Original article:

PROGESTRONE LEVEL ON THE DAY OF HCG TRIGGER AND IVF OUTCOMES: AN OBSERVATIONAL STUDY

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Abstract:

Aim: To Evaluate Serum Progestrone levels on the day of HCG trigger and its relation to IVF/ICSI outcome

Method: Study of 120 IVF/ICSI cycles where serum progesterone was measured on the day of hCG trigger. Both stimulation protocols i.e. GnRH agonist and antagonist protocols were included for analysis. Pregnancy rates were compared between those cycles with progesterone levels greater than or equal to 1.5ng/ml versus those below 1.5ng/ml.Cycles with premature LH surge were excluded.

Results: Serum progesterone level was measured on the day of hCG trigger in 120 patients of IVF/ICSI cycles in the ten month period between September 2013 and November 2014 in NIMS Infertility and Reserach Centre, Jaipur

Ongoing pregnancy rates were inversely associated with serum progesterone levels on the day of hCG . Patients with serum progesterone levels ≤1.5 ng/ml had significantly higher ongoing pregnancy rates than those with progesterone levels >1.5 ng/ml (46.6 % Vs 17.24%.; P = 0.028).

Conclusion: Pregnancy rates were higher in IVF/ICSI cycles where serum progesterone was less than 1.5ng/ml when compared with cycles where progesterone levels were greater than 1.5ng/ml on the day of hCG trigger.Our data demonstrate no deleterious effect of elevated P on embryo quality. However, high serum P adversely affects implantation and pregnancy rates.

Keywords: Progestrone , HCG trigger,ICSI

Introduction

The impact of premature serum progesterone elevation at the end of the follicular phase under controlled ovarian stimulation (COS) cycle `for in vitro fertilization (IVF) is still debated. While several studies reported lower pregnancy rates in patients with high progesterone concentration on the day of human chorionic gonadotropin (hCG) administration, one found a favourable effect on pregnancy outcome and others failed to demonstrate any association . Although the mechanism by which premature serum progesterone elevation might alter the embryo transfer outcome is still unclear, there are accumulated data suggesting a negative impact on endometrium Elevated progesterone levels might induce premature endometrial maturation and, as a consequence, earlier opening of the implantation window that leads to asynchronization of the crosstalk between embryo and endometrium.[1]. During controlled ovarian stimulation (COS), progesterone levels rapidly increase following the administration of human chorionic gonadotrophin (hCG) that is given to induce final oocyte maturation . However, premature luteinizing hormone (LH) surges, caused by the modulatory actions of estradiol (E_2) levels induced by gonadotrophins, have led to premature luteinization and cancellation of treatment cycles in patients undergoing in vitro fertilization (IVF) The majority

of studies that failed to demonstrate an association between serum progesterone levels and pregnancy rate used a threshold value of 0.9 ng/ml, which was mostly chosen arbitrarily without performing a trend analysis to identify an association between progesterone levels and pregnancy .[3]

. Here is a study that investigated the relationship between serum progesterone levels on the day of hCG administration and the probability of ongoing pregnancy, in an unselected population of women undergoing COS for IVF/ICSI–ET.

Aims and Objectives:

The main objective was to determine the relationship between serum progesterone levels on the day of hCG administration and the ongoing pregnancy rate.

Materials and Methods Study population and design

This was a non-interventional, retrospective, observational, single-centre cohort study of patients undergoing routine practice. Patients were treated at a single-centre at the National Institute of Medical Sciences(NIMS) Medical College and Hospital Fertility & Research Centre, Jaipur, Rajasthan , during the period September 2013 to July 2014..

A total of 120 IVF and/or ICSI–ET cycles were included in which serum progesterone levels were determined on the day of hCG administration. Patients underwent COS using either a GnRH agonist long protocol (n =90) or a GnRH antagonist daily protocol (n =30) for pituitary down-regulation. Ovarian stimulation was carried As this was a retrospective study, no specific criteria for selection of stimulation protocol were defined; the choice of protocol was made on a case-by-case basis according to patient characteristics and clinician preference.

The only exclusion criteria was ....

Ovulation induction:

Ovulation induction was performed using a routine protocol of gonadotropin-releasing hormone analog. GnRh long protocol and antagonist protocol were used for ovulation induction. In this,first down-regulation with a GnRH analogue (Luperolin) which was administered 0.5 cc subcutaneously from the 21st day of the previous menstrual cycle was done. When pituitary suppression was achieved (on the second day of the menstrual cycle follicle-stimulating hormone (FSH) $\leq$ 5 IU/ml, LH $\leq$ 5 IU/ml, progesterone $\leq$ 1 ng/ml, estradiol $\leq$ 50 pg/ml), its dose was reduced to 0.2 cc and 150-225 IU human menopausal gonadotropin (Menopur, Ferring, Germany) or 150-225 IU recombinant FSH (Gonal-F, Sereno, Italy) was administered intramuscularly from the 2nd day of the menstrual cycle daily. After 3 or more follicles had reached 17 mm in diameter,10,000 IU human chorionic gonadotropin (Pregnyl, Daropakhsh, Iran) was used to induce oocyte maturation. After 34-36 hours ,oocytes aspiration was done by transvaginal ultrasound guidance . Then IVF or ICSI was done according to the requirement. Uterine embryo transfer was performed 48-72 hours after oocyte retrieval. Beta hCG test was performed after fourteen days. Clinical pregnancy was defined as the presence of at least one gestational sac with detectable fetal heart activity by transvaginal sonography

The starting dose of gonadotrophins were indivisualized for each patient according to age, basal LH, basal FSH levels, antral follicle count, BMI and previous response to COS. Dose adjustments were performed according to ovarian response, which was monitored by means of vaginal scans and E_2 determinations. As a part of routine clinical practice, a single determination of serum progesterone was performed on the day of hCG administration, which was indicated when

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three or more follicles reached mean diameter of 18 mm.

The ongoing pregnancy rate was defined as the presence of cardiac activity on ultrasound. A started cycle was considered when patients had their first injection of gonadotrophins.

Progesterone measurement

Serum progesterone levels were measured on the day of hCG administration. Samples were tested with a microparticle enzyme immunoassay Axsym System (Abbott Cientifica S.A., Madrid, Spain), which had a sensitivity of 0.2 ng/mlBesides the Result:

internal quality control checks performed daily by the institution laboratory, caliberation checks were also done.

Statistical Analysis: An elevated P level was arbitrarily defined as 1.5 ng/ ml; this cut-off facilitated comparison with other reported data. Comparisons were made by Student's t test and chi square analysis where applicable; $P<0.05$ was considered statistically significant. The online program 'Graphpad Instat' was used for analysis of data. Results are interpreted as mean +/- standard error (SE). '

Table no. 1. Distribution of Stimulation cycle

Stimulation protocol	No. Of cycles
1. GnRh agonist(Long and short protocol)	90
2. Antagonist	30

Out of 120 stimulation cycles, 90 cycles were of GnRh agonist long and short protocol both ,and 30 cycles were of antagonist protocol.

Table no.2. Distribution of IVF /ICSI cycles

Procedure	No. Of cycles
IVF	30
IVF+ICSI	90

In the given study, IVF+ICSI were done in 90 cycles and IVF alone was done in 30 cycles.

Table no. 3. Cycle characteristics of study group

	Group A	Group B	P value
Progestrone level	<=1.5ng/ml	>1.5ng/ml	
No. Of embryo transfer cycles	81	39	
Mean age	31.3	33.2	P=0.009
Duration of infertility	7.3	6.3	P=0.1
No. Of oocyte retrieved	8.7	12.8	P<0.005
Grade 1 or 2 embryos	78%	64%	P=0.2
Clinical pregnancy rate	46.6% (26)	17.24% (5)	P=0.028

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Patients were divided into two groups according to the level of P on day of hCG administration. Group A comprised 81 cycles in which the P level was less than or equal to 1.5 ng/ml and group B comprised 39 cycles with P levels more than 1.5 ng/ml. Mean age was significantly higher in group B than in group A (31.3 years vs. 33.2 years; P value =0.009). No differences were found between the two groups in the etiology of infertility, the protocol of controlled ovarian stimulation, or embryo quality (grade 1 and 2 embryos: 78% vs. 64%; p value 0.2). In cycles with lower P levels, the clinical pregnancy rate was significantly higher (46.6% vs. 17.24%;P value =0.028). Furthermore we found an inverse relationship between P level and pregnancy rate

Discussion:

The effect of plasma progestrone on IVF cycle is controversial issue.Dirnfeld et al concluded that pregnancy rate per embryo transfer was 53% (15/28) in group I and 10% (8/80) in group II (P < 0.025). Of 15 pregnancies achieved in group I, 14 were ongoing pregnancies, compared to 4 of 8 ongoing pregnancies in group II (P <0.03).[4]Silverberg KM et al suggested serum progesterone (P_4) levels greater than 2.86 nmol/L (0.9 ng/mL) on the day of hCG administration was reportedly associated with decreased pregnancy rates in in vitro fertilization/embryo transfer (IVF/ET) cycles.Serum P_4 measurement done .Clinical pregnancies occurred in 9 of 18 patients in group I (P_4, <1.27 nmol/L) compared to 11 of 81 patients in group II (1.27 < P_4 < 2.86 nmol/L; P = 0.001) and 0 of 14 patients in group III (P_4, ≤2.86 nmol/L) (P = 0.001).[5] Schooldraft and colleagues were the first to report low pregnancy rates in women with progeatrone >0.5.[7]Varoius studies done and concluded that progestrone levels were responsible for reduction in endometrial receptivity rather than oocyte or embryo quality.[5,8,9,10]

In a study, 655 IVF-ET cycles, the thresholds were set to 2.0 and 2.5ng/ml, the clinical pregnancy rate was lower in the elevated P4 group (41.6% and 37.3%) than in control (46.3% and 46.0%), but the difference were not statistically significant (p=0.197and p=0.144). In our study , this difference was statistically significant.[6]

In our study the pregnancy rate was significantly lower in group B with progestrone more than 1.5 ng/ml,furthermore the average age of the patient in this group was higher as compared to low progestrone group.The number of oocytes retrieved were more in high progestrone group but no statistically significant difference was found on embryo quality, thus by above findings it was suggested that the elevated Progestrone levels might affect the synchrony of implantation processes, namely apposition and adhesion. In mice, P administration caused closure of the uterus with only primary apposition, and estrogen supplementation was essential for successful implantation [11]

Now a days , advances have been made to assess the reason for implantation failure and one of the recents which favour progestrone role for implantation is endometrial pinopodes. These are flower like projactions which appears in endometrial cavity at the time of implantation and is affected by increased progestrone levels. Accumulating evidence supports their clinical use as a marker to assess endometrial receptivity. Pinopode appearance, loss of steroid receptors and maximal expression of a(v)b(3) integrin, osteopontin and leukaemia inhibitory factor and receptor have been demonstrated in the same biopsy, showing a consistent association of pinopode appearance and other receptivity changes.[12]

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