Original Article

A Comparison of Oral Dydrogesterone with Vaginal Progesterone for Luteal-Phase Support in *In vitro* Fertilization: A Randomized Controlled Trial

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Abstract

Background: The quality of the luteal phase is the most important issue affecting pregnancy outcomes in assisted reproductive technology (ART). Luteal-phase support with the administration of gonadotropin-releasing hormone (GnRH) agonist or progesterone improves the likelihood of pregnancy in ART. Due to disagreements regarding the best pharmaceutical form of progesterone for success of *in vitro* fertilization (IVF) in ART methods, the present study aimed to compare the clinical efficacy of oral dydrogesterone with vaginal progesterone on the outcome of pregnancy in IVF.

Materials and Methods: This unblinded randomized clinical trial was conducted at the Shahid Beheshti Hospital, Obstetrics and Gynecology Centre in Isfahan, Iran, between June 2021 and September 2021. In total, 126 couples were included in the study. All patients underwent controlled ovarian stimulation and IVF. Patients were randomly divided into two groups (n = 63 per group). After embryo transfer, group I was treated with Cyclogest 400 mg twice daily, and group II was treated with oral Duphaston 10 mg twice daily.

Results: No significant differences were observed between the two groups in terms of the mean endometrial thickness (P = 0.613), the mean number of transferred embryos (P = 0.100), and the number of implanted embryos (P = 0.338). Additionally, no statistically significant differences in the pregnancy rate were detected between the two groups (P = 0.875).

Conclusions: The evidence from this study indicates that Duphaston is as effective as Cyclogest for luteal-phase support.

Keywords: Dydrogesterone, fertilization *in vitro*, infertility, luteal phase, progesterone

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Introduction

Infertility is a common global and medical phenomenon affecting many reproductive-aged couples. According to the World Health Organization (WHO), infertility is considered as a failure to achieve pregnancy after 12 months of regular and unprotected intercourse.[1] Over recent decades, an increasing number of approaches, such as assisted reproductive technology (ART), have been designed to provide treatments according to the etiology of infertility.[2] A challenging problem that arises in this domain is the success of these procedures that is influenced by numerous factors such as sperm quality and women's physical and mental health, like hormonal balance.[3]

The corpus luteum plays a vital role in providing a proper hormone balance for establishing uterine receptivity for implantation in the luteal phase.[4] The primary function of

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the corpus luteum is to secrete progesterone, maintain it at the appropriate level, and consequently induce secretory transformation of the endometrium.[5] In this regard, the quality of the luteal phase is the most important issue affecting pregnancy outcomes in ART.[6]

Luteal phase deficiency is defined as a luteal phase duration shorter than 11 days, resulting in abnormal progesterone production after ovulation and leading to early pregnancy loss.[7,8] More recent evidence reveals that the luteal phase is supported with the administration of gonadotropin-releasing hormone (GnRH) agonist or progesterone and improves the likelihood of pregnancy in ART.[9,10] An increasing number of studies have presented oral dydrogesterone or vaginal progesterone as effective approaches for luteal-phase support in ART.[11–13]

Dydrogesterone is a retro isomer of progesterone that has been used worldwide for luteal-phase support in ART cycles.[14] It has good oral bioavailability, and in cases of threatened or recurrent miscarriages, dydrogesterone has been extensively recommended without any androgenic or estrogenic effects on the fetus.[15] Vaginal progesterone is a type of progesterone with high uterine bioavailability and minimal maternal side effects that is used to reduce the risk of spontaneous abortion.[16,17]

Despite the positive evidence for the effect of progesterone on the continuation of pregnancy in cases of threatened abortion, results of studies on its pharmaceutical form and routes of administration have been controversial. The results from two systematic reviews revealed that progesterone therapy was generally effective in cases of threatened abortion. But they have found that the use of dydrogesterone was more successful than vaginal progesterone. However, the researchers in these studies pointed out that due to the limitations of the studies, there are controversies over the best pharmaceutical form of progesterone.[18,19]

Regarding the disagreements on the best pharmaceutical form of progesterone for the success of *in vitro* fertilization (IVF) in ART, the present study aimed to compare the clinical efficacy of oral dydrogesterone with vaginal progesterone on the outcome of pregnancy in IVF.

Materials and Methods

This unblinded randomized clinical trial was conducted at the Shahid Beheshti Hospital, Obstetrics and Gynecology Centre in Isfahan, Iran, between June 2021 and September 2021.

Twenty-to-forty-year-old child-bearing infertile women who were referred to the center for treatment consultation were included in the study. Inclusion criteria were women with normal endometrial thickening (6–12 mm) on the day of oocyte retrieval, women aged between 20 and 40 years old, infertile women with IVF indication, and patient's consent to participate in the study. Women with pelvic adhesion, those with genital tuberculosis, and the subjects with advanced endometriosis were excluded from the study.

Basic information, including sociodemographic characteristics, level of education, employment status, type of infertility, duration of infertility, and the etiology of infertility, was obtained from patients.

The sample size (n = 63 per group) was determined using the method described by previous studies,[20] and the WHO sample size calculator (confidence level = 95%, test power = 80%, P = 0.05). In total, 126 couples who met the inclusion criteria were selected using the sequential convenience sampling method.

Subjects were randomly assigned into two groups using random allocation software (Excel software, Microsoft Office 2010, United States). Furthermore, 126 identical, sequentially numbered, and sealed envelopes were used for allocation concealment. A number was written on a paper and each was placed in an envelope. Then each patient was asked to choose an envelope and according to the number, they were assigned to one of the two groups.

All patients underwent the same ovulation induction protocol with subcutaneous FSH (GonalF, Merck Serono) at 150 IU/day and intramuscular hMG (Menogon®, Ferring Pharmaceuticals A/S, Copenhagen, Denmark) 75–150 IU/day from the third day of the menstrual cycle until the trigger day. Then in all women, transvaginal sonography was done by two experienced gynecologists. After confirming the mature follicle (≥14 mm), 0.25 mg/day of Cetrotide (Merck Serono, Germany) was administrated until the trigger day. When more than two mature follicles of ≥17 mm diameter were observed by transvaginal sonography in ovaries, 10,000 IU intramuscular hCG (Gonasi® HP, IBSA Italia, Rome, Italy) was prescribed. Oocyte retrieval was performed 40 to 36 hours after hCG triggering by needle aspiration under general anesthesia on the 10^{th} to 14^{th} days of the menstrual cycle. Then retrieved oocytes were evaluated, and the existence of the first polar body was considered as a marker of embryology matured oocytes (MII). The retrieved oocytes were fertilized at the laboratory using IVF with fresh semen. Finally, a maximum of three embryos was implanted into the uterus of each patient.

After embryo transfer, Cyclogest® (Actavis; Barnstaple; UK) was administered 400 mg twice daily in group I, and oral Duphaston® (Abbott Healthcare, Tokyo, Japan) was given 10 mg twice daily in group II. Two weeks after embryo transfer, chemical pregnancy was confirmed by measuring blood beta-hCG, and in the case of pregnancy, the drugs were continued in two groups. Clinical pregnancy was determined in the 5^{th} to 6^{th} week of pregnancy by observing the gestational sac through ultrasound scan, and if the gestational sac was seen, the intervention continued until the twelfth week of pregnancy.

Ethical consideration

The research adhered to the tenets of the Declaration of Helsinki for the use of human subjects, and written informed consent was obtained from all participants before any intervention. The Ethics Committee of Isfahan University

of Medical Sciences approved this study (IR.MUI.MED.REC.1398.560). Additionally, the study protocol was approved by the Iranian Registry of Clinical Trial (IRCT) (code: IRCT20200825048515N32).

Statistical methods

Data were entered into the Statistical Package for the Social Sciences (SPSS) version 14.0 (SPSS Inc., Chicago, IL, USA). The descriptive data were presented as mean ± SD for continuous variables, and absolute numbers and percentages for categorical variables. The Kolmogorov–Smirnov test was applied to assess the normality of data distribution. Inferential analysis was conducted by using analysis of variance (ANOVA), Student *t*-test, Chi-squared test, and Fisher's exact test. A *P* value <0.05 was considered as significant.

Results

Six patients were excluded from the study: two cases because of hypothyroidism and four cases because they were not willing to continue the study. The patients were randomly assigned into two groups of 63 each. After the intervention, six more patients were excluded because of discontinued intervention (progressive bleeding or ovarian hyperstimulation syndrome [OHSS]; *n* = 4) and lost to follow-up (*n* = 2). Finally, the study was conducted on a total of 126 infertile women.

The mean age of the women at the time of evaluation was 33.23 ± 5.42 years in the Cyclogest group and 32.15 ± 4.73 years in the Duphaston group (*P* = 0.401). Furthermore, both groups had similar demographic characteristics, including husband's age (*P* = 0.995), occupational level (*P* = 0.662), type of infertility (*P* = 0.507), and duration of infertility (*P* = 0.500) [Table 1].

No significant differences were observed between the two groups regarding the mean of endometrial thickness (Cyclogest group = 7.18 ± 0.46 mm, Duphaston group = 16 ± 0.45 mm; *P* = 0.613), mean numbers of transferred embryos (Cyclogest group = 91 ± 0.57, Duphaston group = 2.16 ± 0.63; *P* = 0.100), and the numbers of implanted embryos (Cyclogest group = 1.85 ± 1.17, Duphaston group = 1.74 ± 1.26; *P* = 0.338) [Table 2].

Table 3 presents the number of transferred embryos in a specific morphological category for all the patients. There were no differences between the groups with respect to trophectoderm morphological score and the number of transferred embryos in specific morphological categories [Table 3].

At the end of the study, 14 women (22.6%) in the Cyclogest group and 16 women (24.2%) in the Duphaston group became pregnant. However, no statistically significant differences in the pregnancy rate were detected between the two groups (*P* = 0.875) and there was also no serious complication to report.

Table 1: Comparison of sociodemographic and clinical characteristics of the study population between the groups

Variable	Cyclogest Group (*n*=63)	Duphaston Group (*n*=63)	*P**
Age of patients (years)†	33.23±5.42	32.15±4.73	0.401
Age of husband (years)†	36.19±5.67	36.12±4.56	0.955
Duration of infertility (years)§	5.53±4	6.04±3.77	0.500
Occupational level *n* (%)‡			
Employed	48 (77.4)	54 (81.8)	0.662
Housewife	14 (22.6)	12 (18.2)	
Type of infertility *n* (%)‡			
Primary	46 (81.5)	46 (74.2)	0.507
Secondary	10 (18.5)	16 (25.8)	
Etiology of infertility *n* (%)$			
Tubal disease	10 (16.1)	14 (21.2)	0.515
Diminished ovarian reserve	24 (38.7)	14 (21.2)	
Male factor	24 (38.7)	34 (51.5)	
Unknown	4 (6.5)	4 (6.1)	

Statistical significance was tested with †t-test, ‡Chi-squared test, §Mann-Whitney *U* test, and $Fisher's exact test. **P*<0.05 shows statistical significance (bold)

Table 2: Comparison of endometrial thickness, transferred embryos, and implanted embryos between the two groups

	Cyclogest Group (*n*=63)	Duphaston Group (*n*=63)	*P*†
Endometrial thickness (mm)			
6 mm	0 (0%)	2 (3%)	0.613
7 mm	54 (87.1%)	50 (75.8%)	
8 mm	6 (9.7%)	14 (21.2%)	
9 mm	2 (3.2%)	0 (0%)	
Number of transferred embryos			
1	8 (12.9%)	14 (21.2%)	0.100
2	36 (58.1%)	44 (66.7%)	
3	18 (29%)	8 (12.1%)	
Number of implanted embryos			
1	34 (54.8%)	26 (39.4%)	0.338
2	22 (35.5%)	36 (54.5%)	
3	2 (3.2%)	0 (0%)	
4	0 (0%)	0 (0%)	
5	0 (0%)	0 (0%)	
6	4 (6.5%)	4 (6.1%)	
Pregnancy rate	14 (22.6%)	16 (24.2%)	0.875

†analyzed by Mann-Whitney *U* tests

Discussion

Luteal-phase support is an effective approach in ART and is used as prophylaxis against corpus luteal insufficiency through supplementation of either GnRH agonist or progesterone.[21]

Table 3: The number of transferred embryos in a specific morphological category

	The First Embryo Transfer Cycle		The Second Embryo Transfer Cycle		The Third Embryo Transfer Cycle	
	Cyclogest (*n*=63)	Duphaston (*n*=63)	Cyclogest (*n*=52)	Duphaston (*n*=54)	Cyclogest (*n*=8)	Duphaston (*n*=18)
TE morphological score						
Grade A	30 (45.5%)	24 (38.7%)	24 (46.2%)	12 (22.2%)	4 (50%)	2 (11.1%)
Grade B	4 (6.1%)	4 (6.5%)	4 (7.7%)	10 (18.5%)	4 (50%)	2 (11.1%)
Grade C	2 (3%)	4 (6.5%)	0 (0%)	2 (3.7%)	0 (0%)	2 (11.1%)
Cleavage stage embryo transfer	2 (3%)	4 (6.5%)	0 (0%)	4 (7.4%)	0 (0%)	6 (33.3%)
Blastocyst transfer	2 (3%)	6 (9.7%)	0 (0%)	4 (7.4%)	0 (0%)	0 (0%)
Compact stage embryo transfer	26 (39.4%)	20 (32.3%)	24 (46.2%)	22 (40.7%)	0 (0%)	6 (33.3%)
P	0.828		0.116		0.283	

Several guidelines have recommended dydrogesterone or vaginal progesterone as treatment options to compensate for corpus luteal insufficiency during ART. Although numerous investigations have recommended vaginal progesterone as a well-accepted drug in the treatment of progesterone deficiency, the information about the efficacy of the dydrogesterone is inadequate.

The present clinical trial study compared the clinical efficacy of oral dydrogesterone (Duphaston) with vaginal progesterone (Cyclogest) on the rate of pregnancy in IVF in 126 infertile women. Our results demonstrated that there was no difference in the pregnancy rate between the Duphaston group (24.2%) and the Cyclogest group (22.6%), whereas the two groups were similar with regard to maternal sociodemographic, clinical, and paraclinical characteristics, as well as the number of transferred embryos in specific morphological categories.

These findings are directly in line with the findings of a phase III clinical trial conducted by Griesinger *et al*.,[12] which indicated that oral dydrogesterone (30 mg/day) had no significant advantage compare to micronized vaginal progesterone (600 mg/day). They mentioned that no systemic tolerability differences were identified between dydrogesterone and vaginal progesterone. Additionally, no new fetal safety concerns was seen by the study. Also, our results have a number of similarities with the findings of Saharkhiz *et al*.[22] They revealed that there were no differences between dydrogesterone and vaginal micronized progesterone for luteal-phase support in terms of fertility outcomes, patient satisfaction, and tolerability among infertile women undergoing IVF. Additionally, the similarity between these two medications in fertility outcome for luteal-phase supplementation in ART cycles have been confirmed by a meta-analysis that included nine studies ($n = 4.61$ patients).[23] This fits well with previous findings in the literature that reported similar efficiency of dydrogesterone and vaginal progesterone for luteal-phase support during IVF cycles.[11,24,25]

These results are different from the results of a meta-analysis by Griesinger *et al*.[26] that highlighted the treatment with dydrogesterone gave a better pregnancy outcome compared to vaginal progesterone for luteal-phase support. However, when comparing our results to this meta-analysis, it must be pointed out that some studies evaluated pregnancy outcomes at different time points during pregnancy and that they used different doses of these medicines. Thus, these differences in evaluations cause differences in the results obtained.

Conclusion

The evidence from this study indicates that Duphaston is as effective as Cyclogest for luteal-phase support. Therefore, it can be concluded that due to its patient-friendly nature and also fewer intolerable side effects compared to vaginal progesterone, dydrogesterone may become the new strategy for luteal phase support in IVF cycles.

Limitations

Our work clearly has some limitations. For instance, the study was limited by small sample size and possible selection bias, so further studies are needed to increase the generalizability of its findings. We also suggest conducting studies to compare and follow-up the pregnancy outcomes of these two methods.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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