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Original Research Article

Day-2 serum progesterone level and IVF/ICSI outcome: a comparative study

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ABSTRACT

Background: Purpose of this study was to evaluate the in vitro fertilisation outcome in patients having normal or elevated day-2 serum progesterone level undergone IVF by using GnRH antagonist.
Methods: A retrospective study conducted in Institute of Reproductive Medicine, Chennai during January 2013 to March 2014. According to patient's Day-2 serum progesterone level the total no of cases (N=151) were divided into two groups group-1 (N=116) with progesterone value ≤1.5ng/ml and group-2 (N=35) with progesterone value>1.5ng/ml. Ovarian stimulation was started with recombinant FSH on day 2 and GnRH antagonist injections started from day 6 of stimulation. Total dose of gonadotropins, days of gonadotrophin injections, no of eggs collected, Clinical pregnancy rate and live birth rate were compared between two groups.
Results: Two groups were similar with regards to age, BMI, days of gonadotrophins and total doses of gonadotrophins. Incidence of elevated P level was 23.17%. Total pregnancy rate was 36.42%. A non-statistically-significant difference was observed in clinical pregnancy (37.06% vs 34.28%) and live birth (32.75% vs 28.57%) between the normal and elevated progesterone groups.
Conclusions: Elevated day-2 serum progesterone level was associated with lower clinical pregnancy rate but it was not statistically-significant.

Keywords: Clinical pregnancy, Gonadotrophins GnRH antagonist, Intracytoplasmic sperm injection, Live birth, Progesterone

INTRODUCTION

Determination of plasma progesterone was a complementary tool before the introduction of GnRH analogues in ART cycles to detect premature endogenous LH surge. Current use of GnRH agonist and antagonist effectively prevent the premature LH surge thus limited the determination of progesterone level.[1] During pituitary desensitisation estimation of progesterone level give worth value about the activity of corpus luteum. Early follicular phase cyst detection at ultrasound needs estimation of plasma progesterone to know the functional nature of the cyst.[2] Some report short term GnRH agonist protocol and GnRH antagonist protocol used to prevent premature LH surge also elevate progesterone at the time of stimulation.[3-5] Hence Delaying administration of gonatotrophin for 1-2 days usually normalize progesterone value in patients.[3] It has been recommended to measure plasma level before starting stimulation in GnRH antagonist protocol to postpone if progesterone values are >1.4ng/ml.[3] Some reports showed that increased plasma level progesterone during follicular phase may be adversely affect follicular development, oocytes qualityand success rate of IVF cycles but other studies showed no effect.[6-8]

Purpose of this study was to evaluate the in vitro fertilisation outcome in patients having normal or elevated day-2 serum progesterone level undergone IVF by using GnRH antagonist.

METHODS

This retrospective study was conducted in Institute of reproductive medicine and women's health unit of madras medical mission during the period Jan2013 to March 2014. Patients were considered once in the study. Patients those were <39 years, not received hormonal treatment in the cycle preceding treatment with fresh embryo transfer were included in the study. Patients those were >39 years, previous history of hormonal treatment in the cycle preceding stimulation and frozen embryo transfer were excluded from the study. All patients underwent day 2 serum estradiol, luteinising hormone and serum progesterone and antral follicle count before stimulation. Ovarian stimulation was started with recombinant FSH on same day and GnRH antagonist injections started from day 6 of stimulation. Final oocyte maturation was induced by administrating inj human chorionic gonadotrophin when at least 3 follicles of ≥18 mm in size during trans vaginal ultrasonography. Oocytes retrieval was performed 35 hours after HCG administration and ICSI was done in all patients. Embryo transfer was done on day 2 or day 3 after retrieval with good quality of Grade A embryo. Luteal support was supplemented with vaginal administration of natural micronized progesterone 400mg twice daily dose from day of egg collection till 12 weeks of gestation. According to the Day-2 serum progesterone level the total no of cases (N=151) divided into two groups normal P level (≤1.5 ng/ml) group (N=116) and elevated P level (>1.5 ng/ml) group (N=35) respectively. Total dose of gonadotropins, days of gonadotrophin injections, no of eggs collected, positive pregnancy rate, clinical pregnancy rate and live birth rate were compared in between two groups. Statistical analysis was done by t-test, mann-whitney test and chi-square test.

RESULTS

Total 151 cases were included in the study during that period and according to their D2 serum progesterone they were divided into two groups. Out of 151 cases 116 patients had in normal P level (≤1.5 ng/ml) and 35 patients had elevated P level (>1.5 ng/ml), (N=35). Table 1 shows the demographic distribution of age, BMI and type of infertility in between two groups. The difference in BMI was statistically significant in between two groups.

Table 1: Demographic distribution in between 2 groups.

Parameters	P≤1.5, N=116	P>1.5, N=35	P value
Age	31.46±4.129	32.69±5.465	0.156 NS
BMI	27.909±4.95	24.858±4.6	0.001
Primary infertility	93	27	0.697 NS
Secondary infertility	23	8	

Table 2: Stimulation characteristics in between 2 groups.

Parameters	P≤1.5, N=116	P>1.5, N=35	P value
Antral follicle count	13.40±5.807	10.43±6.459	0.011
Total dose of stimulation	3020±1075.86	3266.07±1069.469	0.238
Total days of stimulation	10.06±1.301	9.77±1.215	0.244
E2 on day of triggering	2020.94±1090.882	1870±1154.966	0.481
No of oocytes retrieved	7.54±3.74	6.26±4.075	0.083
No of embryos transferred	3.03±0.867	2.86±1.216	0.002

Table 3: Clinical outcome between two groups.

Outcome	P≤1.5, N=116	P>1.5, N=35	P value
β HCG negative	61 (52.6%)	19 (54.3%)	NS
Positive β HCG	55 (47.4%)	16 (45.7%)	NS
Clinical pregnancy	43 (37.06%)	12 (34.28%)	NS (0.362)
Live birth rate	38 (32.75%)	10(28.57%)	NS (0.364)

Table 2 shows the comparison of stimulation characteristics in between 2 groups. No of antral follicle count was statistically significantly higher in group 1 when compared to group 2. Table 3 shows no statistically significant difference in the clinical pregnancy rate and live birth rate between two groups (p value-0.362).

DISCUSSION

Elevated early follicular phase progesterone levels in menstrual cycle indicates an inefficient luteolysis and its mechanism is still remain unclear. During early follicular phase adrenal gland contribute for progesterone secretion but late follicular phase progesterone is secreted mainly

from ovary.[9] Our retrospective study showed no statistically significant difference between clinical pregnancy rate and live birth rate between normal and elevated day 2 serum progesterone level may be due to limited number of cycles. Some reports showed that increased plasma progesterone level during the early follicular phase may adversely affect follicular development, oocyte quality and success rate of the cycle.[7,8] Keck C et al demonstrated the incidence of elevated progesterone level on early follicular phase was 11.4%.[10] But in our study the incidence was 23.17%.

As advanced ovarian age causes shorter follicular phase and abnormalities in luteal phase function which may cause elevated p4 level due to insufficient luteolysis.[4,11] In our study, we have not found any statistically significant difference in age between two groups. Sims et al, using a short GnRH agonist protocol, showed that elevated progesterone levels during cycle days 2-6 were associated with a higher requirement for gonadotropins, lower peak E2 concentrations and fewer mature oocytes retrieved.[8]

In the present study, there was no significant difference found in terms of age, type of infertility, duration of stimulation, total dose of gonadotrophins and triggering estradiol level and number of follicles on the day of HCG administration between the two groups. No significant difference found in no of eggs collected. But a statistically significant difference found on antral follicle count.

In kolibianakis et al prospective study initiation of stimulation was postponed for 1-2 days in elevated progesterone group and started if the progesterone value was normal. In Blockeel et al prospective study in case of elevated p progesterone-group GnRH antagonist was administrated for three consecutive days for the normalisation of p-value. Inspite of intervention in GnRH antagonist cycle by Kolibiankis et al and Blockeel et al in patients with elevated early follicular progesterone level the ongoing pregnancy rate was lower in elevated group comparing to normal progesterone group.[3,4] A randomized controlled trial by Hamdine O et al on comparison of early versus late initiation of GnRH antagonist in elevated p group also demonstrated no statistically significant difference in ongoing pregnancy rate.[12]

A prospective interventional study and systemic meta-analysis review by Hamdine and nicks et al found that early elevated progesterone levels were associated with lower ongoing pregnancy rate in GnRH antagonist but the result was not statistically significant.[13] No differential impact of early or late GnRH antagonist initiation on the effect of elevated or normal progesterone on ongoing pregnancy rate was observed. In our study, we also found lower pregnancy rate in elevated p group (37.06 Vs 34.28% p value-0.362) but it was not statistically significant without any intervention.

CONCLUSION

Based on systemic review and meta-analysis elevated early follicular phase progesterone levels the ongoing pregnancy rate. As the incidence is low and there is lack of effective treatment for elevated progesterone level the routine screening for early follicular phase progesterone is not recommended.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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