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Research Article

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Comparison the Effectiveness of Oral Dydrogesterone, Vaginal Progesterone Suppository and Progesterone Ampule for Luteal Phase Support on Pregnancy Rate during ART Cycles

Mahvash Zargar[1*], Najmieh Saadati[2] and Maryam Sadat Ejtahed[2]

[1]*Fertility Infertility and Perinatology Research Center, Imam Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz Iran*
[2]*Department of Obstetrics and Gynecology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
**Email: dr.zargar199@gmail.com*

ABSTRACT

Luteal phase has an important role in assisted reproductive techniques through enhancing pregnancy rates. The aim of this study was to compare oral dydrogesterone with vaginal suppository (Cyclogest) and progesterone ampule (progestin) for luteal phase support in ART cycles. This was a randomized double blinded clinical trial conducted on 612 infertile women who were candidate for IVF or ICSI in Fertility Infertility and Perinatology Research Center at Ahvaz Imam Hospital during April 2014 to March 2015. The patients were randomly assigned into three groups according to the administration of the medications as: oral dydrogesterone (30 mg), vaginal progesterone suppository (800 mg) or progesterone ampule (100 mg). Inclusion criteria were infertility duration less than 5 years, maternal age below 40 years, normal levels of hormones, normal transvaginal sonography, and regular menstrual cycles. The pregnancy was observed in 53 patients (25%) of 212 in the dydrogesterone group, in 53 cases (26.5%) of 200 patients in the cyclogest group, and 53 patients (26.5%) of 200 in the ampule group. This rates had not statistically significant difference (P= 0.3). Moreover, the miscarriage was occurred in 3 patients (5.6%) of 53 in the dydrogesterone group, in 2 cases (3.8%) of 53 patients in the cyclogest group, and 2 patients (3.8%) of 53 in the ampule group. This rates had not statistically significant difference (P= 0.6). Our findings showed that the efficacy of oral dydrogesterone is comparable with vaginal progesterone and progesterone ampule for luteal phase support in ART cycles in terms of pregnancy rate and miscarriage rate.

Keywords: Luteal phase support, dydrogesterone, vaginal progesterone, assisted reproductive techniques.

INTRODUCTION

The luteal phase starts from ovulation to occurrence of pregnancy or menstrual period begins (1). Previous studies have highlighted the positive role of luteal phase support in assisted reproductive techniques (ART) so that it significantly increases pregnancy rates (2-8). The prevalence of luteal phase defect is 3.7-20% in infertile women (9). Every factor altering the estrogen to progesterone ratio can adversely affect the luteal phase (4, 10-12). An

appropriate level of progesterone is essential for implantation (13); thus, administration of progesterone supplements is necessary in women with progesterone level below 10 ng/ml at mid-luteal phase (14).

Various forms of progesterone for luteal phase support in ART cycles have been studied, but there is no consensus on the best method. Currently, progesterone is the first-line therapy choice for luteal phase defect (9). These products are natural or synthesized types. The body cannot quickly process or remove the synthesized progesterone hence its activity remains longer (14).

There is higher level of progesterone at the uterus in the case of administration of vaginal suppository of progesterone, but it is uncomfortable in the cases of vaginal bleeding and also severe bleeding can wash the drugs (15). Oral administration of progesterone is the easiest and more acceptable method (9). However, oral progesterone exposes to before liver or liver metabolism which destructs it to 5-alpha and 5-beta metabolites (15). Dydrogesterone is an optical isomer of progesterone in which methyl group at carbon 10 is in the alpha position instead of beta position in natural progesterone (6, 8). These changes in formation of oral dydrogesterone makes it more stable and effective and it has been demonstrated that dydrogesterone has excellent compliance, less side effects and pregnancy rate of 31% after IVF (15). It seems that progesterone is associated with higher birth weight, a higher 1-minute Apgar score, and less incidence of developmental retardation. However, these differences are not significant (16).

The aim of this study was to compare oral dydrogesterone with vaginal suppository (cyclogest) and progesterone ampule (progestin) for luteal phase support in ART cycles.

MATERIALS AND METHODS

This was a prospective, randomized, double blind clinical trial conducted on 612 infertile women who had been candidate for IVF or ICSI in the Fertility Infertility and Perinatology Research Center at Ahvaz Imam Hospital during April 2014 to March 2015. The study protocols were clearly explained for all participants, and then written informed consent was obtained from all participants. The study was double-blinded where patients' allocation was concealed and also the assessor of the results was unaware about the type of treatment. Patient's allocation to the groups of the study was based on computer generated random list and concealed packets. Patients were assigned into one of three groups: oral dydrogesterone (10 mg three times daily), vaginal progesterone suppository (cyclogest, 400 mg twice a day), or progesterone ampule (progestin, 50 mg twice a day). Inclusion criteria were infertility duration less than 5 years, maternal age below 40 years, normal levels of hormones, normal transvaginal sonography, and regular menstrual cycles. Exclusion criteria were poor response to treatment (number of follicles less than 4), abnormal uterus such as submucosal myoma, endometrial adhesion, follicle stimulated hormone (FSH) $\geq$ 10 mlU/ml, and sensitivity to the progesterone products. Patients according to the case were treated with agonist or antagonist cycles.

Firstly, patients underwent transvaginal sonography examinations then appropriate drugs were administrated for ovulation stimulation according to the type of cycle. Transvaginal sonography was repeated for each patient once every few days. When at least three follicles reached a diameter of 18 mm then IU 10000 hCG was intramuscularly injected and oocyte retrieval was performed during transvaginal βhCG test at 12 days after embryo transfer and fetal heart is visible on sonography. In the case of a positive pregnancy test, progesterone was administrated for 12 weeks during pregnancy for luteal sonography after 36 hours. Afterwards, progesterone was administrated for luteal phase support in the form of tablet, suppository, or injection. Embryos were transferred to patients with various number and grades after 48-72 hours or at blastocyst stage. Pregnancy was defined according to positive phase support. The first group received 10 mg dydrogesterone tablet (Duphaston, Abbott Laboratories, Chicago, Illinois, United States) three times daily, second group received vaginal progesterone suppository (Cyclogest progesterone, Actavis, Barnstaple, EX32 8NS, UK) twice a day and third group received 50 mg injectable progesterone (Fertigest, Aburaihan Co., Tehran, Iran) twice a day.

Moreover, influential factors which were considered for matching the groups' subjects are as follows: age ($\leq$37 or >37 years old), body mass index (BMI) ($\leq$25 or >25 kg/m^2), endometrial thickness, infertility duration ($\leq$3 or >3 years), cause of infertility (male factors or other factors), endometriosis (yes or no), type of ovulation stimulation (agonist or antagonist), number of transferred embryos, grade of embryos. According to mentioned factors patient's score was calculated. So, we considered a score of zero for favorable factor and a score of one for unfavorable

factor. Then, patients were divided into four grades according to total scores as follows: grade 0 (total score 0), grade 1 (total score 1-3), grade 2 (total score 4-6), and grade 3 (total score 7-9) (Table 1).

Demographic and clinical variables were gathered including maternal age, BMI, infertility duration, number of transferred fetuses, grade of transferred fetuses, the type of ovulation stimulation (agonist or antagonist), FSH level, and ET. Primary outcome was clinical pregnancy rate. Secondary outcome was miscarriage rate. Cause of infertility was classified into male factors or other factors including PCOS, tubal factor, endometriosis-related infertility, and unexplained infertility. The flow chart of the allocation of patients into intervention groups is presented in Figure 1.
Statistical analyses was conducted using SPSS version 22 (Statistical Package for the Social Sciences, version 22, SPSS Inc., Chicago, Illinois, USA). Quantitative variables were summarized with mean ± SD and categorical and nominal variables were presented with frequency (percentage). One-way ANOVA test was used for finding any significant difference between mean of quantitative parameters and chi square test was utilized to compare between qualitative parameters. P value less than 0.05 was considered statistically significant.

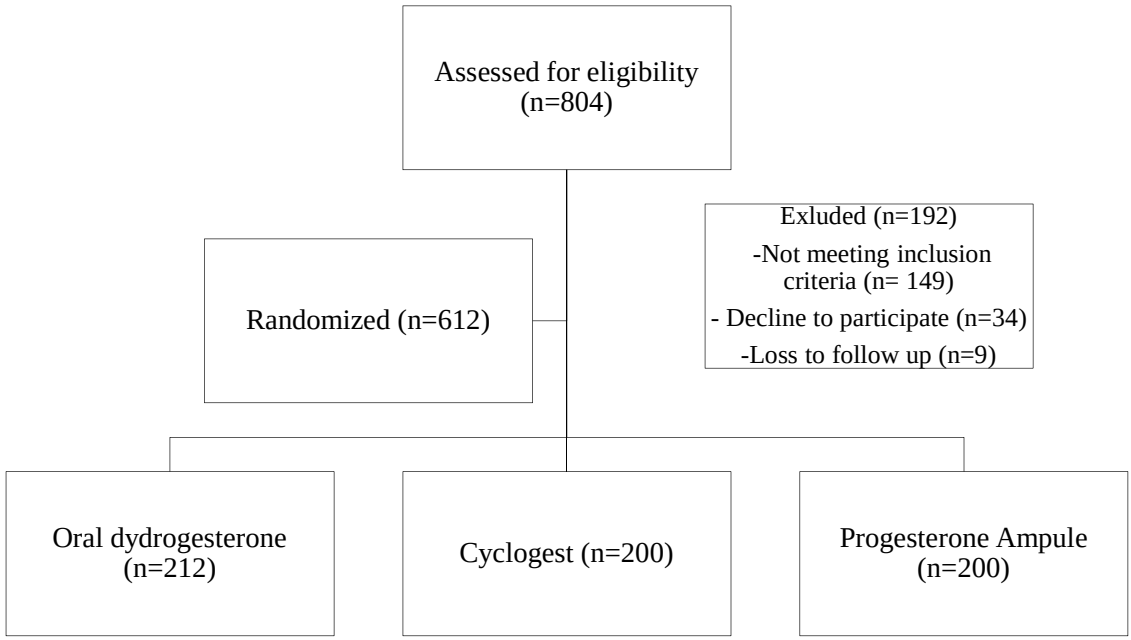


Figure 1. The flow chart of the allocation of patients into the intervention groups

RESULTS

We studied 612 patients who were divided into three groups of oral dydrogesterone, cyclogest, and progesterone ampule. There were 212 patients in dydrogesterone group, 200 patients in cyclogest group, and 200 patients in progesterone ampule group.

Nine influential factors were assessed for matching subjects in three groups (Table 1). The favorable factors received a score of zero and unfavorable factor received a score of one (score= 1). Patients were divided into four grades according to calculated total score. The frequency distribution based on this grading system is depicted in Figure 2.

Demographic and clinical parameters are summarized in Table 2. Of all subjects, 45 (92.5%) of dydrogesterone group, 42 (79.2%) of cyclogest group and 49 (92.5%0 of ampule group had age ≤ 37 years old. In total, the mean age of women in dydrogesterone group was significantly higher that two other groups (P< 0.0001). Moreover, 24 (45.3%) patients of oral dydrogesterone group, 18 (34%) patients of cyclogest group and 19 (35.8%) of ampule group had BMI ≤ 25 kg/m^2 which had not statistically significant difference (P= 0.4). In addition, FSH level did not

differ significantly. The mean ET was higher in oral dydrogesterone and ampule groups in compare to cyclogest group. However, this difference was not significant (P= 0.7).

The characteristics of transferred fetuses and study outcomes are presented in Table 3. The most proportion of patients in dydrogesterone, cyclogest and ampule groups had infertility duration equal or less than 3 years, 88.7%, 86.8% and 81.1%, respectively. Seven patients (13.2%) of dydrogesterone group, 26 (41.1%) cases of cyclogest group and 3 (5.7%) patients of ampule group had transferred fetuses with grade A. While in other cases the fetus grade was B or grade C or a combination of B and C. The average number of transferred embryos in all three groups was 2 to 3 embryos. In 25 (47.2%) patients in the dydrogesterone group, in 18 (34%) patients in the first group and 28 (52.8%) subjects in ampule group were treated with agonist cycle.

Finally, the pregnancy rate was observed in 53 patients (25%) of 212 in the dydrogesterone group, in 53 cases (26.5%) of 200 patients in the cyclogest group, and 53 patients (26.5%) of 200 in the ampule group. This rates had not statistically significant difference (P= 0.3). Moreover, the miscarriage was occurred in 3 patients (5.6%) of 53 in the dydrogesterone group, in 2 cases (3.8%) of 53 patients in the cyclogest group, and 2 patients (3.8%) of 53 in the ampule group. This rates had not statistically significant difference (P= 0.6).

Table 1. Scoring system for favorable and unfavorable IVF outcome

Factor	Favorable (score=0)	Unfavorable (score= 1)
Age (y)	≤37	>37
BMI (kg/m^2)	≤25	>25
Baseline FSH (mlU/mL)	≤9	>9
Cycle type	Agonist	Antagonist
Grade of embryo	A	Other than A
Infertility duration (yr)	≤3	>3
Cause of infertility	Male factor	Other factors
Number of transferred	≤2	>2
ET	≤9	>9
Total score	0	9

Note: Grading: grade 0 (total score 0), highly favorable; grade 1 (total score 1-3), favorable; grade II (total score 4-6), unfavorable; Grade III (total score 7-9), highly unfavorable.

Table 2. Baseline patients characteristics

Characteristics		Oral dydrogesterone	Cyclogest	Progesterone ampule	P value
Mean Age, years		30.02 ± 5.02	31.92 ± 4.82	28.04 ± 5.04	<0.0001
Age group, years	<=37	45 (92.5)	42 (79.2)	49 (92.5)	0.053
	>37	4 (7.5)	11 (20.8)	4 (7.5)	
BMI, kg/m^2	<=25	24 (45.3%)	18 (34%)	19 (35.8%)	0.4
	>25	29 (54.7%)	35 (66%)	34 (64.2%)	
FSH (IU/L)		6 ± 1.6	5.7 ± 1.8	6.04 ± 1.8	0.5
ET (mm)		8.57 ± 0.5	8.64 ± 0.48	8.60 ± 0.49	0.7

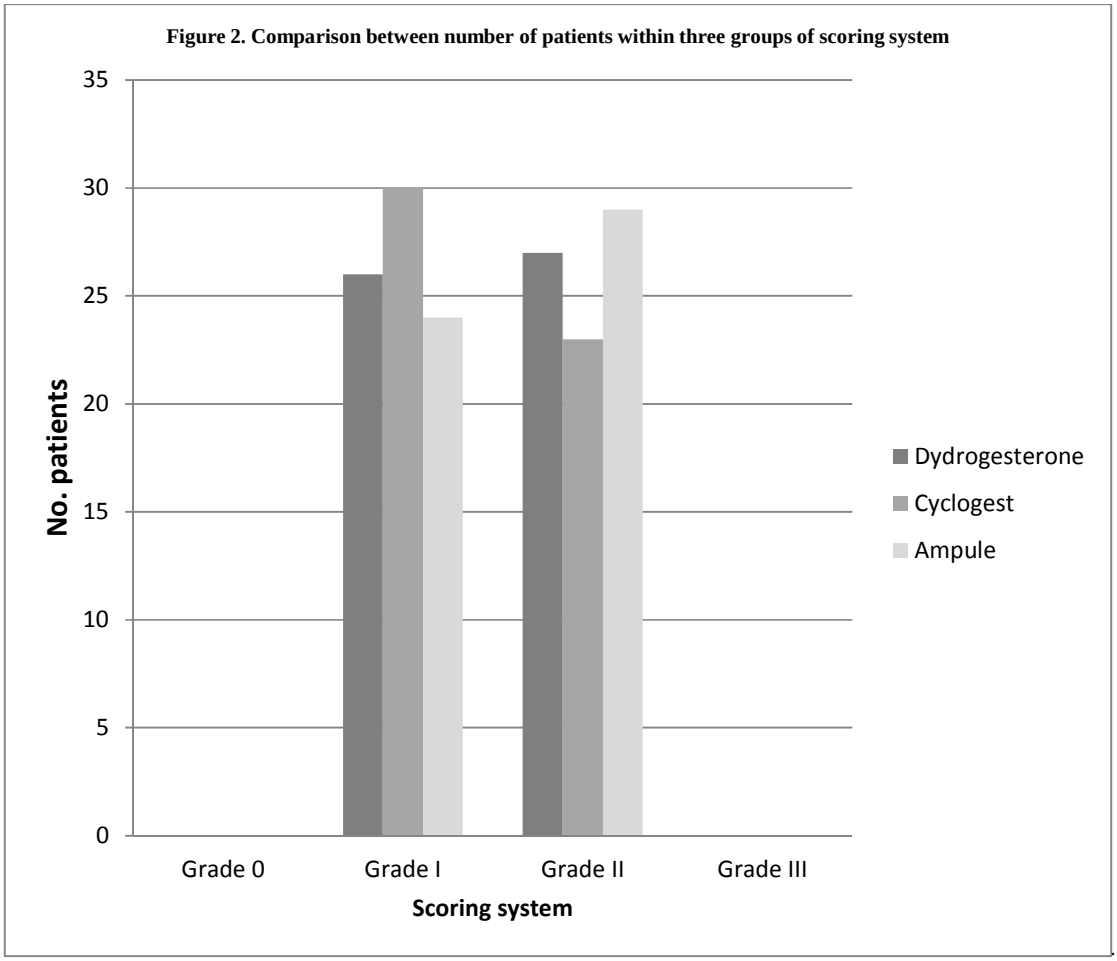
BMI: Body mass index
FSH: Follicle stimulating hormone
ET: Endometrial thickness
One way ANOVA, Chi square test

Table 3. Characteristics, clinical outcomes in three groups

Characteristics		Oral dydrogesterone	Cyclogest	Progesterone ampule	P value
Infertility cause	Male factors	15 (28.3%)	-	19 (35.8%)	<0.001
	Others	38 (71.7%)	53 (100%)	34 (64.2%)	
Infertility duration	<=3	47 (88.7%)	46 (86.8%)	43 (81.1%)	0.5
	>3	6 (11.3%)	7 (13.2%)	10 (18.9%)	
Grade of embryo	A	7 (13.2%)	26 (41.1%)	3 (5.7%)	<0.001
	B, C	46 (86.8%)	27 (50.9%)	50 (94.3%)	
Number of transferred embryos	1	5 (9.4%)	11 (20.8%)	8 (15.1%)	
	2	25 (47.2%)	22 (41.5%)	27 (50.9%)	0.4
	3	22 (41.5%)	18 (34%)	17 (32.1%)	
	4	1 (1.9%)	2 (3.8%)	1 (1.9%)	
Cycle type	Agonist	25 (47.2%)	18 (34%)	28 (52.8%)	0.1
	Antagonist	28 (52.8%)	35 (66%)	25 (47.2%)	
Scoring system	Grade 0	-	-	-	
	Grade I	26 (49.1%)	30 (56.6%)	24 (45.3%)	0.2
	Grade II	27 (50.9%)	23 (43.4%)	29 (54.7%)	
	Grade III	-	-	-	
Clinical outcomes	Pregnant	53/212 (25%)	53/200 (26.5%)	53/200 (26.5%)	0.3
	Miscarriage	3/53 (5.6%)	2/53 (3.8%)	2/53 (3.8%)	0.6

One way ANOVA, Chi square test
Scoring system adopted for favorable and unfavorable IVF outcome

Figure 2. Comparison between number of patients within three groups of scoring system



DISCUSSION

Recent years have witnessed a substantial progress in the treatment of infertility and assisted reproductive techniques. The ultimate goal of these therapies is to achieve pregnancy and a healthy baby. Luteal phase support is one of the factors affecting the probability of pregnancy (9). Historically, luteal phase support in assisted pregnancy techniques is an important issue among researchers (17). Recently, progesterone supplementation has achieved improved results during ART cycles (17, 18). Dydrogesterone is a retro-progesterone with a good oral bioavailability which is an active biological metabolite of progesterone (9, 19). On the other hand, some studies have shown that dydrogesterone with systemic effects on immunological factors may improve the implant and reduce the abortion rate (9).

In this study, the benefits of taking dydrogesterone in compare to other forms of progesterone including cyclogest and ampule were assessed for luteal phase support in ART cycles in terms of clinical pregnancy and miscarriage rate. In present study, patients who achieved pregnancy were compared in terms of age, BMI, infertility duration, cause of infertility, ET length, FSH level, number of transferred embryos, quality of transferred embryos and type of ovulation stimulation, then favorable factors received zero and unfavorable factors received 1, then each patients assigned into one of four grades according to total scores. Most of patients were in grades 2 and 3, on the other words patient were similar. Our findings showed that there was no superiority between different forms of progesterone in terms of pregnancy rate and miscarriage rate.

Levine et al. have shown that pharmacokinetics micronized progesterone has less serum progesterone concentrations compared with progesterone vaginal gel. They concluded that progesterone vaginal gel provides higher bioavailability compared to oral dydrogesterone (20). On the other hand, some studies have shown that there is not a significant improvement in pregnancy rates in cycles with luteal phase support in compare to IUI cycles without luteal phase support (21, 22).

In line with the results of the current study, the study by Salehpour et al. has been shown that pregnancy rate in IVF cycles with progesterone suppository for luteal phase support (32.5%) without significant difference was higher than pregnancy rate with oral dydrogesterone for luteal phase support, in addition, the abortion rate was similar between both groups (15). In addition, Chakravarty et al. have reported that there are no significant differences in pregnancy rates, abortion rates and live birth rates between the two groups of dydrogesterone and vaginal progesterone (23). In addition to this the study by Ganesh et al. supports our findings. In a clinical trial, they compared three forms of progesterone including oral dydrogesterone, progesterone gel and micronized progesterone for luteal phase support and have shown there are no significant difference among three groups in terms of pregnancy rates and miscarriage rates (11). In this regard, previous similar studies support our findings on the impact of dydrogesterone and natural micronized progesterone in women undergoing IVF (24, 25). The current study was the first to assess progesterone ampule with the forms of oral dydrogesterone and vaginal progesterone (cyclogest). Our findings demonstrated that the effects of these three forms are comparable. We did not observe any side effects which was associated with three forms of progesterone. Khosravi et al. reported higher satisfaction rate with oral dydrogesterone in compare to cyclogest (9). In another study, Chakravarty et al. observed that satisfaction, efficacy and safety of dydrogesterone are better than cyclogest (23).

Finally, the results of the previous similar studies have shown potential benefits for dydrogesterone and this drug can be alternative option instead of vaginal progesterone suppository for luteal phase support. Our findings also showed that the efficacy of oral dydrogesterone is comparable with vaginal progesterone and progesterone ampule for luteal phase support in ART cycles in terms of pregnancy rate and miscarriage rate.

Acknowledgments
This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.AC.1394.417) and was registered in Iranian clinical trials registry (IRCT2016010825902N1).

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