A comparative study of dydrogesterone and micronized progesterone for luteal phase support during in vitro fertilization (IVF) cycles

Nasrin Saharkhiz, Marzieh Zamaniyan
Preventive Gynecology Research Center (PGRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran.
marziehzamaniyan@gmail.com
**Introduction**

- **Luteal phase defect (LPD)** is defined as a disorder in which endogenous progesterone is not enough to preserve a functional endometrium and subsequently the embryo implantation.

- **Dydrogesterone** is **synthetic progesterone** available as a retro progesterone.

- Several studies have demonstrated that this preparation is safe and does not have androgenic effects compared with previous preparations because of its **different structure**. One study has reported that the dydrogesterone does not virilize even when used in a high dose.
Some authors have compared dydrogesterone with vaginal micronized progesterone and concluded that dydrogesterone has better compliance and tolerability with fewer side effects compared with micronized progesterone.

A few studies have reported significantly better clinical outcomes with dydrogesterone compared with micronized progesterone.

Other studies have reported the benefit of dydrogesterone in prevention of recurrent pregnancy loss (RPL) and preterm delivery and threatened abortion.
In contrast, some authors have reported that the use of dydrogesterone as luteal support fails to demonstrate secretory transformation of the endometrium and induces higher progesterone and lower LH and FSH concentrations on day 21 of the cycle among donor oocyte recipients.

Therefore, the use of dydrogesterone in LPS is still doubtful. Hence, due to the ease of use, better patient compliance and satisfaction, and negligible use of dydrogesterone in assisted reproductive technology (ART), we decided upon further examine this drug in the infertility field.
In a study reported previously, we compared the effectiveness of oral dydrogesterone 20 mg twice a day for LPS in 80 patients undergoing IVF cycles with vaginal micronized progesterone 400 mg twice daily, and found the outcomes to be promising with oral dydrogesterone.

This study was initiated using dydrogesterone 20 mg once a day like previous published studies; however, due to more vaginal bleeding in dydrogesterone group and no evidence regarding androgenic side effects of this drug during pregnancy; the dosage was increased to 20 mg twice daily.
In most previous studies, dydrogesterone 20 mg daily has been used, and only two studies have examined 30 and 40 mg daily doses of dydrogesterone.

We thought it possible that prior comparable or undesirable results by dydrogesterone might be related to lower dosage and may be improved by increasing the dosage.

This further encouraged us to increase the sample size to verify our former results. The main objective of the present study was to compare the efficacy, tolerability and patients’ satisfaction of oral dydrogesterone (40 mg daily) with vaginal micronized progesterone in LPS among infertile women undergoing IVF.
Methods

prospective randomized clinical trial

between April 2014 and January 2015

in two tertiary infertility care units (Taleghani and Mahdieh hospitals, Tehran, Iran).

This study was approved by ethics committee and the institutional review board of Shahid Beheshti University of Medical Science. Treatment options were discussed with all patients who enrolled in the study and written informed consent was obtained from all participants.
A total of **210 patients** met our criteria and were recruited for the study. Women *(aged 20–40 years)* with

- body mass index *(BMI)* < 30 kg/m² or > 18 kg/m², who were

- undergoing *fresh* intracytoplasmic sperm injection-embryo transfer *(ICSI-ET)* cycles, and had **normal endometrial thickening** *(7–12 mm)* on the day of oocyte retrieval and

- no visible endometrial pathology were included in the study.
Treatment

All women received mid follicular long-protocol GnRH-agonist down-regulation or GnRH-antagonist protocol based on patients’ characteristics (age, AMH, prior failed attempts).

In both protocols, 10 000 IU human chorionic gonadotropin (hCG) (5000 IU, Choriomon; IBSA; Lugano) was administered IM when at least two or more follicles reached 17 mm in diameter.

Oocytes were recovered under trans-vaginal ultrasound guidance 34–36 h after hCG injection.

After egg collection, conventional ICSI was performed.

An average of two or three good-quality embryo in cleavage stage (at the 4–8 cell stage) was transferred 72 h after insemination.

Luteal-phase support began from the day of oocyte retrieval.
Randomization on the day of oocyte retrieval was based on a random-number table.

Patients were randomly selected to receive either intravaginal micronized progesterone (Cyclogest; Actavis; Barnstaple, UK) 400 mg bid (control group) \( n = 114 \) or oral dydrogesterone (Duphaston, Abbot Biological B.V., Olst, the Netherlands) 20 mg twice a day (intervention group) \( n = 96 \).

Pregnancy was determined using blood b-hCG testing 14 days after the embryo transfer (ET).

Progesterone concentrations were measured at the same time using radioimmunoassay.

If the B-hCG test was positive, then LPS was continued up to 12 weeks of gestation. We did not measure the liver function tests (LFT) in our patients because of no previous reported side effects for these drugs.
Possible complications associated with both drugs were documented.

Patients’ satisfaction was also evaluated using a questionnaire. Satisfaction was objectively evaluated among the patients.

Clinical pregnancy was defined as confirmation of a gestational sac by ultrasonography at 4–5 weeks after embryo transfer (ET).

Chemical pregnancy was defined as a pregnancy confirmed by a pregnancy test but not by ultrasonography 4–5 weeks later. Miscarriage was defined as the spontaneous loss of a fetus before the 20th week of pregnancy.

Ongoing pregnancy was defined as the presence of at least one viable fetus at 12th weeks of pregnancy.
**Statistical analysis**

The data analysis was performed using **SPSS for windows, version 21.0** (IBM Corp., Armonk, NY).

**t-test** was used to compare the clinical outcomes between the two groups.

The proportions were compared using **chi-squared test**.

The data were reported as **mean ± SD** and **p < 0.05** were considered as statistically significant.
Results

A total of 240 women were recruited into the study; 30 women were excluded from the study due to various causes, including

withdrawal of consent,

ovarian hyper stimulation syndrome (OHSS),

no fertilization,

discontinued treatment or loss to follow up, which is summarized in Figure 1.
Figure 1. Flow chart of the eligible patients.

Enrollment

Evaluation of eligibility (n=240)

Not included:
Not included:
Did not consent (n=4)
Did not consent (n=4)
Declined to participate (n=2)
Declined to participate (n=2)

Randomly allocated
Allocate to dydrogesterone
group (n=117)

Lost to follow-up (n=6)
Discontinued (n=5)
Withdraw the consent (n=6)
OHSS (n=2)
No fertilization (n=2)

Allocated to control group
(n=117)

Lost to follow-up (n=1)
Discontinued (n=1)
OHSS (n=0)
No fertilization (n=1)

Follow up

Analysis

Allocated to dydrogesterone

group (n=117)

Allocated to control group

(n=117)

Analyz (n=96)

Analysis

(n=114)
The mean age (± standard deviation (SD)) of the women within the dydrogesterone group and the control group was (30.58 ± 5.35) years and (30.95 ± 5.19) years, respectively (p = 0.6).
Table 1. Demographic characteristic of patients in two groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oral hydrogesterone group (N = 96)</th>
<th>Micronized progesterone group (N = 114)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>30.58 ± 5.35</td>
<td>30.95 ± 5.19</td>
<td>0.621</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.99 ± 3.49</td>
<td>26.19 ± 3.84</td>
<td>0.709</td>
</tr>
<tr>
<td>AFC</td>
<td>11.87 ± 5.97</td>
<td>11.77 ± 6.82</td>
<td>0.912</td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>4.15 ± 3.32</td>
<td>3.78 ± 26</td>
<td>0.494</td>
</tr>
<tr>
<td>Day 3 FSH (mIU/ml)</td>
<td>6.07 ± 2.52</td>
<td>6.19 ± 3.86</td>
<td>0.843</td>
</tr>
<tr>
<td>Day 3 LH (mIU/ml)</td>
<td>5.53 ± 3.38</td>
<td>5.70 ± 3.73</td>
<td>0.740</td>
</tr>
<tr>
<td>Infertility duration (years)</td>
<td>4.96 ± 3.93</td>
<td>6.06 ± 4.21</td>
<td>0.060</td>
</tr>
<tr>
<td>Infertility kind</td>
<td></td>
<td></td>
<td>0.867</td>
</tr>
<tr>
<td>Primary</td>
<td>76%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>24%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Infertility etiology</td>
<td></td>
<td></td>
<td>0.867</td>
</tr>
<tr>
<td>Male factor</td>
<td>51%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Tubal factor</td>
<td>6%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>DOR</td>
<td>5%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Unexplained infertility</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>PCOS</td>
<td>2%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Multiple factors</td>
<td>35%</td>
<td>39%</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as percentage or mean ± SD unless otherwise indicated. AFC, antral follicle count; DOR, diminished ovarian reserve.
There were no significant differences between two groups with the respect to patients’ baseline characteristics (Table 1) and ICSI cycle characteristics (Table 2).

Whereas, Serum progesterone levels were significantly lower among the dydrogesterone group than the control group

(13.62 ± 13.83 ng/ml versus 20.66 ± 18.09 ng/ml; p = 0.002).
Table 2. ICSI cycle characteristics in two groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oral hydrogesterone group (N = 96)</th>
<th>Micronized progesterone group (N = 114)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial thickness on HCG day</td>
<td>7.69 ± 1.46</td>
<td>8.25 ± 4.52</td>
<td>0.304</td>
</tr>
<tr>
<td>No of follicles ≥14 on HCG day</td>
<td>8.29 ± 1.60</td>
<td>8.06 ± 1.6</td>
<td>0.604</td>
</tr>
<tr>
<td>Day number of stimulation</td>
<td>9.51 ± 2.06</td>
<td>9.67 ± 1.83</td>
<td>0.564</td>
</tr>
<tr>
<td>Mean no of oocyte retrieval</td>
<td>11.05 ± 5.66</td>
<td>9.68 ± 6.45</td>
<td>0.540</td>
</tr>
<tr>
<td>No of fertilized eggs</td>
<td>6.45 ± 4.17</td>
<td>5.19 ± 3.97</td>
<td>0.390</td>
</tr>
<tr>
<td>No of embryo transferred</td>
<td>2.30 ± 0.74</td>
<td>2.33 ± 0.86</td>
<td>0.793</td>
</tr>
<tr>
<td>No of mature oocytes (metaphase II)</td>
<td>8.55 ± 5.20</td>
<td>7.43 ± 5.52</td>
<td>0.142</td>
</tr>
<tr>
<td>Mean embryo quality score</td>
<td>2.42 ± 0.54</td>
<td>2.47 ± 0.53</td>
<td>0.460</td>
</tr>
<tr>
<td>Mean embryo cleavage score</td>
<td>2.18 ± 0.56</td>
<td>2.75 ± 0.60</td>
<td>0.424</td>
</tr>
<tr>
<td>The mean dose of gonadotropins used</td>
<td>28.09 ± 11.93</td>
<td>29.25 ± 11.62</td>
<td>0.487</td>
</tr>
<tr>
<td>Types of IVF protocols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agonist</td>
<td>38%</td>
<td>62%</td>
<td>0.252</td>
</tr>
<tr>
<td>Antagonist</td>
<td>62%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Mean serum progesterone levels</td>
<td>13.62 ± 13.83</td>
<td>20.66 ± 18.09</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are given as percentage or mean ± SD unless otherwise indicated.
• Oral dydrogesterone was associated with similar

• chemical pregnancy rate (4.0% versus 1.0%; \( p = 0.369 \)),
clinical pregnancy rate (31% versus 33%; \( p = 0.888 \)) and
miscarriage rate (5.0% versus 3.0%; \( p = 0.721 \)) compared
with control group (micronized vaginal progesterone)
(Table 3).

• There was not a significant difference regarding to
satisfaction rate between the two groups and similar
absolute satisfaction rates was observed between the
two groups (92.0% versus 93%; \( p = 0.825 \)).

• Results showed no statistically significant differences
considering the drugs side effects between two groups
\( (p = 0.790 \) (Table 3))
Table 3. Clinical outcomes, satisfaction and tolerability of patients in two groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Oral dydrogesterone (N = 96)</th>
<th>Micronized progesterone (N = 114)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical pregnancy rate (%)</td>
<td>4.0%</td>
<td>1.0%</td>
<td>0.369</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>31.0%</td>
<td>33.0%</td>
<td>0.888</td>
</tr>
<tr>
<td>Ongoing pregnancy rate (%)</td>
<td>30.0%</td>
<td>30.0%</td>
<td>1.000</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>22.0%</td>
<td>24.0%</td>
<td>0.254</td>
</tr>
<tr>
<td>Multiple pregnancy rate (%)</td>
<td>5.30%</td>
<td>7.20%</td>
<td>0.394</td>
</tr>
<tr>
<td>Miscarriage rate (%)</td>
<td>5.0%</td>
<td>3.0%</td>
<td>0.721</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td></td>
<td></td>
<td>0.825</td>
</tr>
<tr>
<td>Absolute satisfaction (%)</td>
<td>92.0%</td>
<td>93.0%</td>
<td></td>
</tr>
<tr>
<td>Partial satisfy (%)</td>
<td>1.0%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Absolutely dissatisfcation (%)</td>
<td>7.0%</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td>0.790</td>
</tr>
<tr>
<td>Vaginal discharge and irritability (%)</td>
<td>0.0%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Breast fullness (%)</td>
<td>5.0%</td>
<td>4.0%</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain (%)</td>
<td>8.0%</td>
<td>6.0%</td>
<td></td>
</tr>
<tr>
<td>Vaginal bleeding (%)</td>
<td>14.0%</td>
<td>13.0%</td>
<td></td>
</tr>
<tr>
<td>Constipation (%)</td>
<td>3.0%</td>
<td>2.0%</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as percentage.
Discussion

It is well known that in all of ART cycles, the progesterone levels are low and luteal function is insufficient.

Some evidence has indicated that there is a statistically significant decrease in pregnancy rates in absence of LPS in women undergoing IVF cycles.
Linden et al. conducted a Cochrane review.

They showed a significant effect in favor of progesterone for LPS, especially synthetic progesterone over micronized progesterone.

A recent review of birth defects has investigated the use of dydrogesterone during pregnancy and found no evidence of a relationship between maternal usage during pregnancy and birth defects.
• Our previous study about LPS in women undergoing IVF cycles showed no significant differences in pregnancy and miscarriage rates among women receiving oral dydrogesterone and vaginal micronized progesterone.

• Drug side effects such as vaginal bleeding, nausea and epigastric pain were significantly higher in dydrogesterone group compared with vaginal micronized progesterone group, which may be due to early pregnancy symptoms; therefore, we could not attribute it to the dydrogesterone alone.

• The present results on a slightly larger population validated our prior results.
Pregnancy and miscarriage rates were also found to be comparable between the two groups.

Our findings are supported by other authors who observed comparable effectiveness by dydrogesterone and natural micronized progesterone in patients undergoing IVF cycles.
Moreover, serum progesterone concentrations were significantly lower in the dydrogesterone group compared with control group (13.62 ± 13.83 ng/ml versus 20.66 ± 18.09 ng/ml; p = 0.001).

In line with our findings, a study on LPS in women undergoing IVF by Ganesh et al., which compared the efficacy of oral dydrogesterone with vaginal progesterone gel and micronized progesterone capsules for LPS among women undergoing IVF cycles, demonstrated that pregnancy and miscarriage rates were similar between the groups.
Another randomized clinical trial by Chakravarty et al. supports our results.

They compared oral dydrogesterone with vaginal micronized progesterone as LPS in ART cycles, and found that both drugs were associated with similar pregnancy and miscarriage rate.

These authors found no effect of dydrogesterone on the liver function tests (LFT). Nevertheless, they used lower doses of dydrogesterone compared with our dosage and did not measure the progesterone concentrations in that dose.
Patki et al. compared the dydrogesterone with vaginal micronized progesterone and placebo for LPS in ART and reported

- significant higher pregnancy rates (PR) with dydrogesterone compared with micronized progesterone and placebo in fresh IVF and donor oocyte cycles.

- They used 20 mg and subsequently 30 mg dydrogesterone once daily in two study periods and found significant higher PR when using 30 mg.
• **Tomic et al.** compared oral dydrogesterone with vaginal progesterone gel for LPS and showed that

• **ongoing pregnancy rate was similar** between two groups.

• These authors suggested that **earlier prescription of progesterone within 24 h of oocyte pick-up may result in lower pregnancy rates of vaginal progesterone gel**

• because of **premature endometrial advancement**.
We did not find a significant difference considering the satisfaction rate within the dydrogesterone group compared with vaginal micronized progesterone. Other researchers have found more tolerability of dydrogesterone when they compared both drug’s side effects.

In the present study, the tolerability of two different types of progesterone was examined by a questionnaire, including various side effects related to these supplements such as breast fullness, vaginal irritability, abdominal pain, vaginal bleeding and constipation, however; there was no significant difference between two groups regarding these side effects.
• This study was not blind for the physicians and patients that could affect the study results.

• Another concern is about the safety of dydrogesterone during pregnancy; since, only vaginal routes of progesterone such as cream and vaginal insert have been approved by the Food and Drug Administration (FDA), for LPS.
In conclusion, oral dydrogesterone even at a dose of 40 mg/day was verified to be similarly effective as the vaginal micronized progesterone in LPS of ART cycles with similar satisfaction and side effects, which should be further examined by the clinical trials with larger patient populations.