Factors related to the dose of intramuscular progesterone for luteal phase support during in vitro fertilization cycles

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Abstract

Background: Progesterone (P) supplementation of the luteal phase is prescribed routinely for women undergoing in vitro fertilization (IVF). Dosing schedules of intramuscular (IM) P in women undergoing IVF or intracytoplasmic sperm injection (ICSI) are based on empirical evidence rather than on randomized controlled trials.

Methods: A randomized, investigator-blind comparative trial in 480 patients undergoing their first cycle of IVF. Of those who completed the study, 203 patients were treated with 60 mg of P in oil IM daily, and 210 patients received 80 mg of P in oil IM daily.

Results: There were no significant differences in the implantation (23.8% vs. 23.2%), clinical pregnancy (36.5% vs. 32.9%), miscarriage (5.4% vs. 11.6%), and live birth rates (33.0% vs. 27.6%) between the 60 mg and 80 mg groups, respectively. In the subgroup of women based on age, body mass index (BMI), peak estradiol (E2) level, or type of ovarian hyperstimulation (COH) protocol, there were no significant differences in any IVF parameters or outcomes between the two doses of IM P.

Conclusion: The dose of IM P is not dependent on the age and BMI of the women, the peak E2 level, and the type of COH protocol used.

Introduction

Progesterone (P) supplementation of the luteal phase is prescribed routinely for women undergoing in vitro fertilization (IVF). Although most reproductive endocrinologists recommend P supplementation, and consider P essential for optimal success and support of pregnancy during the first trimester, the dosages as well as the regimens used vary considerably [1]. Clearly, intramuscular (IM) P-in-oil has been shown to enhance implantation and pregnancy rates, but the optimal dose of IM P is unknown [1].

Dosing schedules of IM P in women undergoing IVF or intracytoplasmic sperm injection (ICSI) are based on empirical evidence rather than on randomized controlled trials. The usual IM dosing is from 25-100mg daily in single or divided doses. There is but one small study involving 100 patients which has compared the dose of IM P [2]. The study showed no differences in clinical, ongoing pregnancy, and miscarriage rates when 25 mg and 100 mg of daily IM P were used [2]. However, this finding may be biased because multiple cycles of IVF treatment from the same patients were included, and these cycles were likely to correlate with each other.

It is relevant to ask whether or not the dose of P is dependent on the age of the women because several studies have reported decreased luteal phase P levels with increasing age [3,4]. In addition, in older women undergoing assisted reproduction techniques (ART), lower rates of pregnancy and live births have been reported, as well as higher miscarriage rates [5]. However, P and pregnanediol glucuronide have also been shown to be lower in women with a high body mass index (BMI) [6-8]. Some studies have suggested that obesity and the associated endocrine alterations may affect corpus luteal function [9,10,11]. Further, an increased BMI is related to a lower liver birth rate and a higher incidence of early pregnancy loss among women undergoing IVF or ICSI [9]. It is still unknown whether or not loss of early pregnancies could be prevented by a more vigorous luteal phase support in women with a high BMI.

We hypothesized that increasing the dose of IM P may improve the pregnancy rates in older or overweight women undergoing IVF. The objective of this study was to determine whether or not the dose of P is dependent on the age or BMI of women undergoing IVF. The secondary objective of this study was to determine which other variables, such as peak estradiol (E2) level or the type of controlled ovarian hyperstimulation (COH) protocol used, were associated with the dose of IM P for luteal phase support in IVF.

Materials and methods

This was a prospective, randomized, investigator-blind clinical trial involving patients undergoing IVF treatment at the Reproductive Medicine Center of Tongji Hospital. The subjects were recruited for a period of 4 months between March 2009 and June 2009. The study was approved by the Institutional Review Board of the Tongji Hospital with informed written consent being obtained from each patient.

Inclusion criteria were as follows: early follicular phase serum follicle-stimulating hormone (FSH) concentration <15 IU/L; first cycle of IVF/ICSI; and not participating in any other ongoing studies.

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Patients were excluded from the study if they were considered to be at risk for development of ovarian hyperstimulation syndrome (OHSS).

All patients within the study underwent the long or short gonadotropin releasing hormone (GnRH) agonist protocol. Ovarian stimulation protocols and embryo laboratory procedures used for IVF or ICSI were performed using previously established protocols [12]. Patients were randomly assigned to either group in a ratio of 1:1 by means of computer-generated random numbers on the day of oocyte retrieval. This randomization was done by the research nurse without influence from the clinicians. The study was not patients-blinded because the patients were aware of the treatment group. The 60 mg group (n = 203) received 60 mg of P in oil IM daily for luteal support. The 80 mg group (n = 210) received 80 mg of P in oil IM daily for luteal support. Treatment was continued until a negative pregnancy test or a positive fetal heartbeat was documented by transvaginal ultrasound.

The primary endpoint was the clinical pregnancy rate. Secondary variables of interest were implantation, biochemical pregnancy, miscarriage, and live birth rates. Clinical pregnancy was defined as an ultrasonically detected gestational sac with visible cardiac activity, usually 2-3 weeks after a positive serum β-hCG test. The implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred. A biochemical pregnancy was defined as a transient elevation of the serum β-hCG level without ultrasound evidence of a gestational sac. Miscarriage was classified as clinical loss of an intrauterine pregnancy between the 7th and 12th weeks of gestation [13]. The miscarriage rate was calculated among women who were identified as having a clinical pregnancy.

The clinical pregnancy rate was the primary outcome variable used for sample size calculation. Based on a 0.05 two-sided level of significance, we calculated that a sample size of 4462 subjects in each group would provide 80% power to detect a 5% relative difference, considered as clinically important, assuming a 35% clinical pregnancy rate in the 80 mg group and a 30% clinical pregnancy rate in the 60 mg group. This was not feasible for a single centre study. Thus, we arbitrarily chose a large set of patients to provide data that would be clinically useful, and that could be included in a future meta-analysis.

Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS, version 11.5; SPSS Inc., Chicago, IL, USA). An independent sample t-test was used for continuous variables that were normally distributed, and the Wilcoxon’s rank sum test was used for data that was not normally distributed. The χ², Fisher’s exact tests, or Mantel-Haenszel χ² test were used for categorical variables where appropriate.

A logistical regression analysis was used to assess the impact of age, BMI, the peak E₂ level, the type of COH protocol, and the dose of IM P on treatment outcomes. Then, each group was divided into subgroups according to women’s age (≤33 years, 34-36 years, and ≥37 years), BMI (≤18.5 kg/m², 18.5-24.9 kg/m², and ≥25.0 kg/m²), the peak E₂ level, the type of COH protocol, and the dose of IM P. A negative correlation was observed between the BMI (Table 5). When classified based on BMI, the peak E₂ level, the type of COH protocol, and the dose of IM P. A negative correlation was observed between the women’s age and the clinical pregnancy rate (OR = 0.70; 95% CI, 0.50-0.98, P = 0.0384).

When adjusted for age, the implantation, biochemical pregnancy, clinical pregnancy, miscarriage, and live birth rates were similar between the 60 mg and 80 mg groups independent of BMI (Table 5).

### Table 1. Baseline characteristics.a

|                | 60 mg group (n = 203) | 80 mg group (n = 210) | P value |
|----------------|-----------------------|-----------------------|---------|
| Age, y         | 30.6 ± 4.2            | 31.1 ± 4.6            | 0.26    |
| Duration of infertility, y | 5.4 ± 4.6            | 4.9 ± 3.6            | 0.22    |
| Body mass index, kg/m² | 21.3 ± 3.0            | 21.8 ± 3.1            | 0.40    |
| Baseline serum FSH, IU/L | 5.4 ± 3.8            | 5.8 ± 3.2            | 0.28    |
| Ovarian stimulation protocol: | | | |
| Long GnRH agonist | 173 (85.2)           | 168 (80.0)           | 0.16    |
| Short GnRH agonist | 30 (14.8)            | 42 (20.0)            | 0.10    |

Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin releasing hormone.

aValues are given as number (percentage) or mean ± standard deviation unless otherwise indicated.

### Table 2. Outcome of ovarian stimulation.a

|                | 60 mg group (n = 203) | 80 mg group (n = 210) | P value |
|----------------|-----------------------|-----------------------|---------|
| Duration of ovarian stimulation, days | 8.9 ± 1.2            | 8.7 ± 1.3            | 0.256   |
| Total dose of gonadotropins, IU | 1630.0 ± 447.2        | 1582.9 ± 459.8       | 0.301   |
| Serum E₂ on day of trigger, pg/mL | 4036.0 ± 2112.6       | 3682.8 ± 1880.7      | 0.163   |
| Oocytes, n | 11.9 ± 6.3            | 11.7 ± 6.6           | 0.742   |
| Proportion of MII oocytes | 0.9 ± 0.5            | 0.9 ± 0.1            | 0.350   |
| Fertilization rate, % | 0.6 ± 0.2            | 0.6 ± 0.2            | 0.957   |
| Embryos transferred, n | 2.0 ± 0.4            | 2.0 ± 0.4            | 0.606   |
| Embryos frozen, n | 3.9 ± 4.0            | 3.6 ± 3.5           | 0.425   |
| Mean embryo quality | 10.9 ± 2.0            | 10.7 ± 2.0           | 0.440   |

Abbreviations: E₂, estradiol.

aValues are given as mean ± standard deviation unless otherwise indicated.

Results

Four hundred and eighty patients were recruited, and 413 completed the study. Sixty-seven patients dropped out of the study for fertilization failure, failed embryo development, or development of OHSS. Of those who completed the study, 203 patients were treated with 60 mg of P in oil IM daily, and 210 patients received 80 mg of P in oil IM daily.

There were no statistically significant differences between the 60 mg and 80 mg groups with respect to patient age, duration of infertility, BMI, or baseline serum FSH levels (Table 1). There were no differences between the two groups in the number of patients who used the different types of COH protocol (Table 1). The two patient groups had a similar duration of ovarian stimulation, total dose of gonadotropins, and peak E₂ levels. There were no differences in the number of oocytes retrieved, proportion of MII oocytes, fertilization rates, number of embryos transferred, and number of embryos frozen. Both groups had comparable overall embryo quality, as determined by the mean embryo quality scores (Table 2).

Implantation, biochemical pregnancy, clinical pregnancy, miscarriage, and live birth rates did not differ significantly between the 60 mg and 80 mg groups (Table 3). There were 1 and 5 ectopic pregnancies in the 60 mg and 80 mg groups, respectively.

Logistic regression analysis showed that treatment outcome is independent of BMI, the peak E₂ level, the type of COH protocol, and the dose of IM P. A negative correlation was observed between the women’s age and the clinical pregnancy rate (OR = 0.70; 95% CI, 0.50-0.98, P = 0.0384). There were also no differences in the implantation, biochemical pregnancy, clinical pregnancy, and live birth rates between the two groups for the age groups ≤ 33, 34-36, and 37-44 years (Table 4).
### Table 3. Overall outcome of treatment cycle.

|                  | 60 mg group (n = 203) | 80 mg group (n = 210) | Odds ratio (95% CI) | P value |
|------------------|-----------------------|-----------------------|---------------------|---------|
| Implantation rate| 95/400 (23.8)         | 97/418 (23.2)         | 0.99 (0.92, 1.07)   | 0.854   |
| Biochemical pregnancy rate | 11/203 (5.4)      | 17/210 (8.1)         | 1.54 (0.70, 3.37)   | 0.280   |
| Clinical pregnancy rate | 74/203 (36.5)       | 69/210 (32.9)        | 0.85 (0.57, 1.28)   | 0.443   |
| Miscarriage rate  | 4/74 (5.4)           | 8/69 (11.6)          | 2.30 (0.66, 8.00)   | 0.184   |
| Live birth rate   | 67/203 (33.0)        | 58/210 (27.6)        | 0.77 (0.51, 1.18)   | 0.234   |

Abbreviations: CI, confidence interval.

*Values are given as number (percentage) unless otherwise indicated.

### Table 4. Post hoc analysis of outcome of cycle by the women’s age.

|                  | 60 mg group (n = 203) | 80 mg group (n = 210) | Odds ratio (95% CI) | P value |
|------------------|-----------------------|-----------------------|---------------------|---------|
| Implantation rate: |                       |                       |                     |         |
| ≤ 33 y           | 79/293 (27.0)         | 74/291 (25.4)         | 0.92 (0.64, 1.34)   | 0.674   |
| 34-36 y          | 11/76 (14.5)          | 13/69 (18.8)          | 1.37 (0.57, 3.30)   | 0.481   |
| ≥37 y            | 5/31 (16.1)           | 10/58 (17.2)          | 1.08 (0.33, 3.51)   | 0.894   |
| Biochemical pregnancy rate: |               |                       |                     |         |
| ≤ 33 y           | 10/150 (6.7)          | 14/150 (9.3)          | 1.44 (0.62, 3.35)   | 0.395   |
| 34-36 y          | 0/38 (0)              | 2/33 (6.0)            | 6.11 (0.28, 131.99) | 0.126   |
| ≥37 y            | 1/15 (6.7)            | 1/27 (3.7)            | 0.54 (0.03, 9.28)   | 0.670   |
| Clinical pregnancy rate: |               |                       |                     |         |
| ≤ 33 y           | 61/150 (40.7)         | 52/150 (34.7)         | 0.77 (0.48, 1.24)   | 0.284   |
| 34-36 y          | 10/38 (26.3)          | 10/33 (30.3)          | 1.22 (0.43, 3.43)   | 0.712   |
| ≥37 y            | 3/15 (20.0)           | 7/27 (25.9)           | 1.40 (0.30, 6.47)   | 0.670   |
| Miscarriage rate  |                       |                       |                     |         |
| ≤ 33 y           | 3/61 (4.9)            | 4/52 (7.7)            | 1.61 (0.37, 3.55)   | 0.544   |
| 34-36 y          | 0/10 (0)              | 3/10 (30)             | 9.80 (0.44, 219.25) | 0.067   |
| ≥37 y            | 1/3 (33.3)            | 1/7 (14.3)            | 0.33 (0.01, 8.18)   | 0.513   |
| Live birth rate   |                       |                       |                     |         |
| ≤ 33 y           | 56/150 (37.3)         | 47/150 (31.3)         | 0.77 (0.47, 1.23)   | 0.275   |
| 34-36 y          | 9/38 (23.7)           | 7/33 (21.2)           | 0.87 (0.28, 2.66)   | 0.805   |
| ≥37 y            | 2/15 (13.3)           | 4/27 (14.8)           | 1.13 (0.18, 7.04)   | 0.897   |

Abbreviations: CI, confidence interval.

*Values are given as number (percentage) unless otherwise indicated.

### Table 5. Post hoc analysis of outcome of cycle by the women’s BMI.

|                  | 60 mg group (n = 203) | 80 mg group (n = 210) | Odds ratio (95% CI) | P value |
|------------------|-----------------------|-----------------------|---------------------|---------|
| Implantation rate: |                       |                       |                     |         |
| ≤18.5            | 13/55 (23.6)          | 16/51 (31.4)          | 1.48 (0.63, 3.48)   | 0.374   |
| 18.5-24.9         | 73/300 (24.3)         | 68/307 (22.1)         | 0.88 (0.61, 1.29)   | 0.525   |
| ≥25.0             | 9/45 (20.0)           | 13/60 (21.7)          | 1.11 (0.43, 2.87)   | 0.836   |
| Biochemical pregnancy rate: |               |                       |                     |         |
| ≤18.5            | 0/28 (0)              | 1/26 (3.8)            | 3.35 (0.13, 86.03)  | 0.299   |
| 18.5-24.9         | 11/153 (7.2)          | 12/154 (7.8)          | 1.09 (0.47, 2.55)   | 0.841   |
| ≥25.0             | 0/22 (0)              | 4/30 (13.33)          | 7.64 (0.39, 149.73) | 0.076   |
| Clinical pregnancy rate: |               |                       |                     |         |
| ≤18.5            | 10/28 (35.7)          | 12/26 (46.2)          | 1.54 (0.52, 4.60)   | 0.440   |
| 18.5-24.9         | 58/153 (37.9)         | 49/154 (31.8)         | 0.76 (0.48, 1.22)   | 0.264   |
| ≥25.0             | 6/22 (27.3)           | 8/30 (26.7)           | 0.97 (0.28, 3.35)   | 0.962   |
| Miscarriage rate  |                       |                       |                     |         |
| ≤18.5            | 1/10 (10)             | 1/12 (8.3)            | 0.82 (0.04, 14.99)  | 0.895   |
| 18.5-24.9         | 3/58 (5.2)            | 6/49 (12.2)           | 2.56 (0.60, 10.82)  | 0.191   |
| ≥25.0             | 0/6 (0)               | 1/8 (12.5)            | 2.60 (0.09, 75.49)  | 0.387   |
| Live birth rate   |                       |                       |                     |         |
| ≤18.5            | 9/28 (32.1)           | 10/26 (38.5)          | 1.32 (0.43, 4.04)   | 0.630   |
| 18.5-24.9         | 52/153 (34.0)         | 41/154 (26.6)         | 0.70 (0.43, 1.15)   | 0.161   |
| ≥25.0             | 6/22 (27.3)           | 7/30 (23.3)           | 0.81 (0.23, 2.87)   | 0.748   |

Abbreviations: BMI, body mass index; CI, confidence interval.

*Values are given as number (percentage) unless otherwise indicated.
For patients with a peak serum E2 level <5000 pg/mL, there were no differences in the implantation (54/221 [24.4%] vs. 57/262 [21.8%]; \( P = 0.486 \)), clinical pregnancy (41/114 [36.0%] vs. 43/130 [33.1%]; \( P = 0.636 \)), miscarriage (0/51 [0%] vs. 7/43 [16.3%]; \( P = 0.199 \)), and live birth rates (40/114 [35.1%] vs. 33/130 [25.4%]; \( P = 0.099 \)) between the 60 mg and 80 mg groups. Similarly, in patients with peak serum E2 levels ≥5000 pg/mL, there were no differences in the implantation (33/137 [24.1%] vs. 34/122 [27.9%]; \( P = 0.489 \)), clinical pregnancy (27/70 [38.6%] vs. 21/62 [33.9%]; \( P = 0.312 \)), miscarriage (4/27 [14.8%] vs. 0/21 [0%]; \( P = 0.577 \)), and live birth rates (22/70 [31.4%] vs.21/62 [33.9%]; \( P = 0.766 \)) between the two groups.

For patients who used the long GnRH agonist protocol, there were no differences in the implantation (83/444 [19.4%] vs. 84/335 [25.1%]; \( P = 0.775 \)), clinical pregnancy (65/173 [37.6%] vs. 60/168 [35.7%]; \( P = 0.722 \)), miscarriage (4/65 [6.2%] vs. 6/60 [10%]; \( P = 0.430 \)), and live birth rates (59/173 [34.1%] vs. 52/168 [31.0%]; \( P = 0.535 \)) between the 60 mg and 80 mg groups. Similarly, in patients who used the short GnRH agonist protocol, there were no differences in the implantation (12/56 [21.4%] vs. 13/83 [15.7%]; \( P = 0.387 \)), clinical pregnancy (9/30 [30.0%] vs. 9/42 [21.4%]; \( P = 0.411 \)), miscarriage (0/9 [0%] vs. 2/9 [22.2%]; \( P = 0.145 \)), and live birth rates (8/30 [26.7%] vs. 7/42 [16.7%]; \( P = 0.306 \)) between the two groups.

**Discussion**

In this randomized, investigator-blind trial, no differences in clinical pregnancy, miscarriage, and live birth rates were demonstrated between the 60 mg and 80 mg groups. Moreover, in subgroups of women based on age, BMI, peak E2 level, or the type of COH protocol, clinical pregnancy, miscarriage, and live birth rates (59/173 [34.1%] vs. 52/168 [31.0%]; \( P = 0.535 \)) between the two doses of IM P for younger or older women. Second, it has been reported that the mean luteal phase serum P level was not significantly different across stages of the transition until the late menstrual transition [19,20]. However, the sample in this study was toward women undergoing IVF or ICSI, who were between 20 and 44 years of age. Our results may therefore not be applicable to women >44 years of age.

In this current study, after adjusting for age, no clinical or statistical advantage could be demonstrated for the higher dose of IM P in women with a high BMI (BMI >25 kg/m2). This can possibly be explained by the fact that a considerable amount of the administered P diffuses into the fat tissue of the body when the P concentration in plasma rises to high levels. When the plasma levels decline, the P deposited in the fat tissue then diffuses back into the bloodstream, and a depot effect is thus obtained [18].

Some investigators [1,2] have suggested restricting the role of increasing the dose of P to a subset of women with high peak E2 levels because of the main causes of the luteal phase defect in stimulated IVF cycles is related to the supraphysiologic levels of steroids secreted by a high number of corpora lutea during the early luteal phase, which directly inhibit the LH secretion via feedback mechanisms [21]. It is also reported that high serum E2 concentrations (>5000 pg/ml) may be detrimental to implantation as it can be associated with severe down regulation of the expression of endometrial P receptors [22]. However, the present study showed no significant difference in the clinical pregnancy rate between the 60 mg and 80 mg groups when high serum E2 concentrations were >5000 pg/ml. It is likely that high serum E2 levels could cause lower pregnancy rates either by adverse effects on endometrial receptivity or on oocyte/embryo quality [23].

The type of COH protocol may presumably affect the dose of P for luteal support [1]. However, no studies currently exist to evaluate the dose of P for luteal support in patients using the short GnRH agonist protocol, although such an intervention has been evaluated in the long GnRH agonist protocol [14]. This study showed no significant differences in pregnancy rates between the two doses of IM P in patients who used the short GnRH agonist protocols.

Our study had several limitations. One limitation of our study was the dose of P for luteal support in patients using the GnRH antagonist protocol were not evaluated because the GnRH antagonists were not available in China during the course of the study. Another limitation of our study was the sample size of the obese group. The sample in this study consisted only of Chinese women. According to the World Health Organization criteria [24], there were only 52 in the overweight group (BMI ≥25 kg/m2), including two women who were obese (BMI ≥30 kg/m2), of 412 women. Therefore, our results may not be applicable to women who are obese and morbidly obese (BMI ≥35 kg/m2).
addition, the choice of 60 mg and 80 mg of IM P supplementation in the current study was arbitrary because no dose-finding studies have been performed in women with increasing age or BMI.

In conclusion, the findings of this study suggest that increasing the dose of IM P dose not improve pregnancy rates in women with increasing age or BMI. The dose of IM P is not dependent on the age and BMI of the women, peak E2 level, and the long or short GnRH agonist protocol used. Further studies are needed to confirm the optimal dose of P for luteal phase support in patients using the GnRH antagonist protocol.

**Conflicts of interest**

The authors have no conflicts of interest.

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