Comparison of Intramuscular and Intravaginal Progesterone for Luteal Phase Support in IVF Cycles: a randomized clinical trial

Katayon Berjis, M.D.; Abotaleb Sarem, M.D.; Mansoureh Moaya, M.Sc.; Nahid Mohamad Alaiha M.D.

Obstetrics and Gynecology Department, Azad University of Medical Sciences, Tehran, Iran

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Abstract
Objective: This research was designed to compare the effectiveness of intramuscular progesterone and vaginal progesterone to support luteal phase in IVF cycles.

Materials and Methods: In this randomized clinical trial 182 infertile patients between 20-40 years old were selected for rapid ZIFT cycles. In order to support luteal phase Cyclogest suppository (400 mg BID) was used for 77 cases and the rest used intramuscular progesterone (100 mg daily). Pregnancy and abortion rates were compared between two groups.

Results: Chemical pregnancy rate (positive ß-HCG) was %27.3 in Cyclogest group and %30.6 in intramuscular progesterone group (P = 0.7). Clinical pregnancy (gestational sac visible by transvaginal ultrasound) was observed in %22.1 of cases in Cyclogest group and %27.1 of cases in intramuscular progesterone group (P = 0.4). Ongoing pregnancy rate (fetal heart action visible by transvaginal ultrasound) was %15.6 in Cyclogest group and %18.8 in intramuscular progesterone group (P = 0.6).

Conclusion: Chemical pregnancy, clinical pregnancy and ongoing pregnancy rates were similar in vaginal and intramuscular progesterone groups.

Key words: Rapid ZIFT, Chemical pregnancy, Clinical pregnancy, Progesterone

Introduction

After ovulation induction with clomiphene citrate and gonadotropins, progesterone level would be higher in comparison to natural cycle, so there is no need to additional progesterone for luteal phase support. When GnRH agonists are used for pituitary down regulation, LH secretion is inhibited and its effect will be continued in the luteal phase (1).

Abnormally low level of luteal phase LH may be insufficient to promote endometrial maturation to support an early pregnancy. Endogenous LH secretion can be suppressed for as long as ten days after GnRH agonist treatment (2, 3). In order to compensate the low level of progesterone, injection, gel and suppository forms of this steroid are used.

Numerous studies have shown that supplementary HCG increases the risk of OHSS (ovarian hyper stimulation syndrome), thereafter progesterone seems to be the wiser selection (4, 5). Intramuscular injection is painful and has side effects like abscess formation. On the other hand progesterone suppository may cause lower serum levels which may result in incomplete abortion; however numerous clinical trials in this field had paradoxical results (6-8).
So through this study it is decided to compare the efficacy of intramuscular progesterone and progesterone suppository after the successful rapid ZIFT.

Materials and methods
In this randomized clinical study 284 patients were evaluated. The patients were infertile women between 20 to 40 years of age who come to Sarem Hospital from June 2004 until November 2005. After getting approval from the ethical committee of the hospital, the study was conducted following informed written consents of all participants.

After initial routine investigation all patients received daily GnRH agonist (superfact, Aventis Pharma, Germany) from 21th day of the previous menstrual cycle, and then 225-300 IU/day hMG (Menogon, Ferring Pharmaceuticals, Germany) from the second day of menstruation. From sixth day of the cycle, transvaginal sonography was done every other day to assess the follicular growth. When there was an at least 2-3 follicles with diameter of 18 mm, 10000 unit intra muscular HCG (Pregnyl, Organon, Iran) was injected. After 36 hours, ovum pick up was done (with excluding OHSS patients), so 182 women continued the study. Patients were randomly divided in two groups using random number table. Finally 85 cases in the intramuscular group and 77 cases in the suppository group were evaluated.

One day after ovum pickup in the first group intramuscular progesterone 100mg (Aburaihan pharmaceutical Co., Iran) daily and in the second group cyclogest suppository (Actavis Group, Iceland) 400 mg twice a day were prescribed. Serum pregnancy test was performed on 15 days after per-forming ZIFT and pregnancy sac was investigated three weeks after positive β-HCG by trans-vaginal ultrasound. Treatment was continued until 10th week of gestation.

SPSS 13.0 (SPSS Inc.chicago IL.) was used to analyze the results. Chi-square and t-test were applied for the comparison. P value less than 0.05 was considered statistically significant.

Results
As shown in table 1, two groups were matched regarding the mean age of patients and mean duration of infertility. There was no statistical difference between two groups due to infertility causes (Male and female factor). No statistical difference between two groups was seen regarding the type of infertility as well. There was no relation between the type of infertility and pregnancy rate. The rates of chemical, clinical and ongoing pregnancies are shown in table 2 with no statistical difference.

Discussion
This study showed that chemical pregnancy and clinical pregnancy rates were more in intramuscular progesterone group but regarding the number of cases there was no statistical difference between two groups. In a prospective study, which has been conducted on 206 IVF cases in Texas University in 1999 intramuscular progesterone (50mg daily) and Crinone gel 8% were compared. Vaginal bleeding (11-12 days after ovum pick up) was more frequent in Crinone gel group; however serum progesterone of intramuscular group was higher. In addition positive β-HCG and pregnancy rate were similar in two groups (9). In present study positive β-HCG and clinical pregnancy rates in two groups were similar. Another randomized study which has been done in Pizza University in 1995 comparing intramuscular and vaginal progesterone showed that progesterone level by using

Table 2: Comparison of pregnancy rates between two groups

<table>
<thead>
<tr>
<th></th>
<th>Cyclogest (n = 77)</th>
<th>Progestrone (n = 85)</th>
</tr>
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<tbody>
<tr>
<td>Chemical pregnancy</td>
<td>21 (27.3%)</td>
<td>26 (30.6%)</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>17 (22.1%)</td>
<td>23 (27.1%)</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>12 (15.6%)</td>
<td>16 (18.8%)</td>
</tr>
</tbody>
</table>

Table 1: The comparison of variables between two groups

<table>
<thead>
<tr>
<th>Support</th>
<th>Cyclogest (n = 77)</th>
<th>Progestron (n = 85)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>32.3 ± 4.9</td>
<td>31.3 ± 4.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Duration of infertility (year)</td>
<td>7.4 ± 5.3</td>
<td>6.9 ± 4.8</td>
<td>0.18</td>
</tr>
<tr>
<td>N. of follicles</td>
<td>6.7 ± 3.6</td>
<td>7.1 ± 4.2</td>
<td>0.16</td>
</tr>
<tr>
<td>N. of embryos</td>
<td>3.3 ± 1.0</td>
<td>3.2 ± 1.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Age (year)</td>
<td>32.3 ± 4.9</td>
<td>31.3 ± 4.7</td>
<td>0.42</td>
</tr>
</tbody>
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vaginal gel was more stable and comfortable (10). In another open label comparative assessment that has been done in Harvard University in 2001 on 201 women who used Crinione gel or intramuscular progesterone in IVF cycles, pregnancy and live birth rates were higher in the second group (11). In present study the frequency of pregnancy and alive fetus was reported to be more in intramuscular progesterone group with no statistical differences. In some studies which have been conducted from 2003-2006 cyclo-steg suppository was compared to Crinone gel. There was no difference in hormonal levels after embryo transfer, pregnancy rate and implantation rate between two groups, but gel was more comfortable (12-14). In a study which was done in Finland on 39 women with tubal factor infertility, endometrial histology assessment proved that vaginal proges-terone is quite effective for supporting luteal phase in the IVF cycle (15). On the other hand some researches have compared vaginal gel and intramuscular progesterone to support luteal phase in IVF cycles in which vaginal gel was introduced as an alternative to support luteal phase (16-17). Another research was done at Messina infertility research center in Italy, on 156 women who received 50 mg/day intramuscular progesterone or 90 mg/day vaginal progesterone gel. Still birth and pregnancy rate in intramuscular progesterone were reported to be more (18). In another comparison which was done with intramuscular and vaginal progesterone in IVF cycle, endometrial morphology and its vascularity have been investigated. Intramuscular progesterone (100mg /day) or vaginal progesterone (200 mg/twice a day) showed similar effects on the endometrium (19). In our study the rates of chemical and clinical pregnancy in intramuscular progesterone group were more but with regard to the number of cases there was no statistical difference between two groups.

Acknowledgement
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There exists no conflict of interest to declare.

References
13. Tay PY, Lenton EA. The impact of luteal supplement on pregnancy outcome following stimulated IVF


