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# Effect of High Progesterone Level on Day of Human Chrionic Gonadotropin Triggering on Pregnancy Rate in Frozen Embryo Transfer

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## ABSTRACT

**Background:** The endometrial morphology and receptivity, the embryo implantation procedure and the success rate of In vitro fertilization (IVF) are all significantly influenced by progesterone. The increased progesterone adversely affected the endometrial environment of fresh cycles, reducing the chance of pregnancy. However, the embryo quality is equally as crucial to the embryo-endometrial cross-dialog as endometrial receptivity, based on the rate of pregnancy in frozen cycles. **Objective:** The aim of the current study was to determine how Day of human chorionic gonadotropin (HCG) was impacted by early progesterone rise.

**Patients and methods:** A retrospective cohort research was conducted in the Obstetrics and Gynaecology Department of the Zagazig University Hospital. The study included records of all cases fulfilling the next inclusion criteria: Women with any type of subfertility who underwent frozen embryo transfer, Age less than 40 years old, gonadotropin-releasing hormone (GnRH) antagonist stimulation protocol in fresh Intracytoplasmic Sperm Injection (ICSI) cycle, Basal serum follicle stimulating hormone (FSH) concentration less than 15 mIU/mL. Over 5 years, 200 records were included as a comprehensive sample undergoing ICSI and subsequent frozen embryo.

**Results:** Using a threshold value for serum progesterone previously described of 1.5 ng/ml, 142 from 200 (71%) frozen embryo transfers that involved the transfer of embryos from low progesterone level ICSI cycles, and 58 from 200 (29%) frozen embryo transfers in which embryos from elevated progesterone level. The evolution of pregnancy outcomes following ICSI cycles demonstrated that there was no discernible difference between the groups with higher blood levels. **Conclusion:** Elevated progesterone levels on the day of HCG do not negatively affect pregnancy outcomes in frozen cycles triggering.

**Keywords:** Intracytoplasmic Sperm Injection, Transfer of frozen embryos, Progesterone, Embryo quality, Retrospective Cohort, Zagazig University.

## INTRODUCTION

Because Infertility is a growing medical and psychological concern issue for an increasing percentage of the population, governments all across the world are investing extensively in Assisted Reproductive Technology (ART).

Results of ART have improved because of better knowledge of male reproductive mechanisms, improvements made to gamete manipulation, gamete preservation, and solid knowledge about female reproductive systems [(1)].

Progesterone strongly affects endometrial morphology, receptivity, the embryo implantation process and In vitro fertilization (IVF)/ Intracytoplasmic Sperm Injection (ICSI) operation success rates [(2)].

Previously, it has been noted that blood progesterone levels rise on the day of the release of human chorionic gonadotropin (HCG) as a result of gonadotropin-releasing hormone (GnRH) agonists' inhibition of endogenous gonadotropins and antagonists, together with controlled ovarian stimulation (COS) cycles trigger.

Progesterone increase was discovered in 13-46% of IVF or ICSI cycles [(3)]. The receptivity of the endometrium is assumed to be affected by progesterone's activity on the tissue, which is regarded to have a detrimental effect on pregnancy rates. More specifically, the increase in progesterone likely accelerates the endometrium, slowing the development of the embryo and the responsiveness of the endometrium [(4)].

The quality of the embryo is equally crucial to endometrial receptivity. Another explanation is that the quality of the resulting oocyte or embryo is negatively impacted by the high amounts of progesterone. Uncertainty exists over how higher progesterone levels may impact the viability of embryos [(5)].

**Santos *et al.*** [(6)] showed that individuals with both low and high live birth rates (LBRs) had considerably lower (≤0.05 ng/mL) and high (≥1.5 ng/mL) levels of progesterone the day before the HCG trigger.

Because patients with high progesterone had reduced pregnancy chances with fresh embryo transfer IVF, doctors now keep an eye on progesterone levels throughout the late follicular phase or on the day of the HCG trigger IVF/ ICSI cycles than patients without elevated progesterone. It has been argued that a policy of keeping all embryos from a new IVF/ICSI cycle and replacing them in a subsequent round will help to mitigate the possible dangers of high progesterone on pregnancy [(7)].

The aim of the current study was to determine whether an early progesterone surge on the day of HCG triggering would have any bearing on the likelihood of conception in frozen cycles.



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## PATIENTS AND METHODS

A retrospective cohort research was conducted in the Obstetrics and Gynaecology Department of the Zagazig University Hospital. Over 5 years, a total of 200 records were included as a comprehensive sample undergoing ICSI and subsequent frozen embryo.

The study included records of all cases fulfilling the next inclusion criteria: Women with any type of subfertility who underwent frozen embryo transfer, Age less than 40 years old, GnRH antagonist stimulation protocol in fresh ICSI cycle, Basal serum follicle stimulating hormone (FSH) concentration less than 15 mIU/mL.

Exclusion criteria were GnRH agonist stimulation protocol, testicular sperm aspiration cases, uterine anomalies or malformations that affect embryo transfer, and patients with systemic diseases.

**Data Collection:**

**Tools of data collection**: Clinical (history and examination), laboratory investigations, radiological investigations (ultrasound), hysteroscopy and/or laparoscopy.

**All patients were subjected to the following:**

**Complete history taking:** Length of the infertility, Periodic history past pregnancies, Earlier forms of contraception. Sexual dysfunction, regular sex, prior hospital stays, previous surgeries, pelvic or abdominal pain, hirsutism, thyroid illness, galactorrhea, dyspareunia, Medication, allergies, a family history of infertility, developmental delays, and early menopause are among the risk factors, or congenital malformations Workplace dangers, smoking, and exposure to recognised environmental hazards.

**Physical Examination:** Body mass index (BMI), blood pressure, pulse the existence of any nodules or discomfort, thyroid enlargement breast features and a secretions evaluation, excess androgen symptoms, abnormalities or discharge in the vagina or cervical region, Tenderness in the abdomen or pelvis, tumours or enlargement of some organs size, location, and mobility of the uterus, lumps or soreness in the adnexa.

**Laboratory Investigations:** Basal serum FSH, LH, E2 and AMH on cycle day 3.

**Vaginal U/S examination:** For the ovaries, uterus, endometrium with AFC and ovarian volume.

**Controlled Ovarian Stimulation:** Patients who were presented with infertility and underwent ICSI were subjected to the following COS using a GnRH antagonist protocol, Women began with daily gonadotropin subcutaneous injections (hMG – IBSA) from menstrual cycle day two, doses ranged from 150 to 375 IU per day according to baseline characteristics as age, previous ovarian response, AMH, AFC and BMI.

Ovarian response was monitored by transvaginal ultrasound, on cycle day 8, follicles during COS were followed according to ovarian response and the GnRH antagonist (Cetrotide 0.25 mg daily S.C injection) was added when at least 1 leading follicle reached 14 mm in size.

The GnRH antagonist and Gonadotropin were repeated until the day of the HCG trigger, the ovarian response was carefully watched, when at least 2 follicles ≥17-18 mm in size, 10,000 IU of HCG trigger (Chorimon) was administered to stimulate the final oocyte maturation and trigger ovulation. E2 and Progesterone levels were monitored on day of HCG triggering, 34 to 36 hours later, women underwent TVS– guided oocyte retrieval, ICSI, and fertilization of the oocytes were done**,** After ICSI, the presence of 2 pro-nucli and the development of the embryo were monitored daily until the blastocysts were frozen.

**Frozen embryos transfer endometrial preparation:**

In artificially supplemented cycles, Down regulation of pituitary gland was done by using GnRH agonist (zoladex 3.6 mg) subcutaneous injection early follicular on day 1-5, 14 days later serum E2 and endometrium thickness were measured to ensure complete down regulation, if serum E2 ≤40 pg/ml down regulation was completely done, after complete pituitary down regulation estradiol valerate is started 0.2 mg for 5 days, thereafter 2 tablets from day 6 to day 9 and 3 tablets onward from day 10, then endometrium thickness was measured by using an ultrasonography examination (GE volason P8 ultrasound) if endometrium thickness was less than 8 mm increase dose of estradiol valerate for 4 tablets, if endometrium thickness was more than 8 mm, progesterone (prontogest 100 mg ampule intramuscular injection) was started daily. Thawed frozen embryo transfer was done 5 days later after progesterone supplementation started. Estrogen and progesterone were continued if pregnancy occurred up until 11 weeks of gestation, pregnancy test quantitative B-HCG was measured 14 days later.

**Measurements of Outcomes:**

**Main outcomes:** The ratio of clinical pregnancies to all begun, aspirated, or embryo transfer cycles is known as the clinical pregnancy rate (CPR). If a biochemical pregnancy is only recognized by the presence of HCG in the serum or urine and does not progress to a clinical pregnancy [(8)].

**Other outcomes**: totals of retrieved oocytes, the overall quantity of embryos, and the quantity of frozen embryos and the rate of blastocysts.

**Ethical Consideration:**

**This study was ethically approved by the Institutional Review Board of the Faculty of**

**Medicine, Zagazig University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.**

***Statistical analysis***

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS IBM Inc., Chicago, IL, USA) version 22.0 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Shapiro Walk test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/ Mann-Whitney U test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

**RESULTS**

**Patients were divided into two groups: *Group A:*** progesterone levels that are ≤1.5 ng/ml at day of HCG triggering and ***Group B:*** Those with progesterone level >1.5 ng/ml at day of HCG triggering.

**Table 1** showed that there was significant difference between both groups regarding to duration of infertility that was higher in group B than group A.

**Table (1):** Comparison between both groups regarding to demographic data and BMI.

| Variable | Group A Progesterone level ≤1.5 (N=142) | Group B Progesterone level >1.5 (N=58) | P-value |
|---|---|---|---|
| **Age (years)** | 28.2 ± 5.5 | 28.4 ± 4.5 | 0.84 |
| **BMI (kg/m2)** | 24.8 ± 4.3 | 24.4 ± 4.6 | 0.42 |
| **Basal FSH (IU/L)** | 6.9 ± 0.9 | 7.3 ± 1 | 0.45 |
| **Duration of infertility** | 5.01 ± 3.4 | 6.6 ± 4.3 | 0.006 |

**Table 2** showed that there were significant differences between both groups regarding to estradiol level and progesterone/estradiol ratio that were higher in group B than group A.

**Table (2):** Comparison between both groups regarding to estradiol level and progesterone/estradiol ratio at Day of HCG triggering.

| Variable | Group A Progesterone level ≤1.5 (N=142) | Group B Progesterone level >1.5 (N=58) | Statistical Analysis | P-value |
|---|---|---|---|---|
| **Estradiol level at Day of HCG Triggering (Pg/ml)** | 5272.9 ± 734.3 | 10230 ± 1621.4 | t= 3.11 | 0.002* |
| **Progesterone/estradiol ratio** | 1.67 ± 3.09 | 2.83 ± 4.03 | t= -3.2 | 0.001* |

Data are represented as number (%). Data are analyzed by independent student t test.

**Table 3** showed that there were significant differences between both groups regarding number of Oocyte retrieved and progesterone/ oocyte ratio.

**Table (3):** Comparison between both groups regarding to number of oocyte retrieved and progesterone/ oocyte ratio.

| Variable | Group A Progesterone level ≤1.5 (N=142) | Group B progesterone level >1.5 (N=58) | Statistical Analysis | P-value |
|---|---|---|---|---|
| **Number of Oocyte Retrieved** | 21.9 ± 11.2 | 35.5 ± 14.7 | t= -7 | <0.001* |
| **Progesterone/ oocyte ratio** | 0.20 ± 0.05 | 0.56 ± 0.09 | t= 54.1 | <0.001* |

**Table 4** showed that there were no significant differences between both groups regarding to rate (%) MI, MII, G.V and fertilization rate but there was significant difference between both groups regarding blastulation rate which was higher in group A than group B that means better oocyte development in group A.

**Table (4):** Comparison between both groups regarding to different parameters.

| Variable | Group A Progesterone level ≤1.5 (N=142) | Group B progesterone level >1.5 (N=58) | Statistical Analysis | P-value |
|---|---|---|---|---|
| MI% | 6.6 % ± 13.4 | 7.5% ± 19.4 | t= 0.39 | 0.69 |
| MII % | 75.3 %± 20.4 | 69.3 %± 22.4 | t= 1.2 | 0.21 |
| G.V % | 4.7 %± 7.1 | 7.2 %± 10.3 | T= -0.82 | 0.41 |
| **Blasulation Rate %** | 50%±7.6 | 34.8%±5.8 | t= 13.6 | <0.001* |
| **Fertilization Rate %** | 65.8%±24.1 | 65.9%±26.1 | t= -0.01 | 0.99 |

Data are represented as number (%). Data are analysed by independent student t test.

**Table 5** showed that the blastulation rate was significantly increased in the subgroup of patients with <18 oocyte retrieved with low progesterone levels, while in patients with >18 oocyte retrieved progesterone level has no effect.

**Table (5):** Blastulation rate percent versus number of Oocyte retrieved.

| Blastulation rate % | | | | | |
|---|---|---|---|---|---|
| Variable | | Group A Progesterone level ≤1.5 (N=142) | Group B progesterone level >1.5 (N=58) | T | P-value |
| **Number of Oocyte Retrieved** | **<18** | 60.1 ± 3.4 | 27 ± 1.8 | 2.5 | 0.03* |
| | **>18** | 22.9 ± 1.1 | 22.7 ± 1.6 | 0.05 | 0.95 |

Concerning to pregnancy outcome, **table 6** showed that there was no significant difference between both groups.

**Table (6):** Comparison between both groups regarding to the pregnancy outcome**.**

| Outcome | Group A Progesterone level ≤1.5 (N=142) | Group B Progesterone level >1.5 (N=58) | P-value |
|---|---|---|---|
| **Negative** | 80 (56%) | 28 (48%) | 0.53 |
| **Positive** | 62 (44%) | 30 (52%) | |

Data are represented as number (%). Data are analysed by Fischer's exact test.

**Table 7** showed that there was no significant relation between pregnancy outcome and number of oocyte retrieved.

**Table (7):** Pregnancy outcome grouped by different ovarian responses.

| Variable | | Pregnancy outcome | Group A Progesterone level ≤1.5 (N=142) | Group B progesterone level >1.5 (N=58) | Odd ratio (95%CI) | P-value |
|---|---|---|---|---|---|---|
| **Number of Oocyte Retrieved** | **≤10** | **Positive** | 4 (3%) | 0 (0%) | 0.07- infinity | 0.99 |
| | | **Negative** | 20 (14%) | 2 (3%) | | |
| | **11-19** | **Positive** | 12 (8%) | 2 (3%) | 1.2 (0.23-7.1) | 0.99 |
| | | **Negative** | 20 (14%) | 4 (7%) | | |
| | **≥20** | **Positive** | 46 (32%) | 28 (48%) | 0.9 (0.43-1.81) | 0.85 |
| | | **Negative** | 40 (29%) | 22 (39%) | | |

CI, confidence interval; OR, odds ratio. Data are expressed as ORs (95% CIs)

## DISCUSSION

Although GnRH analogues are frequently used in COS for IVF/ICSI cycles, an elevation in blood P4 levels is frequently noticed near the follicular phase's end. For a number of years, the clinical effect of premature progestrone rise has been extremely contentious, a study's showing that there is no connection between P4 levels and rates of conception [9], whereas some have noticed a negative impact on cycle results [10,11].

The majority of research to far have shown that increased P4 negatively affects the endometrial environment. However, there is little information on the impact on embryo quality and development currently available [12-15]. For recognizing early progesterone elevation, several centers used various cutoff values, with each clinic establishing their own threshold values for examination. Additionally, when the number of oocytes is stimulated cycles increased, early progesterone rise became increasingly common. Another study found that increasing progesterone did not reduce the likelihood of pregnancy in high-responder individuals, indicating that different progesterone cutoff values may be needed in these patients [16].

As a measure of an early progesterone surge, most studies used an absolute progesterone level on the day of hcg treatment, with different cut-off values from 0.8 ng/ml to 2.5 ng/ml.

This cut-off concentration was typically established in recently published research that utilized novel techniques for measuring serum progesterone at 1.5 ng/m [17]. Evidence demonstrating a notable variation between patients with blood progesterone levels above and below the cutoff in endometrial gene expression patterns of 1.5 ng/mL on the day after hCG treatment supports the choice of this cut-off.

One probable explanation for Higher serum progesterone levels have a detrimental influence on clinical and ongoing pregnancy rates following fresh embryo transfer due to the hormone's endometrial-damaging effects. Numerous researches have proven that there is such a connection [18].

Because patients with high progesterone had reduced pregnancy chances with fresh embryo transfer in vitro fertilization, doctors now keep an eye on progesterone levels on the day of the hCG trigger or throughout the late follicular phase (IVF)/ ICSI cycles compared to those of patients with normal levels of progesterone. A policy of preserving all embryos has been implemented to mitigate the possible effects of high progesterone on pregnancy from a new IVF/ICSI cycle and replacing them in a subsequent round has been suggested [19].

In this retrospective cohort study, we sought to determine how well ICSI results in frozen cycles might be predicted by blood P4 levels on the day of hCG administration (hCG-P4).

A total of 200 patients were enrolled, and they were split based on the amounts of serum progesterone, into 2 groups: Group A (142 patients), which included those with serum hCG-P4≤1.5 ng/ml and Group B (58 patients) including patients with serum hCG-P4> 1.5 ng/m.

Using a GnRH antagonist strategy, control ovarian stimulation was administered to all patients.

Age, BMI, and baseline FSH comparing the 2 groups in this investigation, not substantially, however duration did the 2 groups differ greatly from one another. The greater rate of infertility in people with high progesterone levels could be attributed to the affection of oocyte quality, embryo development or implantation rate in this group **(Table 1).**

Also, regarding estradiol levels and the progesterone/estradiol ratio, which was higher in the individuals with high progesterone levels, significant variances were between the 2 groups **(Table 2).**

The higher estradiol level which was found in high progesterone group may be due to production of high progesterone per follicle or possibly because there are more follicles in this group.

Similarly as a study conducted by **Hung *et al.*** [20] that found significantly higher estradiol level and P/E2 ratio compared to individuals with low progesterone levels in people with high levels of progesterone which explained by high P4 levels occurred when the number of follicles is increased and E2 levels are high.

We found that patients with high progesterone levels had significantly more oocytes retrieved, indicating that more follicles are responsible for producing more progesterone.

Additionally, we discovered that the progesterone/oocyte ratio was much greater in patients with high progesterone levels, which may indicate that the high progesterone level is caused by enhanced progesterone production per follicle rather than just an increase in follicle number **(Table 3).**

Similarly as a study conducted by ***Silverberg et al.*** [21] who used a modified natural cycle frozen-thawed embryo transfer to examine the effects of high hcg-p4 levels on ART outcomes found that patients with high progesterone levels had significantly greater oocyte recovery and progesterone/oocyte ratio.

Also **Lahoud *et al.*** [22] who assessed a correlation between hcg-p4 levels Live birth rate using a GnRh agonist downregulation Frozen-thawed embryo transfer occurs in modified Patients with high progesterone levels had considerably increased oocyte retrieval in artificial cycles, which may have been a confounding factor. This result confirms the physiological theory that infertility is caused by an overall increase in the number of follicles generated.

In current study, there were no notable variations between the 2 groups regarding to MI, MII, G.V and fertilization rate which may be reflect that high progesterone level has no effect on oocyte maturity or fertilization rate **(Table 4).**

As a retrospective study by **Berger *et al.*** [23] included 234 patients who later underwent frozen embryo transfers discovered that late follicular progesterone level not affects oocyte maturity**.**

However, a retrospective analysis by **Woo *et al.*** [24] indicated found the maturity rates of oocytes were significantly higher in patients with high blood P4 levels, and that the maturation rates were inversely correlated with hcg-P4 levels. The study, which used 982 completely frozen IVF procedures (IVF) cycles employing GnRh antagonist down regulation.

Also the same study evaluated the relationship between hcg-p4 levels and fertilization rates which found lower rates of fertilization with high progesterone level group.

We found the higher blastulation rate in the low progesterone level group, which indicates that high progesterone level; is a substantial difference between the two groups affect embryo development **(Table 4).**

On the other hand the study done by **Vanni *et al.*** [25] embryo development on the day of oocyte maturation in GnRH antagonist frozen thawed ET cycles was identical but was not sufficiently powered to detect a difference in blastocyst quality between groups of patients receiving a freeze-all treatment with or without increased progesterone.

By further analysis of blastulation rate according to number of oocyte retrieved, we found that blastulation rate was significantly increased in subgroup of patients with <18 oocyte retrieved with low progesterone level group this mean that high progesterone level affect blastulation rate only in subgroup of patients with <18 oocyte retrieved **(Table 5).**

This result as in a study done by **Rose *et al.*** [26] who assessed the blastulation rate in modified artificial frozen-thawed embryo transfer cycles and how it was effected by oocyte retrieved**,** found that the blastulation As more oocytes were extracted, the rate tended to drop. The blastulation rates of groups of cycles where 1 to 5, 6 to 7, and more than 18 oocytes were retrieved differed considerably from the overall group.

On the other hand the retrospective study by **Kofinas *et al.*** [27] which included 238 Patients who underwent frozen ET after preimplantation genetic testing discovered that increased P4 levels more than 1.5 ng/ml on hCG day had no discernible effect on the quantity of oocytes harvested or the quantity of embryos accessible for biopsy.

In our study, only 1 frozen cycle transferred per patient due to time limitation and found that between the 2 groups, there was no discernible change in the pregnancy rate **(Tables 6 and 7).**

This means that the pregnancy rate was unaffected by elevated progesterone levels, but the cumulative pregnancy rate may be affected which was not in the scope of this study.

As a study done by **Lahoud *et al.*** [22] that revealed frozen embryos from cycles with high pre-HCG progesterone exhibited similar live birth rates to patients with frozen embryos from conventional cycles. This would support the idea that endometrial receptivity exists is more likely to be decreased by premature progesterone exposure than it is by the quality of the embryos.

However, in a study conducted by **Groenewoud *et al.*** [28] they looked at how greater progesterone levels affected modified natural cycle frozen-thawed embryo transfer cycles and discovered that patients who had modified natural cycle frozen-thawed embryo transfer had higher pregnancy rates are not significantly affected.

Also **Racca *et al.*** [29] found that the lower embryo quality scores which have been linked to cycles did not result in a worse live birth rate in freeze all cycles despite having higher late follicular phase progesterone levels.

## CONCLUSION

The effect of high progesterone on embryonic development did not affect the pregnancy rate, but the cumulative pregnancy rate may be affected, which was outside the scope of this study. In addition, the effect of high progesterone on oocyte quality did not affect the pregnancy rate, but it did affect the blastulation rate in the subgroup of patients with 18 oocytes retrieved in frozen cycles. To determine the impact of high progesterone levels on the hcg triggering day on the cumulative pregnancy rate in frozen cycles, additional research is necessary.

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