Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

Pharmacophore
an International Journal
ISSN 2229-5402

EFFECT OF ORAL DYDROGESTERONE COMPARED WITH PROGESTERONE SUPPOSITORY FOR LUTEAL PHASE SUPPORT IN CYCLES OF FROZEN EMBRYO TRANSFER

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ARTICLE INFO

Received:
03th Jun 2017
Accepted:
29th Nov 2017
Available online:
14th Dec 2017

Keywords: *LPS, Dydrogesterone, IVF..*

ABSTRACT

Background:Dydrogesterone is an analog of oral progesterone, which can reduce the side effects of vaginal progesterone and has advantages such as greater tolerance to luteal phase support (LPS). In this connection the limited studies available and needs more study. the aim of this study was to evaluate the protective effect of this drug on LPS after frozen embryo transfer in IVF cycle.
Methods:In this trial, 200 women with infertility and IVF candidate again, divided in two equal one hundred groups that include: consumers of progesterone (intravaginal, 800 mg daily) and oral Dydrogesterone (20 mg daily) for luteal phase support groups. The frozen embryos from IVF are transferred to the uterus and implantation rate, clinical pregnancy (CPR), ongoing pregnancy (OPR) and abortion were compared.
Results:Respectively,the mean age of patients in intravaginal and Dydrogesterone was 5.2 ± 33.5 and 5.1 ± 32.9 years (p = 0.2) and the mean duration of infertility was 2.8 ± 5.6 and 2.5 ± 6 years (p = 0.7). Implantation rate was 8.9% and 7.3% (p = 0.6), average CPR was (20 patients) and 20% (n = 18) 18% (p = 0.04). Average OPR after 3 months of embryo transfer was 18% (n = 18) and 9% (n = 9) (p = 0.09). Among pregnant women after three months of pregnancy the rate of aborton was 18.1 and 37.7% (4 nd5 patients) (p = 0.4), respectively, in the intravaginal and Dydrogesterone groups.
Conclusions:In this small study the intravaginal regimen compared to Dydrogesterone was associated with higher CRP significantly and implantation, OPR and abortion rate, had not significant difference between two groups. The intravaginal progesterone against orally Dydrogesterone for LPS after IVF may be the superior choice.

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To Cite This Article: Afsoon Zareii, Asieh Naseri rad, Zahra Shomali[1] ,Elham Askari* , (2017), "Effect of Oral Dydrogesterone Compared with Progesterone Suppository for Luteal Phase Support in Cycles of Frozen Embryo Transfer", ***Pharmacophore, 8(6S),*** *e-1173631.*

Introduction

Currently, the frozen embryo transfer (FET) in IVF is an important part of assisted reproductive techniques (ART), as it is associated with better health of embryo and successful IVF (1,2). Moreover, compared with fresh embryo transfer, it reduces pregnancy complications, such as preterm delivery, and low birth weight (3). Still, finding ways to increase FET success is being investigated. A variety of reasons are raised for IVF failure. Reports indicate an important role in the success of endometrial implantation and live infant's birth, so that it seems that artificial endometrial preparation during FET is an inseparable process in freeze cycles of IVF. Moreover, endometrial thickness may also affect IVF success, although results are contradictory (4,5).

There are various methods for endometrial preparation before embryo transfer, including embryo transfer during natural cycle without hormonal intervention, transfer in synthetic hormonal cycles with exogenous estrogen and progesterone with

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and without GnRh prescribed before embryo implantation, and transfer in ovulation induction cycles, but the debate continues about the preferred method (6).

Patients undergoing FET and endometrial preparation with exogenous estrogen lack progesterone, due to no corpus luteum formation following inhibitory effect of estrogen, as the secretion source of estrogen is the corpus luteum. Therefore, it seems that despite progesterone deficiency in these patients, the endometrium is not completely developed, and does not have sufficient and ideal stability. This affects embryo transfer and is associated with embryo transfer failure (7). So, adding exogenous progesterone regimens has a major impact on successful embryo implantation that is called protecting and supporting the luteal phase. Earlier, studies have emphasized the necessity of administering exogenous progesterone to improve IVF success by freezing and more live births that have reported significant results in this regard (8-10).

In many ART centers, using vaginal progesterone is routine. Vaginal progesterone has direct effects on the endometrium and its high concentration in this region is more considered, compared with the oral and injection forms. However, disadvantages include frequent daily use, adverse effects such as vaginal irritation and secretion, and restrictions in case of vaginal bleeding (11). Thus, using other types regarding its effectiveness is an important issue.

Dydrogesterone is an isomer of progesterone and is pharmacologically and structurally similar to endogenous progesterone. Its formulation leads to suitable oral stability and bioavailability, and no side effects have been reported for mother and fetus, and its ORR after IVF is 31% (12,13).

Due to the advantages of oral dydrogesterone versus vaginal progesterone, few studies have assessed its effectiveness after IVF and the results are conflicting. Patki and colleagues, reported significantly higher pregnancy rates with dydrogesterone than vaginal progesterone (14).

In the study by Guo and colleagues, there was no difference in the outcome of this drug with injected progesterone following FET (15). Salehipour and colleagues found no difference in pregnancy rates between injectable and oral progesterone (16).

The aim of the present randomized clinical trial was to compare the supportive effect of vaginal progesterone and oral dydrogesterone for luteal phase. The results of this study provide useful information about the effects of dydrogesterone on IVF outcome by FET.

Materials And Methods

The present study was a single-blinded randomized clinical trial. The study population included infertile women admitted to the Mother and Child Hospital who were candidates of IVF with embryo freezing after initial assessment between March 2014 to March 2015.

According to a similar study (15), the success rate of pregnancy was considered 30% and abortion rate of 14% in women consuming dydrogesterone and a sample size of 100 women in each group was calculated, considering α=0.05, β=0.02, and $Z_{1-\frac{\alpha}{2}} = 1.96$.

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})\,(p_1 q_1 + p_2 q_2)}{d^2} \qquad P_1 = 0.30 \qquad p_2 = 0.14$$

Sampling was performed by general census method, so that patients who were candidate of frozen embryo were randomly divided into two groups receiving dydrogesterone or cyclogest, after considering the inclusion and exclusion criteria. The study was approved by the local ethic committee of Shiraz University of Medical Sciences. Since the retrospective nature of the study and lack of research purposes during management of patients, no informed consent was obtained from the patients.

- **Inclusion criteria:** patients with unexplained infertility, infertility due to tubal factor, mild male factor, premature ovarian failure, infertility due to the polycystic ovary, ages 18 to 40 years, normal uterine cavity, and at least one month after previous IVF.

- **Exclusion criteria:** endometriosis stage III and IV, Hydrosalpynx, infertility due to severe male factor, poor uterine cavity, and those with at least 3 unsuccessful embryo transfer cycles.

The patients underwent IVF cycle based on the patient's condition with agonist or antagonist protocol and IVF with ICSI or both were performed in the process of taking ovum from ovaries. About 16 to 19 hours after fertilization, they were assessed to confirm the presence of egg with male and female pronucleus (PN2) and were excluded in absence of microscopic evaluation.

Then, the eggs were classified in terms of quality, so that on the third day of conception (66 to 68 hours) after ICSI or IVF, blastomers≥8 and fragmentation <20% in the embryo group with excellent quality were placed in A and embryos of lower quality were placed in the groups B, C, and D and were isolated from one another.

The 8-cell stage embryos (Cleavage) were frozen by vitrification and stored according to standard protocol.

Patients in their next menstrual cycles with no intervention for at least one month who referred for endometrial preparation for IVF, received 6 mg oral estradiol daily since the second day of menstrual cycle, and the dose of estradiol increased

based on the response rate, until the endometrial thickness reached 8 to 14 mm in the follow-up ultrasonography. Then, 100 mg progesterone daily was administered (for 3 days).
On the day of embryo transfer, fetuses were evaluated after melting in terms of quality, but decision to transfer Top embryos during freezing, rather than transit. Embryos were transferred to the uterus using 20 ml cook catheter. The number of embryo transfer according to maternal age included:

1. Younger than 35 years: 2 fetus class A
2. Age group 35 to 40 years: 3 fetus class A

Patients were divided by odds and even scores from 1 to 200 into two groups of 100, so the odd numbers were placed in vaginal progesterone group and even numbers in oral dydrogesterone.
Drug regimen intervention in both study groups included the following:
1. Vaginal progesterone group: 400 mg intravaginal suppositories twice daily.
2. Oral dydrogesterone group: 10 mg oral dydrogesterone once daily.
The study was single-blind and patients did not know the effects of these drugs. Use of estradiol continued based on the last effective dose for each patient to maintain endometrial thickness.
20 days after embryo transfer, BHCG blood tests was performed for patients. And if positive, transvaginal ultrasound was performed after 6 weeks to detect fetal heart rate and confirm live pregnancy. Transvaginal ultrasound was repeated in week 12 of embryo transfer to detect ongoing pregnancy. The luteal phase support continued according to the protocol until 12 weeks after embryo transfer. Variables in this study included implantation, abortion rates, clinical pregnancy rate (CPR) and ongoing pregnancy rate (OPR) in two groups.
After gaining approval of the Ethics Committee of the University, patients signed written informed consent before entering the study, in accordance with the form approved by the University for Clinical Trials and then, they were enrolled into the study.
Descriptive data are presented as mean (± SD) and relative frequency. The data was analyzed by chi square or Mann-Whitney tests. Data was analyzed by SPSS18 software and the results were significant at $P<0.05$.

Results

200 infertile women who referred for IVF with frozen embryo transfer were divided into two groups of 100 receiving oral dydrogesterone and intravaginal cyclogest, and were compared for pregnancy outcome following IVF. Table 1 shows the baseline characteristics of patients.

Table 1: Baseline characteristics of patients.

		Cyclogest	Dydrogesterone	P-value
Age, years		33.5 ± 5.2	32.9 ± 5.1	0.2
During of infertility, years		5.6 ± 2.75	6 ± 2.5	0.7
The cause of infertility (%)	Tubal factor	10 (10%)	15 (15%)	0.5
	Endometriosis	20 (20%)	13 (13%)	0.6
	Male factor	20 (20%)	28 (28%)	0.3
	Unexplained	22 (22%)	14 (14%)	0.1
	POF	8 (8%)	13 (13%)	0.6
	PCO	20 (20%)	17 (17%)	0.3
Endometrial thickness (mm)		8.37±0.48	8.44±0.6	0.8

Implantation and pregnancy

In the follow-up of patients after 20 days, the level of BHCG and vaginal ultrasound after 6 weeks was significantly greater in terms of pregnancy sac, fetal heart rate, and pregnancy rate in cyclogest group than dydrogesterone groups. The implantation rate was not significantly different between the two groups.
After 12 weeks, ultrasound was repeated to evaluate the ongoing pregnancy. In this regard, the two groups had no significant difference. Patients in the first 20 weeks of pregnancy were followed for abortion. In this regard, the two groups had no significant difference.

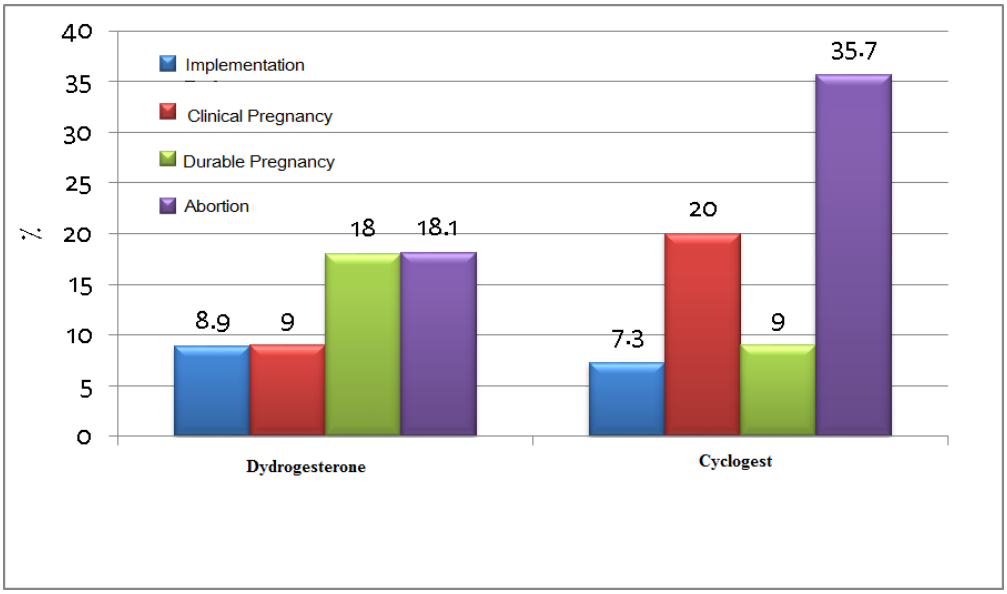

Figure 1: Implantation rate, clinical and ongoing pregnancy rate, and abortion in patients

Discussion and conclusion

The aim of the present clinical trial study was to compare vaginal cyclogest and oral dydrogesterone in luteal phase support after frozen embryo transfer in IVF cycles. The results showed that cyclogest significantly increased clinical pregnancy more than 2.2 times, compared to dydrogesterone. The two groups showed no significant difference in terms of abortion and OPR.

Luteal phase support has an important role for IVF outcome. The use of exogenous progesterone is an inseparable part of luteal phase support after IVF since it is associated with increased pregnancy and live birth (17,18). In addition, vaginal progesterone is preferred for luteal phase support by gynecologists and is now the drug of choice in this regard (19). The administration method and type of the administered exogenous progesterone, considering local and systemic side effects, ease of use, and higher patient tolerance are challenging. Vaginal and muscular progesterone administration are two common forms for luteal phase support. Vaginal administration might be associated with vaginal irritation, and discharge and the muscular form is painful and may cause infections, such as cellulitis and abscesses that can reduce patient's tolerance. According to systematic reviews, CPR and OPR were not significantly different between vaginal and muscular forms and vaginal form was more tolerable than the muscular form (20, 21). In this regard, few studies have been conducted on oral administration of progesterone and the results are contradictory.

Previously, the use of oral progesterone analogues for luteal phase support, including utrogestan and micronized progesterone, have yielded in poor results, associated with doubtable effectiveness of the oral form. In one study, oral utrogestan and vaginal progesterone were not different in terms of biochemical pregnancy, clinical and live births, however, confusion occurred in about 60% of pregnant women within a one-month follow-up. Moreover, vaginal gel (Crinon 8%) more than 90 mg daily versus 100 mg utrogestan 3 times a day reduced its advantage (22).

In a study evaluating the protective effect of micronized progesterone (600 mg daily) with intramuscular progesterone (50 mg daily), poor results were found for the oral form. In their study, 28 days after administration, serum levels of the oral form gradually decreased compared with the muscular form and was associated with less clinical pregnancy rate (45.8% vs. 57.9%) and less implantation success rate per embryo (18.1% vs. 40.9%) (23).

However, dydrogesterone, another analog of oral progesterone, showed promising results for luteal phase support (14). Dydrogesterone, compared to cyclogest, needs a lower dose for luteal phase support and high affinity to progesterone receptor, its oral form is active and will not break down in the digestive tract, and has high tolerability for the patient. Also, more than 10 million pregnant women consumed dydrogesterone during 1977 and 2005 and, according to the reports, the drug seems safe for the mother and fetus (12-14).

In the study by Ganesh and colleagues, in 2007, that compared 20 mg oral dydrogesterone to placebo in the first phase of trials, fertility rate was 33 to 42.9% versus 15.6 to 28.1%, respectively. In the second phase, 30 mg dydrogesterone, compared to 600 mg vaginal micronized progesterone had 39.1% and 26.7% clinical pregnancy rate. However, further studies are needed in this regard (13).

In the study by Patki and colleagues, in 2007 in India, dydrogesterone, vaginal progesterone gel, and micronized progesterone in cases with high probability of clinical and laboratory IVF had fertility rates of 31.5, 34.1, and 28.9% and in

low probability were 26.5, 28.6, and 15.9%, respectively. Their results suggested higher fertility rate and better luteal phase support for dydrogesterone (14).

In the study by Tomic and colleagues, in 2015, women underwent IVF/ICSI and received vaginal progesterone gel (Crinon 8%) (90 mg daily) or dydrogesterone (20 mg twice a day) and the fertility rate was 30.3% and 28.1%, respectively, with no significant difference (17).

In the study by Chakravarty and colleagues, in 2005, which compared 20 mg daily dydrogesterone and 600 mg daily micronized vaginal progesterone, live births were 24.1, and 22.8%, respectively, and the abortion rate was 7.6, and 8.3%, with no significant difference between the two groups (25).

In an Iranian study by Salehpour and colleagues in 2013, there was no difference in terms of fertility, abortion, number of antral follicles, duration of luteal phase, and number of the oocytes in metaphase 2 in the published abstract (16). The reasons for the difference between our findings and lower fertility rates with above-mentioned studies can be the dydrogesterone dose, since 30 mg dose was used for luteal phase support, compared to 20 mg (14). In the study by Salehpour and colleagues, 40 mg daily dydrogesterone was used, although other studies, like ours, used dose of 20 mg daily. We did not measure serum levels of progesterone during treatment, therefore, dydrogesterone may not have provided appropriate blood levels in early pregnancy. Accordingly, significantly lower ongoing pregnancy rates in dydrogesterone group and no significant difference in clinical pregnancy between the two groups could support such a view.

In our results, similar to the above-mentioned studies, the two groups did not differ regarding OPR and abortion rate (13, 16, 17, 26). In other words, dydrogesterone was able to maintain the pregnancy in pregnant women, like cyclogest. Previously, dydrogesterone has shown an effective role in reducing abortions, stillbirths and increased live births in supportive therapies without adverse effects and complications of pregnancy, increasing spotting, and significant bleeding, and was well tolerated (50-27). Accordingly, dydrogesterone can potentially support the pregnancy product, endometrium, and endometrial interaction with the placenta and fetus. FET from original parents or other donors have some degrees of alienation than mother's surface cell due to differences in the genome of the fetus with the mother, that can cause hypersensitivity reaction and reject the implanted embryos after IVF. It seems. Dydrogesterone has a protective effect in this regard. One study reported the preventing effect of this drug on the incidence of preterm birth that led to increased anti-inflammatory interleukin-10 (IL-10) (28). In other words, it has immunity regulating role.

Limitations of our study were not matching the patients, not measuring serum level of progesterone during the study, no follow-up till the birth of the pregnancy product in fertilized women and failure to assess the adverse effects of dydrogesterone and cyclogest; future studies can reduce these limitations.

In conclusion, the findings of our study showed that a daily intake of 800 mg cyclogest, compared with 20 mg dydrogesterone, following FET by freezing, was associated with increased clinical pregnancy rate, but the ongoing pregnancy and abortion rates did not differ.

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