Clinical outcomes of using three gonadotropins and medroxyprogesterone acetate (MPA) during ovarian stimulation in normal ovulatory women undergoing IVF/ICSI treatments

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Objective To compare the clinical characteristics in a gonadotropin (Gn) and medroxyprogesterone acetate (MPA) protocol using three types of Gn in normal ovulatory women undergoing IVF/ICSI treatments.

Methods A total of 258 normal ovulatory IVF/ICSI patients undergoing ovarian stimulation in a Gn and MPA protocol were analyzed in this retrospective study and allocated into three groups according to the Gn used: group A, hMG-A (brand name: Fengyuan, n=105); group B, hMG-B (brand name: Lebaode, n=90); group C: u-FSH (brand name: Lishenbao, n=63). The hormone profile, embryological characteristics, and the pregnant results after frozen-thawed embryo transfer (FET) were compared among the three groups.

Results There was no significant difference in the number of oocytes retrieved among the three groups (12.1 ± 6.9 vs 12.1 ± 5.6 vs 13.1 ± 8.8, P>0.05). Other indicators such as the number of mature oocyte, fertilization, cleavage and viable embryo were similar (P>0.05). No premature LH surges were detected, with a range of 0.04~7.38 IU/L. No differences were found in the clinical pregnancy rate per transfer (43.48% vs 37.93% vs 40.74%, P>0.05) and the implantation rate (34.88% vs 22.22% vs 26.42%, P>0.05).

Conclusion MPA is an effective oral alternative for the prevention of premature LH surges. Progestin-primed ovarian stimulation (PPOS) is a novel regimen of ovarian stimulation in combination with embryo cryopreservation, in which the two types of hMG are as effective as u-FSH.

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Gonadotropin (Gn) was introduced to induce multiple follicle development during controlled ovarian stimulation (COH) since 1960s. High cancellation rate owing to spontaneous luteinizing hormone (LH) surges was the principal problem in this stage [1]. It was demonstrated that the traditional down-regulation scheme was effective to reduce the occurrence of premature LH surges, however, there were still some deficiencies, such as the administration time prolonged, increasing patients’ costs and incidence of ovarian hyperstimulation syndrome (OHSS)[2]. Thus seeking a simple, safe and effective protocol was the focus in the field of reproductive endocrinology.

Frozen-thawed embryo transfer (FET) has been used recently in more and more departments of assisted reproduction with the cryopreservation techniques improved and the safety of FET proved[3-5]. Luteal-phase ovarian stimulation was feasible for producing competent oocytes and embryos with optimal pregnancy outcomes in FET cycles in our previous studies, and no premature LH surges were detected[6,7]. Knobil et al.[8] found that the LH surges were blocked when circulating estrogen and progesterone (P) rose simultaneously or when P was introduced 12 h after the estrogen injection. Based on the clinical experience and experimental research, we hypothesized that P co-treatment may suppress premature LH surge in COH, and Gn and medroxyprogesterone acetate (MPA) protocol was tried in our clinic. Such protocol was called progestin-primed ovarian stimulation (PPOS) in which progesterone was delivered from the early follicular phase to mimic the P priming in luteal phase.

A variety of Gn preparation were widely used including human menopausal gonadotropin (hMG) and follicle stimulation hormone (FSH), however, the compositions were different in Gn produced by different manufacturers, and hMG-A, hMG-B and urinary FSH (u-FSH) were employed in our clinic. It was still a controversy which was the optimal Gn preparation in traditional down-regulation protocol[9-13], while related research had not yet been reported in PPOS. The aim of our study was to explore the endocrine characteristics and the clinical outcomes of using two types of hMG during PPOS in normal ovulatory women undergoing IVF/ICSI treatments compared with u-FSH.

Materials & Methods

Study setting and patients

Patients undergoing IVF/ICSI treatments between June and September in 2014 were enrolled in this retrospectively study. The inclusion criteria were: 1) no more than 38 years of
age; 2) regular menstrual cycle over the previous 3-month period (25–35 d); 3) antral follicle count (AFC) was more than 4 on menstrual cycle (MC) 2–3; 4) basal serum FSH concentration was no more than 10 IU/L. The exclusion criteria were: 1) endometriosis grade 3 or higher; 2) diagnosis of polycystic ovary syndrome (PCOS); 3) any contraindications to ovarian stimulation treatment; 4) received hormonal treatments in the previous 3 months; 5) documented oocytes pick-up failure or embryo transfer failure more than 3 times.

**Controlled ovarian stimulation**

Gn and MPA protocol: Gn 225 IU and MPA (Zhejiang Xianju Pharmaceutical Co., China) 10 mg/d were administered from MC3 onwards. Follicular monitoring was performed 6–8 d later started on MC9–11 and using a transvaginal ultrasound examination to record the number of follicles. When 3 dominant follicles reached 18 mm in diameter, Gn and MPA ceased simultaneously, the final stage of oocyte maturation was triggered by triptorelin 0.1 mg (Decapeptyl, Ferring pharmaceuticals, Germany) and hCG 1 000 IU (Lizhu Pharmaceutical Trading Co., China).

A total of 258 patients were allocated into three groups according to the type of Gn used: group A, hMG-A (n=105, brand name: Fengyuan, Maanshan Pharmaceutical Trading Co., China); group B, hMG-B (n=90, brand name: Lebaode, Lizhu Pharmaceutical Trading Co., China); group C, u-FSH (n=63, brand name: Lishenbao, Lizhu Pharmaceutical Trading Co., China). No data about the dose of hCG contained in hMG were illustrated in the instruction. Thus, the three types of Gn were measured with abbott ARCHITECT system, which detected only \( \beta \)-hCG. The \( \beta \)-hCG values with one ampoule hMG were 16.77 IU/L in hMG-A and 7.86 IU/L in hMG-B.

Serum FSH, LH, E2, P and \( \beta \)-hCG were collected on MC3, MC9–11 (after 6–8 d of stimulation), the trigger day and the day after trigger. Hormone levels were measured with chemiluminescence (Abbott Biologicals B.V, Netherlands). The lower limits of sensitivity were as follows: FSH=0.06 IU/L, LH=0.09 IU/L, E2=10 ng/L and P=0.1 \( \mu \)g/L, \( \beta \)-hCG=1.2 IU/L. The upper limit of E2 measurement was 5 000 ng/L. The E2 value was recorded as 5 000 ng/L if it was higher than the upper limit.

**Oocyte retrieve, fertilization and embryo culture**

Transvaginal ultrasound-guided oocyte retrieval was conducted 34–36 h after trigger. All follicles with diameter of more than 10 mm were retrieved. Fertilization of the aspirated oocytes was carried out *in vitro*, by either conventional insemination or ICSI, depending on semen parameters. Embryos were examined for the number and regularity of blastomeres and the degree of embryonic fragmentation on the third day. All good-quality embryos (including grade 1 and grade 2, 8-cell embryos) were frozen by vitrification on the third day after oocyte retrieval. Only non-top-quality embryos were placed in extended culture until they reached the blastocyst stage. During this stage, only good-morphology blastocysts were frozen on day 5 or day 6.
Endometrium preparation and FET

Three regimens were used for endometrium preparation in our clinic\(^{[14]}\). Natural FET cycles were used for women with regular menstrual cycle and letrozole was added for the cases with irregular menstrual cycles. For patients with thin endometrium during either natural cycles or stimulation cycles, hormone replacement treatment (HRT) was recommended. Specifically, oral ethinyl estradiol (EE) 25 µg tid (Xinyi Pharmaceutical Co., China) was administered from MC3 onwards. Once the endometrial thickness was greater than 8 mm, estradiol and dydrogesterone yellow tablets (Abbott Healthcare Products B.V, Netherlands) and progesterone soft capsules (Laboratoires Besins International, France) were delivered instead of EE. Day 3 (D3) embryos transfer was arranged to be performed 3 d later. The transfer of blastocysts was performed on the fifth day. A β-hCG test was taken 14 d after FET, and the clinical pregnancy was diagnosed by a transvaginal ultrasound examination with intrauterine gestational sacs in 28 d. The progesterone supplement was continued until 10 weeks of gestation when pregnancy was achieved.

Observation index

The primary outcome measure was the number of oocytes retrieved. The secondary measures included the clinical pregnancy rate, ongoing pregnancy rate, and FET implantation rate. Rate of D3 top-quality embryos was defined as the number of D3 top-quality embryos divided by the number of cleaved embryos. Rate of viable embryos was defined as the number of viable embryos divided by the number of cleaved embryos. Clinical pregnancy was defined as the presence of a gestational sac during ultrasound examination 7 weeks after FET. The implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred. The miscarriage rate was defined as the proportion of patients with spontaneous termination of pregnancy.

Statistical analysis

Data were presented as the mean ± standard deviation (\(\bar{x} \pm s\)) and percentage (%). The significant difference was considered at \(P\) value less than 0.05. Continuous variables were analyzed by One-way ANOVA or Kruskal-Wallis H’s test where appropriate. \(\chi^2\) test was used for categorical comparisons. All data were analyzed using the Statistical Package for the Social Sciences for Windows (SPSS, Version 16.0, SPSS Inc., Chicago, IL, USA).

Results

General information of patients

A total of 258 patients had completed the oocyte retrieval cycles. The basic characteristics of the patients enrolled are shown in Table 1. Of all patients, the female’s age, body mass index (BMI), duration of infertility, the number of antral follicles and basic hormone profile were comparable among the three groups.
cycle characteristics

The clinical and embryological characteristics of the population are shown in Table 2. No significant difference was found in the number of oocytes retrieved among the three groups (P > 0.05). The number of D3 top-quality embryos in group B was lower than that in groups A and C without any statistical significance (P > 0.05), however, the rate of D3 top-quality embryos in group A was significantly higher than that in groups B and C (P < 0.05). Other indicators such as the number of mature oocytes, fertilization, cleavage, viable embryos and rate of viable embryos were similar among the three groups (P > 0.05).

Hormone profile

As shown in Table 3, the FSH level in group B during ovarian stimulation was significantly higher than that in groups A and C (P < 0.05). The LH values gradually decreased and no premature LH surges were detected during COH with a range of 0.04–7.38 IU/L. The average level of LH on the trigger day was significantly lower than the basal LH values, and the LH levels were comparable among the three groups in different time points (P > 0.05). The E2 level in group C was lower than that in groups A and B on the trigger day (P < 0.05), and was comparable on the day after trigger (P > 0.05). The serum β-hCG level in group B

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**Table 1 General information of patients (x ± s)**

<table>
<thead>
<tr>
<th>Index</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle (n)</td>
<td>105</td>
<td>90</td>
<td>63</td>
</tr>
<tr>
<td>Age (year)</td>
<td>31.2 ± 3.4</td>
<td>31.6 ± 3.6</td>
<td>31.1 ± 3.9</td>
</tr>
<tr>
<td>Duration of infertility (a)</td>
<td>3.3 ± 2.6</td>
<td>3.5 ± 2.7</td>
<td>3.1 ± 2.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.90 ± 3.94</td>
<td>20.85 ± 3.87</td>
<td>21.25 ± 3.83</td>
</tr>
<tr>
<td>No. of previous transfer failures (n)</td>
<td>0.4 ± 0.8</td>
<td>0.3 ± 0.7</td>
<td>0.5 ± 1.0</td>
</tr>
<tr>
<td>Antral follicle count (n)</td>
<td>10.9 ± 5.3</td>
<td>11.1 ± 4.4</td>
<td>12.3 ± 5.0</td>
</tr>
</tbody>
</table>

**Table 2 The stimulation and embryological characteristics of the patients (x ± s)**

<table>
<thead>
<tr>
<th>Index</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gn dosage (IU)</td>
<td>2 121.4 ± 629.5</td>
<td>1 996.7 ± 297.6</td>
<td>2 064.3 ± 337.3</td>
</tr>
<tr>
<td>Gn duration (d)</td>
<td>9.5 ± 2.1</td>
<td>9.1 ± 1.1</td>
<td>9.4 ± 1.4</td>
</tr>
<tr>
<td>No. of &gt;10 mm follicles on the trigger day (n)</td>
<td>15.3 ± 8.5</td>
<td>13.3 ± 6.1</td>
<td>15.3 ± 9.5</td>
</tr>
<tr>
<td>Interval from trigger to oocyte retrieval (h)</td>
<td>35.8 ± 3.6</td>
<td>35.6 ± 3.8</td>
<td>35.5 ± 4.6</td>
</tr>
<tr>
<td>No. of oocytes retrieved (n)</td>
<td>12.1 ± 6.9</td>
<td>12.1 ± 5.6</td>
<td>13.1 ± 8.8</td>
</tr>
<tr>
<td>No. of MII oocytes (n)</td>
<td>10.7 ± 5.8</td>
<td>10.7 ± 5.1</td>
<td>12.1 ± 8.3</td>
</tr>
<tr>
<td>No. of fertilized oocytes (n)</td>
<td>8.8 ± 4.9</td>
<td>8.4 ± 4.4</td>
<td>9.8 ± 6.8</td>
</tr>
<tr>
<td>No. of cleaved embryos (n)</td>
<td>8.6 ± 4.9</td>
<td>8.2 ± 4.4</td>
<td>9.6 ± 6.6</td>
</tr>
<tr>
<td>No. of D3 top-quality embryos (n)</td>
<td>4.9 ± 3.8</td>
<td>4.0 ± 2.6</td>
<td>4.9 ± 3.7</td>
</tr>
<tr>
<td>No. of viable embryos (n)</td>
<td>5.1 ± 3.5</td>
<td>4.5 ± 2.6</td>
<td>5.4 ± 4.0</td>
</tr>
<tr>
<td>Rate of D3 top-quality embryos (%)</td>
<td>56.48 (510/903)</td>
<td>49.18 (362/736)</td>
<td>50.50 (306/606)</td>
</tr>
<tr>
<td>Rate of viable embryos (%)</td>
<td>59.25 (535/903)</td>
<td>55.57 (409/736)</td>
<td>55.78 (338/606)</td>
</tr>
</tbody>
</table>

*: P < 0.05, compared with group A
Table 3 The endocrine characteristic during ovarian stimulation (X ± s)

<table>
<thead>
<tr>
<th>Index</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FSH (IU/L) Day 3 of MC</strong></td>
<td>4.65 ± 2.42</td>
<td>4.66 ± 2.34</td>
<td>4.79 ± 2.46</td>
</tr>
<tr>
<td><strong>LH (IU/L)</strong></td>
<td>2.88 ± 2.13</td>
<td>2.83 ± 1.88</td>
<td>3.13 ± 2.19</td>
</tr>
<tr>
<td><strong>E2 (ng/L)</strong></td>
<td>26.06 ± 17.44</td>
<td>28.72 ± 18.44</td>
<td>26.27 ± 22.02</td>
</tr>
<tr>
<td><strong>P (µg/L)</strong></td>
<td>0.24 ± 0.16</td>
<td>0.23 ± 0.17</td>
<td>0.21 ± 0.12</td>
</tr>
<tr>
<td><strong>β-hCG (IU/L)</strong></td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>The trigger day</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>15.88 ± 4.37*</td>
<td>17.00 ± 4.72a</td>
<td>14.52 ± 5.01*</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>1.46 ± 1.16</td>
<td>1.42 ± 1.20</td>
<td>1.41 ± 1.07</td>
</tr>
<tr>
<td>E2 (ng/L)</td>
<td>3 259.18 ± 1 471.85a</td>
<td>3 267.23 ± 1 399.39a</td>
<td>2 780.30 ± 1 559.91</td>
</tr>
<tr>
<td>P (µg/L)</td>
<td>0.70 ± 0.49</td>
<td>0.65 ± 0.34</td>
<td>0.66 ± 0.48</td>
</tr>
<tr>
<td>β-hCG (IU/L)</td>
<td>2.56 ± 1.01**</td>
<td>1.79 ± 0.44a</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>The day after trigger day</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>20.28 ± 7.03</td>
<td>23.25 ± 5.66ª</td>
<td>19.87 ± 8.25</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>46.65 ± 27.08</td>
<td>49.68 ± 22.98</td>
<td>44.07 ± 26.65</td>
</tr>
<tr>
<td>E2 (ng/L)</td>
<td>3 614.06 ± 1 433.46</td>
<td>3 688.63 ± 1 292.32</td>
<td>3 185.86 ± 1 609.21</td>
</tr>
<tr>
<td>P (µg/L)</td>
<td>4.94 ± 2.85</td>
<td>4.86 ± 2.35</td>
<td>5.18 ± 4.09</td>
</tr>
<tr>
<td>β-hCG (IU/L)</td>
<td>21.37 ± 10.26ª</td>
<td>20.74 ± 6.61ª</td>
<td>17.23 ± 9.25</td>
</tr>
</tbody>
</table>

*: P<0.05, compared with group B
#: P<0.05, compared with group C

was significantly lower than that in group A (P<0.05). The P levels were similar among the three groups (P>0.05), and it increased significantly after trigger.

**Pregnancy outcomes during FET cycle**

There were 9 patients undergoing cycle cancellation in group A including 1 patient with immature oocyte, 1 failing to fertilize, 7 patients without high-quality embryos. There were 6 patients cancelled in group B with 1 patient obtaining immature oocyte, 1 failing to fertilize, 4 patients having poor embryos. In group C, the number of cycle cancellation was 3 as 1 patient failed to fertilize, 2 patients obtained poor embryos. The cancellation rate was similar among the three groups (8.57% vs 6.67% vs 4.76%, P>0.05). The number of transferred embryos including D3 embryos and blastocysts was comparable among the three groups (Table 4). The clinical pregnancy rate per transfer was 43.48% in group A, 37.93% in group B and 40.74% in group C, with no significant difference (P>0.05). There was no statistic significance in clinical pregnancy rate and implantation rate among the three groups (P>0.05).

**Discussion**

hMG was employed in infertility treatments since 1960s, then FSH with high purity was produced two decades later[15]. Some practitioners once proposed FSH should replace hMG because LH activity components contained in hMG were detrimental to follicle growth and oocyte maturation[9,10]. Ovarian response was related to Gn, though the usage of FSH would
increase the patients’ financial burden. However, subsequent articles argued that hMG had the similar or beneficial effects compared with FSH\textsuperscript{[11-13]}. Therefore, it was still a controversy whether hMG was as effective as u-FSH in traditional down-regulation protocol.

Ovarian response was influenced not only by Gn but also by the protocol used. PPOS as a novel protocol was different from the traditional down-regulation protocol, during which MPA was used to inhibit the LH surge, related researches about Gn in PPOS have not yet been reported. In our study, the dose of Gn used was comparable in groups A, B, C and there were no significant differences in the number of oocytes retrieved, mature oocyte, fertilization, cleavage and viable embryos. In addition, no statistic significances were found in the biochemical pregnancy rate, the clinical pregnancy rate and the implantation rate. Therefore, the oocytes and embryos produced in PPOS were potential, and hMG shared the similar clinical efficacy with u-FSH in PPOS.

It has been demonstrated that P was capable of facilitating or blocking LH surge. P enhanced the preovulatory LH surge when administered after E\textsubscript{2} priming\textsuperscript{[16]} and blocked when P was presented before or concurrently with estrogen\textsuperscript{[8,17]}. Thus, MPA started from the MC3 in PPOS as the effect of P depended on the timing of its administration. The P concentration was low after the usage of MPA because MPA did not interfere with measurement of endogenous P determination\textsuperscript{[18]}, while the follicles were actually in a high endocrine milieu of P. No premature LH surges were detected during COH with a range of 0.04–7.38 IU/L, illustrating MPA was effective to prevent premature LH surges.

Some investigators concluded that exogenous LH supplementation during traditional down-regulation regimen in which LH concentration was profoundly suppressed had beneficial influences on follicular maturation and pregnancy outcomes\textsuperscript{[18]}. Furthermore, some literatures suggested the hCG concentration was positively associated with live-birth rate in the long GnRH-a protocol\textsuperscript{[19-21]}. It was unknown whether the addition of LH was necessary during PPOS. There were 24 patients in group A, 19 patients in group B, 11 patients in group C with profound suppression (LH\textless;0.5 IU/L), and the embryological characteristics were comparable in those patients. Thus, in our study no beneficial effects of LH supplement were found in PPOS.

\begin{table}
\centering
\caption{The pregnancy outcomes during FET cycle}
\begin{tabular}{lccc}
\hline
Index & Group A & Group B & Group C \\
\hline
Cycle (n) & 46 & 29 & 27 \\
No. of cycle with D3 embryos (n) & 42 & 27 & 26 \\
No. of cycle with blastocysts (n) & 4 & 2 & 1 \\
No. of transferred embryos (n) & $1.9 \pm 0.3$ & $1.9 \pm 0.4$ & $2.0 \pm 0.2$ \\
Biochemical pregnancy rate per transfer (%) & 58.70 (27/46) & 55.17 (16/29) & 55.56 (15/27) \\
Clinical pregnancy rate per transfer (%) & 43.48 (20/46) & 37.93 (11/29) & 40.74 (11/27) \\
Implantation rate (%) & 34.88 (30/86) & 22.22 (12/54) & 26.42 (14/53) \\
Miscarriage rate (%) & 5.00 (1/20) & 0.00 (0/11) & 0.00 (0/11) \\
\hline
\end{tabular}
\end{table}
Some articles proposed that the high progesterone levels had an adverse effect on the clinical pregnancy rate of fresh transfer\textsuperscript{[22,23]}, because elevated P level damaged the synchronization of endometrium and follicle\textsuperscript{[24]}. A retrospective study including a total of 11 055 women who underwent their first IVF/ICSI and a subgroup of 4 021 women undergoing FET cycles confirmed that elevated P levels on the day of hCG administration negatively influenced the clinical pregnancy rate of fresh transfer, but the detrimental effect of P elevation was unrelated to oocyte quality. In our study, the number of viable embryos was 4.5–5.4 and the clinical pregnancy rate was 37.93%–43.48%. Hence, we considered that P had no negative impacts on the quality of oocytes and embryos.

Compared with gonadotropin releasing-hormone agonist (GnRH-a) and GnRH antagonist (GnRH-A), there are some advantages using MPA. MPA as an oral alternative can reduce the pain of repeated injections, making the treatment user convenience. The usage of MPA can relieve the patients’ financial burden as the price of MPA is inexpensive. Furthermore, MPA antagonizes estrogen-related diseases in the uterus and breast, including endometrial cancer, endometriosis, uterine fibroids, and breast cancer\textsuperscript{[25]}. Due to the effect of MPA on the endometrium, all the viable embryos are freeze in PPOS and FET is employed when appropriated. The efficiency of IVF will not decrease by the strategy of FET regardless of embryo-thawed failure as the success rate of embryo-thawed reaches 98% in our department.

In conclusion, MPA can inhibit the premature LH surges effectively. PPOS is a new alternative to ovarian stimulation based on FET, during which hMG and u-FSH have the similar clinical outcomes. What’s more, the application of hMG will sharply reduce the fees as the price of hMG was one sixth of u-FSH. Due to the limited sample size and only normal ovulatory women included in our study, the conclusion need to be verified by a large scale prospective randomized trial in different subgroups of population in order to make the PPOS protocol individual and optimal.

References

6. Kuang YP, Hong QQ, Chen QJ, et al. Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing IVF/ICSI treatment, with optimal pregnancy outcomes in frozen-thawed embryo


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