Comparable Outcomes Using Oral Dydrogesterone versus Intramuscular Progesterone in Frozen Embryo Transfer: a Retrospective Cohort Study

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Abstract

Background

Optimal intensive luteal support in frozen embryo transfer (FET) cycles in which a corpus luteum is not present has not been determined and several treatment regimens are currently practiced. Previous reports suggest that vaginal progesterone alone is probably insufficient. The use of intramuscular progesterone is considered efficacious but much less tolerable. The objective of this study was to compare a more tolerable regimen using micronized vaginal progesterone (MVP) and oral dydrogesterone versus MVP and intramuscular progesterone (IM) for luteal support.

Methods

A retrospective study of patients undergoing single blastocyst FET in a tertiary center IVF unit. All patients (n = 100) received oral estradiol in the follicular phase and supplemented with MVP for luteal phase support. One group (n = 50) received additional dydrogesterone (10 mg TID) and the other (n = 50) intramuscular progesterone (100 mg every 3 days).

Results

The two groups were similar with regard to age; BMI; infertility etiology and duration; and basal hormonal levels. Biochemical pregnancy rates (34% vs 42%, p = 0.54) and clinical pregnancy rates (26% vs. 36%, p = 0.39) were lower in the MVP + oral dydrogesterone group as compared to the MVP + IM progesterone group. Nevertheless, this difference was not statistically significant. Abortion rates were similar (2%) and there were no ectopic pregnancies in both groups.

Conclusion

This retrospective cohort study demonstrates noninferiority of MVP and oral dydrogesterone as compared to MVP and intramuscular progesterone for luteal support in FET cycles. The better profile of adverse effects and tolerability makes it a suitable protocol for FET.

Background

Frozen embryo transfer (FET) after in vitro fertilization (IVF) has been practiced for over forty years, and due to improvements in cryopreservation its prevalence is ever increasing(1–3). FET advantages over fresh embryo transfer include avoiding ovarian hyperstimulation syndrome (OHSS), allowing for better synchronization between the embryo and endometrium especially in high responders, opting the deferral of embryo transfer for pregestational testing for aneuploidy or specific genetic disorders, and more(4–8). Importantly, FET leads to similar pregnancy rates as fresh embryo transfers(9–11).
High quality embryos are required for a successful FET cycle, but also a receptive and synchronized endometrium. Nevertheless, the optimal protocol for endometrial preparation has not yet been established. Most treatment protocols contain estrogen preparation for the proliferative phase, followed by various regimens of progesterone support for the luteal phase. Several progesterone preparations are available, including oral, vaginal, injectable or subcutaneous progesterone, each of them harboring different tolerability and bioavailability profiles. For example, intramuscular delivery has been reported to lead to side effects, such as pain and inflammation at the injection site and even severe infections and gluteal abscesses; vaginal progesterone is considered to be relative uncomfortable due to excessive vaginal discharge and irritation; and bioavailability of most oral progesterone preparations is quite low due to hepatic first pass metabolism(12, 13). Importantly, most studies have not shown superiority of any of the aforementioned modes of progesterone delivery on clinical pregnancy rates(14, 15).

Dydrogesterone, is a stereoisomer of natural progesterone and acts as synthetic oral progesterone. Compared with other oral progesterone preparations, it has a more favorable pharmacological profile, better bioavailability and faster intestinal absorption(16). Two randomized controlled trials, known as Lotus I and Lotus II, were conducted to compare dydrogesterone and vaginal progesterone preparations in fresh IVF cycles(17, 18). In both studies, noninferiority of oral dydrogesterone, as compared with vaginal progesterone in terms of safety and pregnancy outcomes, was reported. Nevertheless, its efficacy in FET cycles, in which a corpus luteum is not present and there is need for more intensive luteal support, has not been determined. Previous reports suggest that vaginal progesterone alone is probably insufficient(19). The use of intramuscular progesterone is considered efficacious but much less tolerable. The objective of the current study was therefore to compare the outcomes of FET cycles using the more tolerable regimen of oral dydrogesterone + MVP and that of intramuscular progesterone + MVP in endometrial preparation protocols.

**Methods**

**Patient Population**

This retrospective study was conducted reviewing the records of 100 patients undergoing single blastocyst FET in IVF unit, Rambam Medical Center, Haifa, Israel, from October 2021 to August 2022. Data collected included baseline parameters such as age, body mass index (BMI), parity and etiology of infertility. Treatment parameters evaluated included baseline serum levels of estradiol, progesterone and LH as measured at cycle day 3; Pretransfer levels of estradiol, progesterone and LH and endometrial thickness, as measured preceding progesterone addition.

**Treatment protocol**

We analyzed the records of patients undergoing single blastocyst transfer in FET cycles. Estradiol 2 mg TID (Estrofem, Novo Nordisk, Sydney, Australia) was initiated on day 3 of menstruation for at least 8 days. On day 8 endometrial thickness was assessed by transvaginal ultrasound (TVS). If the measured endometrial stripe was 7 mm or above, progesterone was started. Otherwise, estradiol dosage was
increased and the patient was reevaluated after a few days. Due to the need of intense luteal support in artificial FET cycles, all patients received MVP 100 mg TID (Endometrin, Ferring, Misgav, Israel). The oral progesterone group received additional dydrogesterone 10 mg TID (Duphaston, Abbott, Weesp, Netherlands), and the IM progesterone group received additional IM injections of progesterone 100 mg every 3 days (Prontogest, IBSA, Novolog, Lugano, Switzerland). Blastocysts that were frozen at day 5 or 6 of development (5.3 ± 4.2 in IM progesterone vs. 5.7 ± 3.6 in oral dydrogesterone groups, p = 0.60), were all thawed and transferred after 6 days of progesterone administration. β-hCG was measured 10 days after embryo transfer (ET) and values above 20 IU/L were considered a biochemical pregnancy. Clinical pregnancy was established when a gestational sac with fetal heartbeat was visible on ultrasound examination 6 weeks after ET.

Statistical analysis

Data were analyzed on Excel spreadsheets (Redmond, Washington, USA) and SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA). The study was designed to detect a 3-fold difference in biochemical- and clinical pregnancy rates between the groups at a significance level of 0.05 and a power level of 0.80. Comparison of continuous variables were analyzed using Student’s t-test. Proportions were compared using Fisher’s exact test. P values less than 0.05 were considered statistically significant.

Results

We reviewed FET cycles (n = 100) in which single blastocysts were transferred at the IVF unit at Rambam Medical Center. Baseline characteristics of patients that were treated either with IM progesterone or oral dydrogesterone are presented in Table 1. The two groups were similar with regard to age, body mass index (BMI), infertility duration and basal FSH, LH and estradiol levels. Infertility etiology presented in Table 2 was also similar.
Table 1
Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Groups</th>
<th>IM Progesterone (n = 50)</th>
<th>Oral Dydrogesterone (n = 50)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33.0 ± 5.3</td>
<td>33.38 ± 4.9</td>
<td>0.74</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 ± 5.5</td>
<td>24.89 ± 4.8</td>
<td>0.35</td>
</tr>
<tr>
<td>Infertility duration (years)</td>
<td>2.86 ± 2.2</td>
<td>3.6 ± 3.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Basal FSH (I.U/L)</td>
<td>6.72 ± 2.8</td>
<td>7.68 ± 6.9</td>
<td>0.37</td>
</tr>
<tr>
<td>Basal LH (I.U/L)</td>
<td>7.24 ± 4.5</td>
<td>6.38 ± 6.2</td>
<td>0.44</td>
</tr>
<tr>
<td>Basal E2 (pmol/L)</td>
<td>227 ± 140</td>
<td>205 ± 111</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD;
*two sided t-test

The characteristics of the treatment cycles are presented in Table 3. Baseline estradiol and progesterone levels were similar, yet baseline LH was slightly- but significantly elevated in the dydrogesterone group as compared to the IM progesterone group (5.2 ± 2.7 vs. 4.2 ± 2.3, p = 0.05). Even though pretransfer estradiol levels were slightly- and insignificantly lower in the dydrogesterone group (1029 ± 550 vs. 1387 ± 1348, p = 0.08), progesterone levels (1.4 ± 0.7 vs. 1.5 ± 1.3, p = 0.69) and endometrial thickness (9.4 ± 1.5 vs. 9.5 ± 1.8, p = 0.80) were similar as compared to the IM progesterone group.
<table>
<thead>
<tr>
<th><strong>Table 2</strong></th>
<th><strong>Infertility etiology</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups</strong></td>
<td>IM Progesterone (n = 50)</td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Secondary</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>PGT-M</td>
<td>18 (36%)</td>
</tr>
<tr>
<td><strong>Cause of infertility</strong></td>
<td></td>
</tr>
<tr>
<td>Unexplained</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Male factor</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>Anovulation</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Mechanical factor</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Diminished ovarian reserve</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

*Fisher's exact test

<table>
<thead>
<tr>
<th><strong>Table 3</strong></th>
<th><strong>Frozen embryo transfer cycle data</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups</strong></td>
<td>IM Progesterone (n = 50)</td>
</tr>
<tr>
<td>Baseline E2 (pmol/L)</td>
<td>199 ± 106</td>
</tr>
<tr>
<td>Baseline progesterone (nmol/L)</td>
<td>1.7 ± 1.3</td>
</tr>
<tr>
<td>Baseline LH (IU/L)</td>
<td>4.2 ± 2.3</td>
</tr>
<tr>
<td>Pre-transfer E2 (pmol/L)**</td>
<td>1387 ± 1348</td>
</tr>
<tr>
<td>Pre-transfer progesterone (nmol/L)**</td>
<td>1.50 ± 1.3</td>
</tr>
<tr>
<td>Pre-transfer LH (IU/L)**</td>
<td>10.6 ± 8.5</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>9.5 ± 1.8</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD
*two sided t-test
**as measured at the last day before initiating progesterone treatment
The differences in clinical outcomes between the two groups are presented in Table 4. Biochemical pregnancy rates (34% vs 42%, p = 0.54) and clinical pregnancy rates (26% vs. 36%, p = 0.39) were lower in the oral dydrogesterone group as compared to the IM progesterone group. Nevertheless, this difference was not statistically significant. Abortion rates were the same (2%) and there were no ectopic pregnancies in both study groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>IM Progesterone (n = 50)</th>
<th>Oral Dydrogesterone (n = 50)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical pregnancy</td>
<td>21 (42%)</td>
<td>17 (34%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>18 (36%)</td>
<td>13 (26%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Abortion</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Fisher’s exact test

**Discussion**

This study evaluated the outcome of FET cycles treated with MVP and oral dydrogesterone versus MVP and intramuscular progesterone. The main finding of this study is that although the study group treated with intramuscular progesterone had slightly higher biochemical- and clinical pregnancy rates as compared to oral dydrogesterone, these differences were not statistically significant. This finding implies noninferiority of the oral- versus the intramuscular based regimens.

The two study groups were similar with regard to age; BMI; infertility etiology and duration; and basal hormonal levels. Baseline LH was slightly- but significantly elevated in the dydrogesterone group as compared to the intramuscular progesterone group. Additionally, estradiol levels were slightly- and insignificantly lower in the dydrogesterone group. Although progesterone levels and endometrial thickness were similar, these differences may have contributed to the trend toward lower pregnancy rates in the oral dydrogesterone group. Importantly, these differences were not clinically significant.

As mentioned above, progesterone can be administered in various ways such as oral, vaginal, intramuscular or subcutaneous and is an essential supplement for successful FET procedure(12–15), with advantages and disadvantages of each preparation as discussed. It has recently been reported that vaginal-only progesterone replacement is inferior to intramuscular progesterone(19). We have therefore added either intramuscular progesterone or oral dydrogesterone to MVP for intense luteal support in FET cycles. Nevertheless the addition of intramuscular injections is much less tolerable than oral preparations due to local pain and inflammatory complications at the injection sites.
A comparison between intramuscular to oral progesterone has never been done to our knowledge in FET cycles of single warmed blastocysts. Recent studies had evaluated mostly oral progesterone administration compared to vaginal administration of capsules or gel. In the LOTUS trials that analyzed luteal support patients undergoing fresh IVF cycles (17, 18) it was demonstrated that oral progesterone was noninferior to MVP for a primary objective of presence of fetal heartbeats at 12 weeks of gestation (18). Oral progesterone was also compared to vaginal gel in fresh embryos and found similar rates of clinical pregnancy between the groups (17). In FET cycles, one prospective study showed that luteal phase support with oral dydrogesterone added to vaginal progesterone had a higher live birth rate and lower miscarriage rate compared with vaginal progesterone alone (20). In a retrospective study, MVP gel alone was demonstrated to be non-inferior to oral dydrogesterone alone in FET cycles (21). In one single-blind randomized controlled trial, oral progesterone was compared to intramuscular progesterone and intravaginal progesterone (22). They found that oral progesterone was as effective as the other methods of administration. In that study, most of the embryos were in the cleavage stage. Our study now suggests that in FET cycles of single warmed blastocysts, a treatment regimen using MVP and oral dydrogesterone is as effective as MVP and intramuscular progesterone, in terms of successful pregnancy rates.

**Conclusion**

In conclusion, in this study we found similar clinical outcomes between oral- and intramuscular progesterone for luteal phase support in artificial FET cycles. Owing to the patient-friendly aspects of orally administered medication with a reassuring safety profile, it may be a preferable option in clinical practice and may replace painful intramuscular injections.

**Declarations**

*Ethics approval and consent to participate*

This study was approved by the local Institutional Review Board, number 0174-21-RMB-D. Informed consent was not required due to the retrospective nature of the study.

*Consent for publication*

Not applicable.

*Availability of data and materials*

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

*Competing interests*

The authors declare that they have no competing interest.
Funding

Not applicable.

Authors' contributions

GB contributed to the design and implementation of the research.

CH analyzed and interpreted the patient data.

OF verified the analytical methods and contributed to the design and implementation of the research.

All authors read and approved the final manuscript.

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References


