ASSOCIATION BETWEEN PRE-TRIGGER SERUM PROGESTERONE LEVEL AND CONCEPTION RATE AFTER A FRESH EMBRYO TRANSFER IN IVF-ICSI CYCLES

Zhiyan Ahmad Abdullah [a]

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ABSTRACT

Background

High progesterone (P4) level in the late follicular phase during in vitro fertilization (IVF) - intracytoplasmic sperm injection (ICSI) cycles had been claimed to have associations with decreased pregnancy rate; however, the evidence is still not clear.

Objectives

The aim was to determine the effect of serum P4 on pregnancy outcomes among IVF-ICSI cycles.

Patients and Methods

The prospective observational study was conducted on 997 patients who underwent IVF-ICSI cycles in the International Private IVF Center in Sulaimani from January 1st, 2017 to January 1st, 2019. Blood samples were collected for serum P4 on the day of the ovulation trigger. Ovum pickup was done 36 hours later, and serum P4 was correlated with IVF-ICSI outcome in terms of positive conception rate. The patients were subdivided into four subgroups depending on different age groups, conception rates and serum P4 were studied in each age group.

Results

The average serum P4 for positive and negative pregnancy groups among patients was 0.766 ng/ml and 0.803 ng/ml, respectively, with a statistically significant difference (P-value=0.035). Also, P4 for positive and negative groups was 0.852 ng/ml and 0.804 ng/ml, respectively, for the age group of 35-39 years (P-value=0.014).

Conclusion

Pregnancy may still occur with high P4, and the need to identify the subgroup of cycles with elevated P4 does not signify implantation failure or reduction, is still in question. Therefore, more studies are needed before making decisions like freezing all embryo or cycle cancelation based on the level of serum P4 alone.

Keywords: *Intracytoplasmic sperm injection (ICSI); In vitro fertilization (IVF); Kurdistan; Pregnancy; Progesterone (P4); Sulaimani.*

[a] Maternity Teaching Hospital, Sulaimani, Kurdistan Region, Iraq.
Correspondence: zhiyanshaban2@gmail.com

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INTRODUCTION

Progesterone (P4) plays an essential role in promoting receptivity in the estrogen-primed endometrium [1]. Serum P4 levels remain baseline at <1.5 ng/ml during the follicular phase when its origin is mostly the adrenals and increases gradually towards just before luteinization as a result of either accumulation from the growing follicles or due to premature luteinization of one or more follicles [2]. Pre-human chorionic gonadotropin (Pre-hCG), i.e., pre-trigger, P4 increases are thought to cause embryo-endometrial asynchrony, and consequently, reduced implantation rate [3]. However, the unfavorable effect of P4 elevation (PE) has not been found in other studies [2].

Previous studies had shown the effect of PE on pregnancy rates on the day of hCG trigger through simple bivariate analyses [4]. While these studies did not have control over confounders such as the number of oocytes, female age, or body mass index (BMI), and therefore, they may underestimate the actual effect of PE on pregnancy rates [4]. Furthermore, these varying results may also be attributed to the use of different arbitrary cutoff levels.

In in vitro fertilization (IVF) cycles, even after using luteinizing Hormone (LH) analogues or antagonists, the occurrence of pre-hCG P4 rise without LH rise with unknown pathogenesis had been observed [5]. However, the possible effects of these subtle P4 increases on pregnancy outcomes are controversial [5-6]. Most studies have advocated that PE on the day of the hCG trigger adversely affects pregnancy outcome due to its detrimental effect on the endometrium or the compromised quality of the oocyte [7]. Furthermore, a previous publication had shown that the live birth rates (LBRs) were significantly lower in patients with both low (≤0.05 ng/mL) and high (≥1.5 ng/mL) P4 levels on the day of hCG trigger [8].

The objective of this study was to measure serum P4 levels among 997 cycles of IVF- intracytoplasmic sperm injection (ICSI) fresh embryo transfer and its effect on success in terms of a positive pregnancy test.

PATIENTS AND METHODS

This retrospective observational study was conducted at the International Private IVF Center in Sulaimani city from January 1st, 2017 to January 1st, 2019. During the study period, 997 IVF-ICSI fresh embryo transfer cycles were reviewed, and they were subjected to one of four protocols; long, short, antagonist, or superovulation (in hypo-gonadotrophic patients).

Patients' specific characteristics dictated protocol selection and medications used. The long and short protocols utilized triptorelin 0.1mg subcutaneous daily injections until the day of trigger, while the antagonist protocol was the flexible protocol and used cetrorelix 0.25 mg subcutaneous injections at 14 mm diameter of the leading follicle, daily until the day of trigger. Moreover, serial monitoring with a transvaginal ultrasound scan and hormonal profile (LH, P4, estradiol) every two to four days was carried out.

The oocyte maturation was induced using either urinary hCG (5000 IU – 1000 IU) or triptorelin injection or both. Each patient was sent for serum P4 at the time of hCG injection. Oocyte retrieval was performed 35 hours later. The patients' characteristics, primarily women age, embryo grading, and the number of embryos available, governed the number of embryos transferred. Then, all patients received routine follow up and monitored for conception by checking beta hCG titer two weeks later.

Two weeks after embryo transfer, patients with serum beta hCG levels of > 50 mIU/ml were considered a positive result for the conception. No hCG injection was used in the luteal –phase support until serum pregnancy testing. The serum P4 level was compared among positive and negative pregnancy test groups.

Data analysis was performed using the "IBM SPSS Statistics version 25" program. Both descriptive and inferential statistical tests were performed. Also, a P-value of (≤0.05) was considered a statistically significant association.

RESULTS

Out of 997 cycles studied, 521 (52.3%) cycles ended with a positive serum pregnancy test, i.e., conception, and the average number of embryos transferred was 2.76.

The average serum P4 levels were 0.766 ng/ml and 0.803 ng/ml for the positive and negative cycles, respectively, with a statistically significant difference (Table 1).

All age groups were compared in terms of conception rate, average transferred embryos, and serum P4 levels (Table 2).

Table 3 shows the distribution of cycles around an arbitrarily cutoff set of 1.5 for the P4 level (ng/ml).

Table 1. Conception rate and P4 level in the studied groups.

Cycle characteristics (n=997)	Positive pregnancy test (n=521, 52.3%)	Negative pregnancy test (n=476, 47.7%)	P-value
Serum P4 levels	0.766	0.803	0.035
Average embryo transferred		2.76	
Overall conception rate		52.3%	

Table 2. Difference between conception rate and serum P4 in different age groups.

Age groups (year)	Conception rate (%)	Average embryos transferred	Serum P4 in the positive group (ng/ml)	Serum P4 in the negative group (ng/ml)	P-value
<30 (n=265, 26.6%)	64.9	2.73	0.705	0.735	0.233
30-34 (n=325, 32.6%)	55.7	2.83	0.804	0.852	0.089
35-39 (n=237, 23.8%)	52.7	2.86	0.783	0.883	0.014
40-42 (n=95, 9.5%)	32.6	2.53	0.819	0.830	0.096
>42 (n=75, 7.5%)	16	2.52	0.745	0.518	<0.01

Table 3. Conception rate and P4 levels in all patients.

Serum P4 (ng/ml)	Cycle (n=997)	Conceived (n=521)	Not conceived (n=476)
<1.5	918 (92.1%)	486 (48.6%)	432 (43.3%)
≥1.5	79 (7.9%)	35 (3.5%)	44 (4.4%)

DISCUSSION

The PE in the late follicular phase, which is defined as a P4 level of ≥1.5 ng/ml at the day of hCG trigger, had been observed in 6-30% of the controlled ovarian stimulation (COS) cycles [9]. Besides, the worse pregnancy outcomes that were found in IVF-ICSI fresh embryo transfer cycles among patients with PE had led clinicians to monitor P4 levels during the late follicular phase and on the day of hCG trigger [10]. Furthermore, freezing all embryos from IVF/ICSI fresh cycle and then replacing them in a subsequent cycle had been postulated as a solution to avoid the potentially harmful effect of PE on pregnancy [11-12]. Therefore, this study was conducted to answer this clinical question: does progesterone elevation on the day of HCG trigger associated with unfavorable IVF/ICSI fresh embryo transfer outcomes in all age groups.

The results presented in the current study support a difference between the P4 level in positive and negative cycles. Moreover, the overall conception rate was 52.3% at the average number of the transferred embryo of 2.76, and the serum P4 level was significantly lower in the positive pregnancy test group (Table 1).

The study conducted by Venetis et al. [13], which was a systematic review and meta-analysis of 63 studies and more than 60,000 IVF/ICSI cycles, showed that PE in late follicular phase is harmful to fresh embryo transfer, thereby, pregnancy rates. That is, PE is affecting pregnancy success rate with P4 levels as low as 0.8–1.1 ng/ml (OR: 0.79, 95% CI: 0.67–0.95), which is increased as the level reaches 1.2 ng/ml (OR: 0.67, 95% CI: 0.53–0.84), and then it becomes stable thereafter [13]. Additionally, the study of Bosh et al. [10] showed an association between P4 levels of >1.5 ng/ml at the

day of hCG with the IVF/ICSI fresh embryo transfer pregnancy outcomes. Furthermore, they included 4,032 patients who had been subjected to IVF/ICSI and found that pregnancy rates were higher among patients with serum P4 levels of ≤1.5 ng/ml than those with P4 levels of >1.5 ng/ml (P-value = <0.001) [10].

However, the studies had not the same findings. The study conducted by Miller et al. [14] showed PE in 293 patients who had been subjected to COS with human menopausal gonadotropin (hMG) and/or Follicle-stimulating hormone (FSH) in a Gonadotropin-releasing hormone (GnRH) agonist protocol had not to affect the quality of oocyte and pregnancy rate [14]. Besides, the study performed by Shapiro et al. [15] who prospectively included 158 IVF-ICSI patients, confirm the findings of Miller et al. [14]. Furthermore, they found that the incidence of PE was 13.3%, but pregnancy rates were not significantly different between the patients with PE and patients with normal P4 levels (19 versus 27%) [15].

When the patients were subdivided into subgroups in the current study (Table 2), there appeared significant differences in the age groups; the age group of 35-39 years had P4 levels significantly higher in the negative group. While in the age group of > 42 years, the P4 level was significantly lower in the negative group. The small size of the latter subgroup may explain this unexpected finding; otherwise, the age group just before it, i.e., 40-42 years, showed no significant difference between positive and negative groups.

The results of the current study showed that serum P4 level higher than the arbitrarily cutoff set point of 1.5 ng/ml does not uniformly imply failed implantation (Table 3). Furthermore, the results showed that the total number of cycles with P4 of ≥1.5ng/ml is 79, and of them, 35 cycles were positive (conception rate = 44.3%).

The study conducted by Griesinger et al. [16] had analyzed the data from six IVF/ICSI clinical trials to measure the impact of P4 during hCG trigger day on IVF/ICSI fresh embryo transfer pregnancy outcomes. Moreover, they had used the 1.5 ng/ml cutoff point for P4, as a result of this, the pregnancy rate per cycle was significantly lower in women with PE [odds ratio = 0.55, 95% CI = 0.37–0.81] [16]. However, a subgroup analysis showed that the P4 level of >1.5 ng/ml was associated with decreased pregnancy rates in low to normal responders, but not in high responders [16]. Also, they found that pregnancy rates in the high responders with PE were higher than normal responders, but in women without PE, the observed pregnancy rate increased from 29.9% (1–5 oocytes) to 39.2% (>18 oocytes) [16]. Conversely, women with PE showed an increase in the pregnancy rate from 18.2% (1–5 oocytes) to 43.2% (>18 oocytes) [16]. Compared with the subjects without PE, the observed pregnancy rates were numerically lower in all subgroups for the women with PE except for the high responders (>18 oocytes) [16].

In conclusion, pregnancy still occurs with a high P4 level, and the need to identify the subgroup of cycles where elevated P4 does not signify an implantation failure or reduction is still in question. Therefore, more studies are needed before taking an exclusive decision based on the level of serum P4 alone, especially decisions like freezing all embryos or cycle cancellation.

Conflict of Interest

The author had nothing to declare.

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