppositories of progesterone and other forms of progesterone in the luteal phase support. They report that a vaginal suppository was same as other forms of progesterone and had no significant difference on clinical pregnancy rate [18].

Our result showed spontaneous abortion in progesterone suppositories group was higher that control group, however, this difference was not statistically significant. In a prospective study by Hussein Rashid et al. (2012), the results of their study showed that the pregnancy and abortion rate had no significant difference between patients who received progesterone suppositories and control group [6]. In similar of our study, Lockwood showed that in the group who receiving progesterone a suppository, abortion rate was higher than control group [19].

5. Conclusion

The results of our study showed that luteal phase support, by progesterone does not improve the chemical and clinical pregnancy rate in patient undergoing controlled ovarian stimulation and intrauterine insemination cycles.

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Conflict of Interest

The authors have no financial or nonfinancial conflicts of interest.

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