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Original Article

Progesterone level significance in agonist versus antagonist protocols

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ABSTRACT

Objective: to evaluate the impact of serum progesterone level on the clinical outcome across agonist & antagonist protocols.
Design: retrospective cohort study.
Setting: IVF unit at Prince Sultan Military Medical City, Riyadh, KSA.
Material & Methods: A total of 943 cycles were included in the analysis, 605 long agonist protocol cycles, 227 antagonist protocol cycles & 101 short agonist protocol cycles reaching the stage of embryo transfer between November 2012 and March 2015.
Main outcome: clinical pregnancy and miscarriage rates.
Results: Number of retrieved, mature and fertilized oocytes, plus transferred embryos were lowest in the short protocol. Clinical pregnancy rate was the lowest in the short protocol and miscarriage rate was similar in all protocols. Setting progesterone cut off level of >1.5 nmol/L in the agonist cycles, high progesterone groups did not show difference in clinical pregnancy or miscarriage rates. In the short protocol, the group with high progesterone level had higher number of frozen embryos. In long protocol, high progesterone level group showed higher number of fertilized oocytes. A level of >2 nmol/L was set in the antagonist protocol. High progesterone group had lower clinical pregnancy rate and similar miscarriage rate, despite having higher number of fertilized oocytes and better quality of embryos.
Conclusion: high progesterone level did not affect clinical pregnancy or miscarriage rates in all protocols except in the antagonist protocol where it affected the clinical pregnancy rate adversely.

1. Introduction

Progesterone (P4) plays an important role in the menstrual cycle, particularly for pregnancy implantation and progression; however, its role in controlled ovarian stimulation cycles (COS) remains controversial [1–5].

Premature progesterone rise (PPR) is defined as P4 elevation on the day of human chorionic gonadotrophin (hCG) administration. Thus, authors reported that modest pre-ovulatory increase in serum P4 levels was associated adversely with pregnancy rates and had higher incidence of pregnancy loss. The pathogenesis and effects of PPR remain debatable [6–9]. Several studies have evaluated the impact of PPR at the time of hCG trigger in COS, with conflicting results; while some investigators have reported that elevated P4 negatively impacts pregnancy rates, others have failed to do so [10–12].

PPR may have an adverse effect on endometrial receptivity explained by premature endometrial maturation leading to embryo-endometrium dys-synchrony and altered gene expression [1,3,9,13–15]. Patients who respond robustly to COS have higher E2 and P4 levels, impairing the receptivity of the endometrium due to PPR [1].

The PPR frequency in ovarian stimulated cycles varies. Although gonadotrophin releasing hormone (GnRH) agonists and antagonists prevent or decrease PPR frequency, yet it still occurred in some patients [8]. In patients treated with a GnRH agonist, it was estimated in a study to occur in up to 35% of cycles and up to 38% of GnRH antagonist cycles [10,13]. Moreover, some studies have found that it was affecting the clinical outcomes negatively in GnRH antagonist cycles but not in GnRH agonist cycles [2,10,16].

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Some studies showed a negative impact of PPR on the hCG day, in terms of embryo quality and cumulative live birth rate (LBR), regardless of the ovarian response [2,4,17]. Others linked the negative impact on clinical outcomes to cleavage embryo transfer but not to blastocyst or frozen-thawed embryo transfer [2,6,7,14].

Strategies proposed to overcome the PPR negative impact by some studies is to freeze all embryos and transfer in a frozen cycles [3,7,10,12,13,17]. Another suggested solution is to transfer day 5 blastocyst (D5-ET) to improve the clinical outcome [6,7,10,17].

The aim of our study is to evaluate the impact of serum P4 level on the day of triggering on the probability of pregnancy outcome across GnRH agonist & antagonist IVF protocols.

2. Materials and method

After obtaining approval from Prince Sultan Military Medical City Research Ethics Board, the files of all the patients who reached the stage of fresh embryo transfer were manually reviewed from November 2012 till March 2015. A total of 943 cycles were included in the analysis, 605 long GnRH agonist protocol cycles, 227 GnRH antagonist protocol cycles & 101 short GnRH agonist protocol cycles. The protocol and type of gonadotropins were decided by the treating physician before starting the stimulation, according to the department policy for age, follicle stimulating hormone (FSH), antral follicular count (AFC) & previous response.

COS was performed using rFSH (Gonal f or Puregon, Merck) or human menopausal gonadotrophin (HMG) (Menogon, Ferring). In the long protocol, GnRH agonist is started from cycle day 21 before stimulation (Decapeptyl 0.1 mg/day, IPSEN) while in the short protocol (Decapeptyl 0.05 mg/day) is started on the day of stimulation. Another protocol used was the fixed GnRH antagonist protocol (Cetrotide 0.25 mg/day, Merck) added on day 6 of stimulation. When two or more leading follicles reached a mean diameter $\geq$ 1 8 mm or three or more reached $\geq$ 17 mm, 5–10,000 IU hCG was injected. The oocytes were retrieved 36 h after the hCG injection (Pregnyl, Merck).

After IVF or ICSI, embryos were transferred 2–5 days after oocyte retrieval. Only 2 embryos were transferred, unless the patient was $\geq$ 38 years, nulliparous, undergoing her 3rd ET or sperm were obtained by TESA; then 3 embryos will be transferred. Luteal phase support using either a twice daily dose of 400 mg of progesterone pessaries (Cyclogest, L.D.COLLINS & CO.) or 8% progesterone gel (Crinone, Merck), was started on the day of oocyte retrieval until the pregnancy test, or up to 12 weeks if the patient got pregnant. Pregnancy test was considered positive if the serum hCG was $\geq$ 10 ml IU/ml, 12 days after embryo transfer. Two weeks after a positive hCG, transvaginal ultrasonography was performed to confirm the presence of an intrauterine pregnancy and to identify the number of gestational sacs and the fetal viability.

Female age, number of stimulation cycle, BMI, parity, cause of infertility, AFC, basal FSH, male age, stimulation parameters including total dose of the gonadotropins used and duration of stimulation, were collected. On the hCG trigger day the following were collected: number of follicles $\geq$ 14 mm, endometrial thickness and quality (grade 1 was the best and grade 3 was the worst), E2 and P4 levels. Grade 1 endometrium is when the endometrium shows a triple line pattern comprising a central hyper-echoic line surrounded by two hypo echoic layers, grade 2 is when the endometrium has an intermediate *iso*-echogenic pattern with the same reflectivity as the surrounding endometrium and poorly defined central echogenic line and grade 3 is when the endometrium is homogenous and hyper-echogenic.

Number of oocytes retrieved, mature and fertilized, day, number and grade of embryos transferred and frozen were collected.

The clinical pregnancy rate (CPR) was defined by visualizing fetal heart beat by ultrasonography. The miscarriage rate was defined as pregnancy loss before 20 weeks of gestation.

Data was analyzed using StatsDirect statistical package. Two-sided Mann-Whitney *U* test was used to compare medians between two groups, two-sided Unpaired *t* test was used to compare means between two groups, one way ANOVA was used to compare means between more than two groups, Kurskal-Wallis test was used to compare medians between more than two groups, Chi square test in crosstabs, Fisher- Freeman-Halton exact in crosstabs when any cells have expectation of less than 5. P values of less than 0.05 were considered statistically significant.

3. Results

The patients were divided into 3 groups according to the type of protocol, (group 1) Short agonist protocol, (group 2) long agonist protocol and (group 3) fixed antagonist protocol. All groups had similar BMI, parity and male age. Female age and number of cycles were significantly highest in the short protocol (32.9 years old and 2.3 cycles) ($p < .0001$) and lowest in the long protocol (29.7 years old and 1.8 cycles done) ($p < .0001$). Among all protocols the most common cause of infertility was male followed by combined ($p < .0001$). AFC was significantly highest in the antagonist protocol and lowest in the short protocol (24.1 vs 9.7 follicles) ($p < .0001$), FSH was lowest in the antagonist protocol and highest in the short protocol (6.1 vs 8.8 IU/l) ($p < .0001$) (Table 1).

Table 1
Demographic criteria of all stimulated patients.

	Short (n = 111)	Long (n = 605)	Antagonists (n = 227)	P value
Female age	32.9 ± 4.11	29.7 ± 4.26	30.2 ± 4.25	<0.0001[a]
No. of cycles	2.33 ± 1.26	1.8 ± 1.07	1.95 ± 1.11	<0.0001[b]
BMI (kg/m^2)	26.5 ± 3.67	26.8 ± 3.2	26.8 ± 3.0	0.127[b]
Parity	0.35 ± 0.53	0.3 ± 0.6	0.29 ± 0.55	0.72[b]
AFC	9.7 ± 3.9	20.5 ± 9.57	24.1 ± 13.75	<0.0001[b]
Basal FSH (IU/L)	8.8 ± 3.9	6.2 ± 1.9	6.1 ± 2.25	<0.0001[b]
Male age	36.4 ± 6.52	35.3 ± 6.5	34.9 ± 5.79	0.14[a]
Infertility cause	male = 69	male = 283	male = 88	<0.0001[c]
	tubal = 8	tubal = 22	tubal = 12	
	ovarian = 4	ovarian = 54	ovarian = 28	
	endometriosis = 1	endometriosis = 10	endometriosis = 0	
	combined = 14	combined = 176	combined = 80	
	idiopathic = 15	idiopathic = 60	idiopathic = 19	

[a] one way ANOVA.
[b] Kurskal- Wallis test.
[c] Fisher-Freeman-Halton exact.

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