

## The Rise of Serum Progesterone and its Effect on the Success of *In Vitro* Fertilization Treatment

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### Abstract

**Objective:** The aim of this study is to assess the effect of progesterone elevation, measured on the day of human chorionic gonadotropin administration, on the pregnancy and live birth rate of patients attending the IVF clinic at King Faisal Specialist Hospital.

**Materials and Methods:** This study is a retrospective cohort study; 564 patients were divided based on the progesterone level on HCG administration day into 2 groups. The first group (A) (progesterone level <4.6 nmol/L) included 435 patients, the second group (B) (progesterone level > 4.7 nmol/L) included 129 patients. The pregnancy and live birth rate was compared between the two groups as a primary outcome.

**Results:** The overall pregnancy rate was 35.3% (n = 199), of which group A was (n = 166) and group B (n = 33). The Live birth rate was 25.2% (n = 110) in the low progesterone group and 12.4% (n = 16) in the high progesterone group. There was a statistically significant difference in pregnancy and live birth rate between the two groups with p value of 0.009.

**Conclusion:** Elevated progesterone level (> 4.7 nmol/L) has a negative impact on the pregnancy and live birth rate.

**Keywords:** IVF; hCG; Progesterone Elevation; Live Birth Rate

### Abbreviations

IVF: *In Vitro* Fertilization; HCG: Human Chorionic Gonadotropin; KFSHRC: King Faisal Specialist Hospital and Research Center

### Introduction

The introduction of *In Vitro* Fertilization to the medical community was considered an important landmark in medical history, since then it has been extensively studied and analyzed for its progression.

There were many factors and variables that were noted to affect the success rate of IVF. One of which was the level of progesterone on HCG day during ovarian cycle stimulation. Since 1991 many studies have debated the effect of progesterone elevation taken on HCG administration day on the live birth rate in IVF. Some studies have stated that it did not have any effect on the live birth rate [11], while many have illustrated that it did have a negative impact on the live birth rate [1-7].

Del Castillo, *et al.* [8] reviewed the source, mechanism, and the effect of elevated progesterone level during ovarian stimulation and the different strategies to prevent it. The review concluded that many studies used different cutoff points to establish the diagnosis of premature progesterone elevation. The cutoff points ranged ( 1.59 to 6.36 nmol/L) 0.5 to 2 ng/ml depending on the methods used to calculate it and also depending on the strength of the ovarian response during stimulation [4]. The possible reason for this discrepancy between studies was likely due to the fact that some centers used different methods to calculate the progesterone level [4].

The reason of premature progesterone elevation remains unclear; however, the review theorized that the risk factors for progesterone elevation are, ovarian hyper responsiveness, the use of high doses of gonadotropins during stimulation, and the duration of ovarian stimulation [4].

### Aim of the Study

The aim of this study is to assess the effect of progesterone elevation on the live birth rate of patients attending the IVF unit at King Faisal Specialist Hospital and Research Center, for infertility and pre-implantation genetic testing.

### Materials and Methods

This retrospective cohort study was conducted in the IVF clinic at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. All patients who underwent IVF/at KFSH RC for both PGT and infertility, had a serum progesterone level measured on HCG day, and reached the stage of embryo transfer were included in this study. The data was collected from January 2013 to December 2016.

A total of 1133 patients were identified from the KFSH and RC IVF database, 569 were excluded from the study since they did not fulfil the inclusion criteria; They did not complete the cycle, or did not reach the stage of embryo transfer, or did not have a progesterone level tested on HCG day. Therefore, a total of 564 patients who fulfilled the criteria were included in the study.

Patients fulfilling the inclusion criteria were stratified based on the progesterone level on HCG day into 2 groups. Both groups had an initial baseline pelvic ultrasound on day 2 of the menstrual cycle, this evaluation was to measure the antral follicular count, to exclude any endometrial anomaly or thickness, and to exclude ovarian cysts. In addition, the blood progesterone level on HCG day was measured (nmol/L). Furthermore, both groups had the same evaluation, management and testing throughout the stimulation and IVF procedure. The outcome of the pregnancy and the live birth rate were assessed as a primary outcome.

Statistical analysis was done using an electronic software (SPSS 20). Two tailed t-test for parametric data, Mann-Whitney test for non- parametric data, and Chi-squared test for binomial data were used. A P value of < 0.05 is considered statistically significant, logistic regression analysis was performed.

The study was reviewed and approved by the institutional review board at KFSH RC.

### Results

#### Demographics

The total number of patients retrieved from the IVF database were 564 patients (n = 564). The patients were divided based on progesterone level into 2 groups. The first group (progesterone level below 4.7 nmol/L (1.47 ng/mL)) included 435 patients, the second group (progesterone level at or above 4.7 nmol/L (1.47 ng/mL)) included 129 patients. Both groups had similar demographics except the number of oocytes obtained by ovum pickup and aspiration (Table 1). Patients with high progesterone had significantly higher number of oocytes (p = 0.0001).

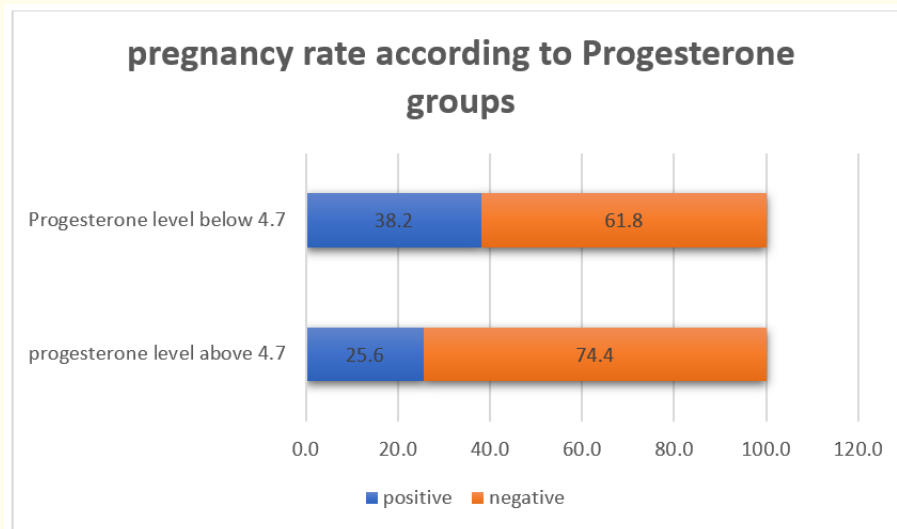
The logistic regression detected the two statistically significant variables that can predict pregnancy outcomes. While, the number of oocyte were found to be a predictor of positive pregnancy outcome (p value = 0.0001 and Odds ratio of 1.04), the progesterone level was a predictor of negative pregnancy outcome (p value of 0.002 and odds ratio of 0.93) (Table 1) Figure 2.

	Group 1 P (< 4.69) N = 435	Group 2 P (> 4.7) N = 129	P Value
Age (mean ± SD)	32.7 ± 5.0	32.4 ± 5.0	0.536
BMI (mean ± SD)	28.7 ± 4.8	28.0 ± 4.3	0.173
AFC (mean ± SD)	20.85 ± 13.7	21.45 ± 11.9	0.6
Number of oocyte (mean ± SD)	11.8 ± 7.1	14.55 ± 8.4	0.0001
Long protocol (%)	268 (61.6%)	66 (51.2%)	0.102
Short protocol (%)	20 (4.6%)	11 (8.5%)	
Antagonist Protocol (%)	146 (33.6%)	52 (40.3 %)	
Embryo transferred (mean ± SD)	1.86 ± 0.36	1.92 ± 0.35	0.1

**Table 1:** The demographics of the patients are presented as frequencies and (percentages) or mean ± standard deviation. The P value is the result of independent sample T test between the two groups or progesterone.

**Pregnancy rates**

The pregnancy rate was higher in the low progesterone group 38.2% (n = 166) compared to 25.2% (n = 33) in the high progesterone group, this difference was statistically significant (p = 0.009) (Figure 1).

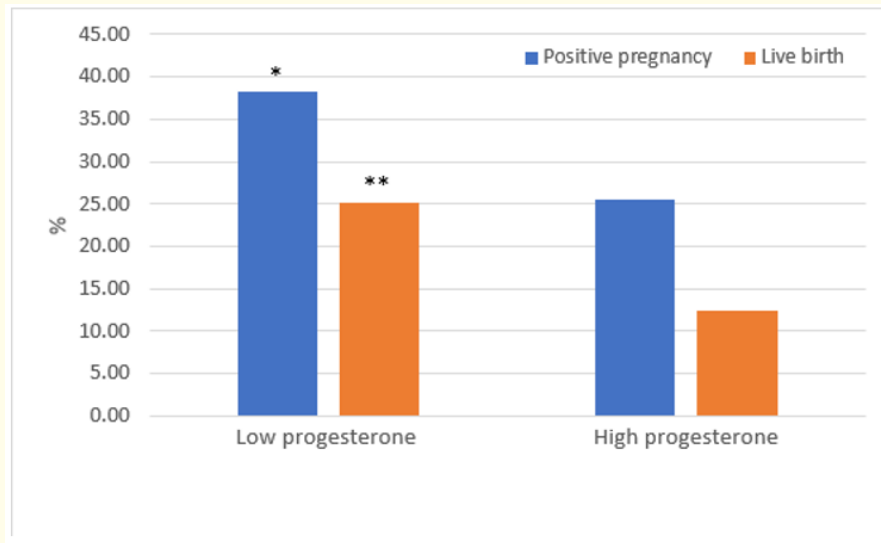


**Figure 1:** This figure depicts the percentages of pregnancy rates among the two main groups.

**Live birth rate**

The live birth rate was 25.2% (n = 110) in the low progesterone group and 12.4% (n = 16) in the high progesterone group. The difference was statistically significant (p = 0.003).

The miscarriage rate was found to be higher in the high progesterone group 51% vs 33%, p = 0.04.



**Figure 2:** Pregnancy and live birth rates in high and low progesterone group. \*p = 0.009, \*\*p = 0.003.

**Discussion**

Our study showed that an increased progesterone level above 4.7 nmol/L (1.47 ng/mL) had a negative impact on the pregnancy and live birth rates. Both groups had similar demographics and the same number of embryos were transferred. There has been a continuous interest since 1991 on the effect of elevated progesterone level on HCG day on the success of the IVF cycle. However, there has been no consensus on this issue. While a systematic review in 2013 concluded that embryos transferred to an endometrium that has been exposed to high levels of progesterone had a lower pregnancy rate than those exposed to low levels of progesterone [2]. More recent work by Martinez, *et al.* (2016) and by Wu, *et al.* (2019) continued this controversy [8,11]. Progesterone elevation only had a negative impact on low and intermediate ovarian responders but had no effect on high responders [8]. In our study, the patient’s average oocyte number were classified in the intermediate group, however they have a much higher BMI average and a totally different ethnic background than those presented in Wu, *et al.* paper. We had an average BMI of 28 kg/M<sup>2</sup> while in his population the average BMI was 21 kg/M<sup>2</sup> and this supports that his theory is applicable on different populations and different BMI. In the earlier meta-analysis, low and high responders had different cut off values of elevated progesterone [2] which might explain the contradicting results mentioned in different publications. The cut off levels of progesterone has been the subject of more discussion. some authors believe that only Progesterone levels above 1.5 ng/ml or 4.77 nmol/l had a negative impact on endometrial receptivity [4]. Hill, *et al.* concluded that an elevated serum progesterone level has a significant negative impact clinically on the live birth rates, therefore a progesterone level between 1.5 ng/mL to 2.0 ng/mL seems to be the best approach for clinicians to use. This was concluded by taking into account the sensitivity and specificity of each previously anticipated progesterone thresholds on the day of HCG administration [6,7].

The mechanism of negative effect of progesterone elevation has also been the subject of discussion. It has been suggested that high progesterone level induced endometrial maturation resulting in the narrowing of the period for implantation, thus; decreasing the pregnancy rates [1,3]. Other studies have noticed an increased rate of miscarriages even if it did not affect the pregnancy rate [10]. In our data we are seeing a negative effect on the pregnancy rate and a higher miscarriage rate with the rise of progesterone level.

It's not clear from our data if this is attributed to the quality of the embryo as was previously suggested by others [9], since we did not analyze the quality of the embryo in our study, however the average number of embryos were similar in both groups.

Although the regression analysis showed that the number of oocytes and progesterone level were independent predictors of pregnancy rate, our study showed that the group with the high oocyte number lost this benefit when the progesterone level was elevated. Our aim that this study can provide additional data that can be used to support future guidelines and can also be used as a basis for future studies, such as; the live birth rate of fresh cycles with high progesterone level versus frozen embryo transfer cycles (non-elevated progesterone level). In addition, the progesterone level might be used as a tool to predict partly the success of an IVF cycle in the future.

### Limitation of this Study

This study is a retrospective cohort study, a more randomized control trial is needed to establish the effect of the progesterone on the pregnancy rate.

### Conclusion

Our study concluded that the overall live birth rate was reduced when the progesterone level was above 4.7 nmol/L on HCG day. Therefore, further studies are needed to assess the factors causing this elevation. In addition, more studies are needed to evaluate the outcome and benefit of freezing the embryo which had progesterone levels above 4.7 nmol/L and transferring the frozen embryo on a new cycle (endometrium not exposed to high progesterone level).

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