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ORIGINAL: Does luteal Phase Support with Vaginal Micronized Progesterone Effect on Pregnancy Rates in Intrauterine Insemination (IUI) Cycles in Two Infertility Center During Six-Year Follow-up?

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ABSTRACT

Introduction: Husband artificial intrauterine insemination (IUI) is a standard method of assisted reproduction for patients with mild male infertility, anovulation, endometriosis, and unknown infertility. In this study, we evaluated the effect of luteal phase support on the success rate of IUI cycles with vaginal micronized progesterone compared to the control.

Material and Methods: This retrospective cohort study included 94 infertile women referring to two infertility centers in Sari, Iran, from 2015 to 2021. In these women, Clomiphene citrate or Letrozole was used, follicular monitoring continued, and human Gonadotropin was added based on ultra-sonographic findings. Intramuscular HCG was added when one or two follicles were to 17 mm. IUI was done 36 hours later, and micronized vaginal progesterone 400mg once daily was added on the day after insemination (n=114). IUI outcomes were evaluated with a serum Beta-HCG test and vaginal ultrasound two and five weeks later. Pregnant women were followed up until the end of the pregnancy. Data were analyzed with SPSS25 and STATA14 software.

Results: Progesterone consumption had no significant relationship with pregnancy rates but a significant correlation with the number of antral follicles. Pregnancy occurrence was significantly associated with patient satisfaction, FSH, and AMH levels but not correlated with the duration and kinds of infertility.

Conclusion: Vaginal micronized progesterone as luteal phase support is not effective in increasing pregnancy occurrences in IUI cycles like IVF cycles, but patients' satisfaction may be increased among women impregnated undergoing IUI and progesterone support.

Introduction

Infertility is a failure to become pregnant after 12 months of regular unprotected sex,

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affecting 10-15% of couples (1). About half of infertility cases are caused by female factors, 20-30% by males, and 20-30% by both sexes (2). Assisted reproductive technologies (ART) are used to treat infertility. This is a wide range of techniques that include intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) (3). Intrauterine insemination (IUI), with or without ovarian stimulation, is an assisted reproductive technique that can be the first treatment choice for unexplained infertility due to mild male factor, endometriosis, tubal causes, anovulation, and ejaculatory disorders (4).

The overall success rate of IUI is no more than 20%, even at best. In some cases, where the cervical mucus and intrauterine aspirate test (PCT-IUA) proves poor sperm entry, IUI may be applicable, and the pregnancy rate increases to 40-45%. In addition, to obesity, other factors, such as smoking habits, are also an obstacle to the success rate of IUI (5).

Several studies have shown that luteal phase support improves the outcome after IVF. Early studies showed that treatment with human chorionic gonadotropin (HCG), which induces steroid production in the corpus luteum, resulted in 18.7 and 50 percent of pregnancy rates, compared with 9.3 and 17 percent in patients who received no luteal support (6, 7). The luteal phase is the period between ovulation and pregnancy or menstruation (8). Luteal phase defects are mainly caused by insufficient production of progesterone, the main product of the corpus luteum, which is essential for establishing and maintaining early pregnancy. Luteal phase defects in infertile women are 3.7-20% (9).

After ovulation, continuous progesterone production from the corpus luteum is necessary to maintain a stable intrauterine pregnancy until luteo-placental displacement occurs and the placenta begins to produce sufficient progesterone (8-10 weeks). Insufficient progesterone production in the ovary may lead to early pregnancy loss or infertility. The condition without endogenous progesterone to maintain a functional secretory endometrium, normal embryo implantation, and development is called luteal phase defect (LPD) (10). Without progesterone, implantation is disrupted, and pregnancy does not occur (11).

Vaginal progesterone via capsule, gel, or tablet is the most common way of luteal phase support (LPS) in Europe. Progesterone for LPS is administered by various routes, including vaginal, intramuscular (IM), oral, and rectal. Different studies showed no significant difference between intramuscular (IM) and vaginal progesterone in terms of live birth rate and pregnancy rate. However, vaginal administration shows high progesterone levels in the uterus with little systemic effects (12). Luteal phase support by Cyclogest pessary increases progesterone levels and prolongs the luteal phase, increasing the chances of fertility. Other studies have shown that vaginal progesterone supplementation significantly increases live birth rates. The purpose of this study was to investigate the effect of cyclogest in supporting the luteal phase in the IUI cycle compared to the control group and to investigate the effect of progesterone after IUI in increasing the pregnancy rate and reducing miscarriage.

Methods

The research ethics committee of Mazandaran University of Medical Sciences has approved the present study by code IR.MAZUMS.IMAMHOSPITAL.REC.1400.045. Before entering the research, informed consent was obtained from the research units by including the research method, the advantages and disadvantages, and the voluntary participation of the samples in the study. To comply with ethical standards, all information was used confidentially and exclusively for the aim of this study, and all files were delivered to the archives without any changes.

Study design

This retrospective cohort study was based on recorded data of infertile women referring to

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the infertility center of Imam Khomeini Hospital in Sari and the mother's infertility center. All the infertile women who were treated with IUI, exposed and not exposed to progesterone were evaluated, were included in the study from 2015 to the end of 2021 by census method, and the number of samples was considered to be 94 people .The exposed group included infertile women treated with IUI who received progesterone, and the control group included infertile women were treated with IUI who did not receive progesterone. The group receiving progesterone and the control group were identical regarding other factors.

Women with laparoscopic or radiological evidence of open tubes for infertility treatment, age less than 40 years, FSH level less than 12, duration of infertility less than five years, less than two previous failed IUI attempts, and no history of chronic liver, kidney, and the heart diseases was included. Among the standard tests, terms of HIV, HCV, heart and kidney failure, congenital heart and liver and kidney disease, valvular heart disease, and liver cirrhosis was evaluated. Also, only couples with a sperm count >10 million/ml were included in the study.

People who are over 40 years of age had infertility for more than five years, have an underlying disease such as thyroid disorders (hypothyroidism and hyperthyroidism), chronic liver, heart, and kidney disease, lack of patient consent to participate in the study, having more than 2 Follicles on the day of HCG injection were excluded from the study too. Vaginal ultrasound was performed on the first to fifth days of the menstruation.

In these patients, basic vaginal ultrasound was performed on the third day of the menstrual cycle, and the treatment was started based on the patient's profile and the record of the previous cycle. -100 mg of clomiphene citrate daily for five days from day 3 to 7. Based on the ovarian response, an intramuscular injection of 75-150 IU highly purified HMG (PDHOMOG, Pooyesh Darou, Iran) was injected from the 8th to the 9th of the menstrual cycles. Ovarian response was assessed by vaginal ultrasound from day 8 of each menstrual cycle by two IVF specialists.

In cases of at least one follicle with a diameter of 18 mm, ovulation was triggered by intramuscular injection of 10,000 IU hCG (PDPREG, Pooyesh Darou, Iran), and 34-36 hours later, IUI was done. In cases of the absence of follicles or more than three or four follicles larger than 17 mm, the cycle was canceled. Patients were placed in one of two treatment groups: vaginal micronized progesterone and the control group.

The day after IUI, the case group was treated with micronized vaginal progesterone once daily (Cyclogest, 400 mg, Actavis, UK) for 14 days. A control group consists of members who do not receive any additional drugs. After 14 days of HCG injection, venous blood (2-3 ml) was collected. Biochemical pregnancy was confirmed from day 14 till 28 after insemination with a positive β-hCG test without an apparent gestational sac. Clinical pregnancy was defined as the observation of a gestational sac on ultrasound at 21-30 days after insemination.

Statistical analysis

STATA 14 and SPSS 25 statistical software were used for data analysis. $P<0.05$ was considered significant. Variables were described using percentage, mean, standard deviation, median, minimum and maximum, and quartile. The two groups' possible confounding variables were compared with independent t-test and chi-square tests. Also, the comparison of clinical pregnancy, chemical pregnancy, and abortion between the two groups with and without exposure was made using the chi-square test.

Results

Ninety-four patients were included in the study. The Mean age was 30.53 ± 5.19 and 29.86 ± 5.07 in the control and case groups, respectively. The overall pregnancy rate was 24 (75%) and 40 (65.6%) in the control and case groups, respectively.

The relationship between women's age, infertility duration, and pregnancy

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occurrence was insignificant (P=0.227). Also, there was a significant relationship between BMI and pregnancy occurrences. No significant relationship was found between the kind of infertility in women and pregnancy occurrence (P=0.960). According to the ANOVA analysis, there was no significant relationship between infertility duration and pregnancy occurrence (P=0.179). There was a significant relationship between the level of satisfaction and pregnancy occurrence (***Table 1***).

Also, there was no significant relationship between progesterone and pregnancy occurrence (P=0.316), but there was a significant relationship between FSH level and pregnancy occurrence (P=0.059). There was no significant relationship between progesterone intake, pregnancy continuation and complications as chemical, clinical, ongoing, and lived birth and abortion (***Table 2***). ANOVA analysis, showed no significant relationship between progesterone intake and pregnancy continuation and complication (***Table 2***).

Table 1. Correlation between patients' characteristic and pregnancy occurrence

Variables	Pregnancy Occurrence P-value*
Age (years)	0.217
Infertility duration (years)	0.179
BMI (kg/m^2)	0.004
Infertility kinds	0.960
FSH levels	0.059
AMH levels	0.717
Satisfaction rates	0.000

*Logistic Regression was used. P<0.05 was considered significant.

Table 2. Relationship between progesterone intake and pregnancy continuation and complication

Variables	Pregnancy kind and stage					P-value*
	Chemical	Clinical	Ongoing	Live birth	Abortion	
Progesterone consumption	17	11	9	3	21	0.316
No progesterone consumption	5	9	6	6	8	

Discussion

Intrauterine insemination (IUI) is an assisted reproductive procedure for patients with mild male factor infertility, anovulation, endometriosis, and unknown infertility. In this study, we investigated the effect of supporting the luteal phase on the success rate of IUI cycles with vaginal micronized progesterone or not using it in the control group.

In this study, it was found that there is no relationship between progesterone consumption in the control and case study groups with pregnancy occurrences. Also, there was no association between the duration and kinds of infertility and pregnancy occurrences. This is even though there was no significant correlation between progesterone consumption and the pregnancy continuation and complication as chemical and clinical and ongoing and live birth and abortion. However, there was a significant relationship between patient satisfaction, FSH and AMH levels, and pregnancy occurrence.

Our study showed a significant relationship between the type of pregnancy continuation and complication and pregnancy occurrence. Also, the results of the study by Salehpour and Mustafa showed no statistically significant difference between the clinical, chemical, and ongoing pregnancy rates with progesterone consumption (1, 8). The inconsistency of our results with other studies can be caused by the different responses of different populations to progesterone treatment, the methods used by the physicians, and the studied subjects. Therefore, deciding on the effect of progesterone according to the different results requires more comprehensive studies. Considering that there was no relationship between the type of infertility and pregnancy occurrences in the present study, IUI can be mentioned as one of the effective methods for infertility without affecting by progesterone support. Also, these results strengthen the role of progesterone in prolonging the luteal phase without increasing success in pregnancy occurrences.

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In different studies, as in our study, no significant advantage was reported in using progesterone to enhance the luteal phase in IUI. In contrast, Green's systematic study reported that the support of the luteal phase of progesterone could be practical for patients who underwent ovulation induction with gonadotropins in IUI cycles (13).

The role of progesterone in supporting the luteal phase needs further investigation. Also, progesterone suppository does not improve the pregnancy rate of stimulated IUI cycles. It was using Cyclogest as micronized vaginal progesterone does not have a significant advantage over other types of progesterone. Instead, the oral type can be a better choice due to its easier consumption, simple and straightforward administration, lack of safety concerns, and better patient tolerance in patients who do not want to use vaginal progesterone (1, 5, 6, 9).

In Salehpour study, there was no patient satisfaction comparing of the two treatment groups. In contrast, our study, showed a significant relationship between pregnancy occurrence and patient satisfaction. In our study and Yasaei, there was no significant relationship between abortions and pregnancy, while the results of Salehpour's study are inconsistent with this (14, 15).

Wang investigated the effect of obesity on the success of IUI cycles. In this study, the fertility rate was reported to be higher in people with average weight and lower in obese people (6).

Our study found a significant statistical relationship between BMI and pregnancy occurrences. Among the reasons for the difference between the results of BMI and pregnancy, the type of population and genetics of people should be mentioned. Also, the impact of underlying diseases on BMI and pregnancy has not been considered.

Our study found no significant correlation between progesterone consumption and AMH levels. This result was in contrast with Kollmann et al. study in that progesterone was significantly correlated with AMH levels. These results showed that progesterone is an influential factor in AMH secretion. However, we did not evaluate the progesterone levels our patients who underwent the progesterone support had higher AMH levels, which may be due to selection bias (16).

Our study showed a significant relationship between FSH levels and progesterone consumption, consistent with Oktem et al. study (17).

While there was a significant relationship between progesterone consumption and the antral follicle number in this study, that differed from Qasimzadeh et al. study. In Qasimzadeh et al. study, the progesterone level was significantly lower in those who had a positive pregnancy, but we did not measure the progesterone levels. Also, in our study, there was no correlation between HCG dose and pregnancy. Qasimzadeh et al. the study showed that a higher progesterone level on the day of HCG injection was associated with a decrease in pregnancy rate (18).

It can be concluded that there is no need to inject HCG in IUI cycles and luteal phase support, and HCG injection can affect the process of luteal phase support and treatment with other support methods. Therefore, more studies and investigations of variables individually in support of the luteal phase are needed.

Conclusion

This study showed that progesterone supplementation does not support the luteal phase of the IUI cycle. Progesterone supplementation leads to satisfaction with the treatment process and the occurrence of pregnancy. Also, high BMI has been associated with decreased pregnancy and increased abortion rates in patients. It is suggested that this study be conducted with a more extensive study population to investigate the outcomes and prognoses of luteal phase support so that apparent horizons can be placed in front of the patients.

Ethical standards statement

This study resulted from a research project

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approved by Mazandaran University of Medical Sciences. The research ethics committee of Mazandaran University of Medical Sciences has approved the present study by code IR.MAZUMS.IMAMHOSPITAL.REC.1400.045.

Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' contributions

Ma.Z., A.E. contributed to the conception and design of this study. M.Z., S.P., M.H. and S.F.K. involved in the acquisition of data. M.M. analyzed and interpreted the data. Ma.Z., A.E. and M.H. drafted the manuscript, which M.Z. and Ma.Z. critically revised. All authors verified the article's content and certified the accuracy or integrity of any part of the study.

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