Premature Progesterone Elevation Does Not Affect Pregnancy Outcome in High-Responder Patients Undergoing Short-Interval Coasting in IVF Cycles

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AD 1 **Mustafa Acet**
E 1 **Lebriz Hale Aktün**
CD 2 **Serdar Başaranoğlu**
F 1 **Betül Yorgunlar**
B 3 **Tuba Acet**
G 4 **Ayşegül Deregözü**

1 Department of Obstetrics and Gynecology, Medipol University, School of Medicine, Istanbul, Turkey
2 Department of Obstetrics and Gynecology, Fatih University, School of Medicine, Istanbul, Turkey
3 Department of Obstetrics and Gynecology, Medicine Hospital, Istanbul, Turkey
4 Department of Obstetrics and Gynecology, Bahçelievler State Hospital, Istanbul, Turkey

Corresponding Author: Serdar Başaranoğlu, e-mail: drsbasaran@gmail.com
Source of support: Departmental sources

Background: We aimed to present the relationship between premature progesterone elevation (PPE) and clinical outcomes in high-responder patients who had a coasting period of <4 days in length due to their high risk of developing ovarian hyperstimulation syndrome (OHSS) and who were treated with a long-acting gonadotropin-releasing hormone agonist (GnRH-agonist) protocol in *in vitro* fertilization-embryo transfer (IVF-ET) cycles.

Material/Methods: This retrospective study was conducted at the University Hospital Assisted Reproductive Technology Center. The outcomes of 101 patients undergoing IVF- intracytoplasmic sperm injection (ICSI) cycles who showed a high response to COH (estradiol >4000 pg/ml and/or >20 follicles each ≥10 mm in diameter and at least 20% ≥15 mm) and who were coasted for <4 days were evaluated. Number of oocytes, 2 pronuclei (PN) embryos, implantation rate, and live birth rate were measured.

Results: The incidence of PPE was 32.6%. Compared with those without PPE, patients with PPE had a higher number of oocytes retrieved. Total mature and fertilized oocytes and the mean number of embryos transferred were not significantly different between groups. Live birth rates (41.9% *vs.* 38.7%) and implantation rates (26.5% *vs.* 23%) were also not significantly divergent in the PPE and non-PPE groups, respectively.

Conclusions: P concentrations ≥1.3 ng/ml on the day of human chorionic gonadotropin (hCG) administration, designated in this study as PPE, does not appear to be related to adverse effects in terms of clinical outcomes in high-responder patients undergoing coasting <4 days due to their high risk of developing OHSS treated with a long-acting GnRH-a protocol in IVF-embryo transfer cycles.

MeSH Keywords: Fertilization *In Vitro* • Gonadotropin-Releasing Hormone • Pregnancy Rate • Progesterone

Full-text PDF: http://www.basic.medscimonit.com/abstract/index/idArt/896244

📄 2362   🖽 2   📊 3   📚 32

Background

Elevated serum progesterone (P) concentrations on the day of human chorionic gonadotropin (hCG) administration [1,2] is regarded as premature luteinization (PL), and was reported to occur in 2% to 35% of GnRH-agonist (GnRH-a) cycles in *in vitro* fertilization-embryo transfer (IVF-ET) procedures [3]. However, although P rise was historically associated with luteinizing hormone (LH), in the context of premature LH surge, genuine PL is in fact rarely encountered with the routine use of GnRH analog protocols. However, the term PL is still used to describe a substantial increase in serum P on the day of hCG administration [4–6]. Most of the studies suggested that elevated P is related to follicle-stimulating hormone (FSH) exposure during the follicular phase [3,7–9]. Therefore, premature progesterone elevation (PPE) is a better term to describe elevated serum P concentrations on the day of hCG administration. In the meta-analysis by Venetis et al., one proposed explanation for the elevated P, at least for studies using GnRH-a to inhibit LH surge, was the presence of an excess number of follicles, each one producing a normal amount of P, consistent with the late follicular phase, and in this way the excess of proliferating granulosa cells led to increased P production, independent of LH exposure [10].

The etiology and possible effects of PPE on cycle outcome remain controversial. Although these high serum P concentrations could adversely affect the quality of oocytes and/or endometrial maturation and receptivity, as suggested by some authors [1–4,11], better outcomes have also been reported by others [12,13]. Some reports have indicated that PPE has no impact on pregnancy outcome during controlled ovarian hyperstimulation (COH) for IVF-ET [10,14,15]. Withholding gonadotropin stimulation while continuing GnRH analogue administration and postponing hCG injection, designated as coasting, has been suggested as a treatment modality in cases of impending ovarian hyperstimulation syndrome (OHSS) [16,17]. Without any significant compromise to IVF cycle outcome, a short coasting interval (<4 days) presents an opportunity to reduce the risk of OHSS [18,19].The incidence of PPE on the day of hCG administration in coasted cycles is not well defined. In addition, treatment outcomes of high-responder patients who exhibit PPE during the coasting period have not been thoroughly described.

The aim of the present study was to evaluate the relationship between PPE and clinical outcomes in high-responder patients who had a coasting period of <4 days due to their high risk of developing OHSS, treated with a long-acting GnRH-a protocol in IVF-ET cycles.

Material and Methods

This retrospective study was conducted at the University Hospital Assisted Reproductive Technology (ART) Center between November 2012 and February 2014 after approval by the Ethics Committee of University Hospital.

We evaluated the outcomes of 101 patients undergoing IVF-intracytoplasmic sperm injection (ICSI) cycles who showed a high response to COH (estradiol >4000 pg/ml and/or >20 follicles each ≥10 mm in diameter and at least 20% ≥15 mm) and who were coasted for <4 days. The distribution of infertility factors was as follows: chronic anovulation (13.8%), tubal factor (9.5%), endometriosis (5.9%), male factor (46.8%), and unexplained infertility (24%). The patients were informed about the coasting procedure and the fact that it did not completely abolish the risk of developing OHSS.

Pituitary suppression was achieved by the administration of a GnRH-a (leuprolide acetate, Lucrin®, 0.1 mg, Abbott Healthcare SAS, Suresnes, France) in the mid-luteal phase of the previous cycle. When the serum estradiol (E_2) concentration fell below 50 pg/ml, ovarian stimulation was started with the administration of a recombinant FSH (follitropin alfa [Gonal-F®], Merck Serono, Bari, Italy; or Puregon®, Organon, Oss, the Netherlands) at a dosage of 150–300 IU. The dosage of gonadotropins was determined according to the patient's ovarian antral follicle count, age, and body mass index (BMI). The starting regimen was fixed for the first 3 days, and thereafter the dose of gonadotropins was adjusted according to the individual ovarian response. An injection of 250 mcg IU rhCG (hCG, Ovitrella®, Serona, Istanbul, Turkey) was given when at least 3 mature (≥18 mm) follicles were observed. Oocyte retrieval was performed 36 h later, and the oocytes were subjected to IVF or ICSI. Embryos were transferred 5 days after oocyte retrieval. Luteal phase was supported by 100 mg/day Progesterone in Oil intramuscular injections. Clinical pregnancy was defined as the presence of a gestational sac detected on ultrasound at least 3 weeks after the first β-subunit hCG (βhCG) test, which was performed 12 days after the ET procedure. Ongoing pregnancy was defined as a pregnancy continuing 12 weeks after embryo transfer.

Coasting was applied according to the institutional criteria, as well as the described series (E_2 >4000 pg/ml and/or >20 follicles ≥10 mm in diameter and at least 20% ≥15 mm), in which high-responder patients were considered to have a high risk of developing OHSS. Daily measurements were taken until the serum E_2 concentration dropped to <4000 pg/ml, on which day hCG was administered, while gonadotropin administration was withheld and GnRH-a was maintained.

Table 1. Clinical data of patients with undergoing controlled ovarian stimulation for IVF.

Cycle characteristic	High P ($\geq$1.3 ng/mL)	Low P (<1.3 ng/mL)	P value
Number of ET cycles	n (33)	n (68)	
Duration of infertility y	7.3±3.8	6.7±3.5	ns
Day-3 FSH (IU/L)	7.41±2.0	7.04±1.6	ns
BMI (kg/m^2)	25.7±3.0	25.2±2.9	ns
Total gonadotropin dose (IU)	1404±184	1437±147	ns
Duration of stimulation (day)	7.76±1.1	7.85±1.1	ns
Endometrial thickness on hCG day	9.7±1.5	9.5±1.6	ns
Duration of coasting (day)	2.4±0.7	2.3±0.8	ns
Serum E$_2$ level on day of hCG (pg/mL)	3141±714	2299±567	**<0.001**
LH on day hCG (mIU/ml)	1.2±1.2	1.2±1.1	ns

P value <0.05 statistically significant; ns – not significant.

In the study by Bosch et al., 1.2 ng/ml was established as the discriminatory serum P level. Values equal to or greater than this level were found to have 85.2% specificity, 47.3% sensitivity, 51.9% positive predictive value, and 82.7% negative predictive value for the absence of any pregnancy (8). For the purposes of this analysis, PPE was defined as a P concentration $\geq$1.3 ng/ml on the day of hCG administration.

Blood samples were obtained from each patient during cycle monitoring to assess the response to COH for determination of serum E2, LH, and P concentrations. Samples were tested using a fully automated random access analyzer (Elecsys 2010®, Roche-Diagnostics, Mannheim, Germany) based on chemiluminescent immunoassay technology. For all measurements, the inter-assay coefficient of variation was <10% and the intra-assay variation was <10%.

Statistical analysis

Statistical analysis was performed using t-test, chi-squared test, and Fisher's exact test, as indicated. Numeric data were compared using Student's t-test, and categorical data were compared using chi-squared and Fisher's exact tests. Results are expressed as the mean ±SD. A *P* value <0.05 was considered statistically significant. SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

In our study, PPE occurred in 33 of 101 patients (32.6%). There were no significant differences between the PPE and non-PPE
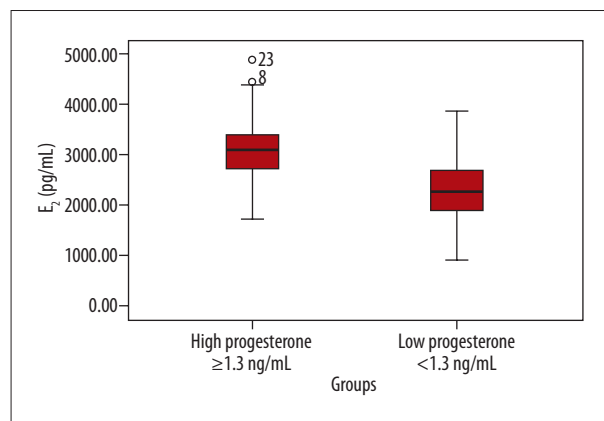

Figure 1. E$_2$ concentrations at the time of hCG administration.

groups with respect to patient age (30.0±4.5 *vs.* 30.8±4.3 years; P=0.38), duration of infertility (7.3±3.8 *vs.* 7.04±1.6 years; P=0.36), FSH levels assessed on day 3 of the cycle (7.41±2.0 *vs.* 7.04±1.6 IU/L; P=0.36), or BMI (25.7±3.0 *vs.* 25.2±2.9 kg/m^2; P=0.49). The total gonadotropin dose used, the days of stimulation, endometrial thickness on hCG day, and the duration of coasting were similar in both groups (Table 1).

E2 concentrations at the time of hCG administration were significantly higher in the PPE group compared with the non-PPE group (3141±714 *vs.* 2299±567 pg/ml, respectively; P<0.001) (Figure 1). P levels on the day of hCG in patients with PPE were 3 times higher (1.5±1.0 ng/ml) compared with patients without PPE (0.5±0.2 ng/ml; P<0.001). However, the LH levels on the day of hCG were similar between the PPE and non-PPE groups (1.2±1.2 mIU/ml *vs.* 1.2±1.1 mIU/ml, respectively; P=0.97). Compared to those without PPE, patients with
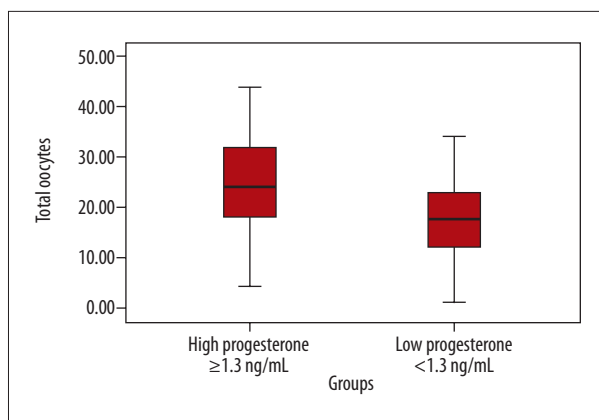
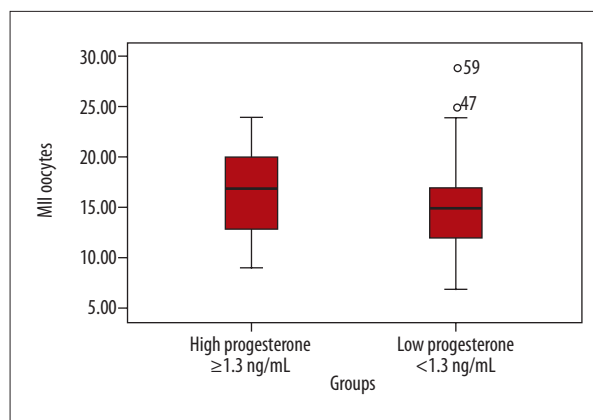**Figure 2.** Number of oocytes compared the patients with PPE and without PPE.

Figure 3. Compared total mature and fertiized oocytes and the mean number of embryos transferred.

Table 2. Outcome in patients with PPE and no PPE for IVF.

Outcome	High P (≥1.3 ng/mL)	Low P (<1.3 ng/mL)	P value
Number of ET cycles	n (33)	n (68)	
Mean number of oocytes	24.7±9.3	17.9±7.8	**<0.001**
No. of MII oocytes (ICSI cycles)	16.6±4.2	14.9±4.2	ns
2PN fertilization with ICSI (%)	86.0	88.5	ns
Mean no. of embryos transferred	1.6±0.4	1.5±0.4	ns
Implantation rates (IR) (%)	26.5	23	ns
Cinical pregnancy (%)	48.3	50	ns
Miscarriage rates (%)	13.3	16.1	ns
Live birth rates (%)	41.9	38.7	ns

P value <0.05 statistically significant; ns – not significant.

PPE had a higher number of oocytes retrieved (24.7±9.3 *vs.* 17.9±7.8 respectively; p<0.001) (Figure 2). Total mature and fertilized oocytes and the mean number of embryos transferred were not significantly different between groups (Figure 3).

No significant differences were observed between the 2 groups for the clinical pregnancy results (48.3% in the PPE group and 50% in the non-PPE group; P=0.88), miscarriage rates (13.3% in the PPE group and 16.1% in the non-PPE group; P=1.0), live birth rates (41.9% in the PPE group and 38.7% in the non-PPE group; P=0.82), and implantation rates (IR) (26.5% in the PPE-group and 23% in the non-PPE group; P=0.73) (Table 2).

Discussion

The mechanism underlying PPE is not clearly understood. PPE could be the result of higher levels of P or endogenous LH during the follicular phase of COH [20]. The increase in serum hCG from the human menopausal gonadotropin preparations used for ovarian hyperstimulation could be another reason for a premature serum P increase [21]. Incomplete GnRH – a pituitary down-regulation – has also been proposed [7,22]; thus, increasing E_2 levels may induce LH secretion for a stimulation of granulosa cells sufficient to produce P but inadequate to trigger ovulation [23,24]. High serum P concentrations have recently been reported to be related to FSH dose [8]. In one report, the authors commented that this was probably a consequence of the activation of other signal transduction pathways of FSH [25]. Recent research has shown that FSH induces the expression not only of the aromatase pathway but also of the other genes stimulating the phosphorylation of kinases that are downstream targets of IGF-1 [26]. Another explanation is related to FSH stimulation of LH receptors on granulosa cells. Therefore, P could be produced even in the presence of low serum LH levels [1,3,22]. This seems to

be the case in the current study, as LH was not elevated, and similar LH concentrations were observed in both groups. P elevation varies widely among reports (e.g., 0.8 ng/ml and 9.54 nmol/l) [8,27]. In our study, a P level ≥1.3 ng/ml was set as the threshold to define PPE, and the incidence of PPE was found to be 32.6%, which is consistent with the 38.3% reported by Bosch et al. and 36.7% reported by Li et al. [8,28]. The effect of P elevation on the day of hCG administration on pregnancy outcomes is a subject of debate. Many authors have studied the effects of PPE on IVF-ET cycle outcomes, and conflicting results were obtained. Fanchin et al., using a level of >0.9 ng/ml as an arbitrary measure of premature serum P elevation, reported a negative effect in terms of pregnancy rates (PR) and suggested that endometrial receptivity may be affected [1]. Hofmann et al. used P levels above 2.0 ng/ml as indicative of PPE in GnRH-a cycles but reported no effect on cycle outcome in terms of PRs or IRs [14]. Segal et al. evaluated the occurrence of PPE (serum P concentration ≥1.3 ng/ml) and its possible effect on outcome when a GnRH antagonist COH protocol was administered in patients with polycystic ovary syndrome (PCOS) [20]. The study has demonstrated that PPE does not have a detrimental effect on pregnancy outcome. In the recent report from Bosch et al., the P threshold was 1.5 ng/ml, and above this level ongoing PR was lower, independent of the GnRH analogue used [29]. To date, only 1 study has explored PPE in coasted cycles and evaluated the impact of the duration of coasting on IVF cycle outcome. In this retrospective study, infertile patients who underwent a long protocol with a GnRH-a were analyzed [25]. The patients with a high response to ovarian stimulation were coasted due to high risk of developing OHSS. The investigators evaluated whether PPE (>1.2 ng/ml) was present in these cycles and whether it might be related to coasting duration. P concentrations and PPE were significantly higher in coasted patients when compared with non-coasted patients. Of the patients with PPE, 60% required ≥3 days of coasting. They mentioned that extended coasting duration, especially coasting ≥4 days, exerts a negative effect on IR, and the effect of PPE on endometrial maturation may explain the negative impact of prolonged coasting on IVF cycle outcome. In the present study, we aimed to evaluate the effects of high P levels in high-responder patients who underwent short-interval coasting, and we found no significant impact on PR and IR.

Bosch et al. reported that higher doses of FSH and longer stimulation is needed in cycles with high P levels on the day of hCG administration [8], but we could not verify the association of gonadotropin dose with serum P levels from the present data. The mean gonadotropin doses administered per cycle and duration of stimulation were not different between the 2 groups. In our study, P levels correlated positively with E_2 levels on the day of hCG administration. Consequently, high-responders may have high levels of E_2 and P. This result shows a positive correlation between P and E_2 in the late follicular phase, as shown in many other studies [30,31]. In the present study, a significantly higher number of total oocytes were retrieved in patients with PPE. These findings are similar to those in other studies, and it has been shown that women with high P levels have an higher number of follicles and oocytes than women with low P levels [8,30,31]. However, mature and fertilized oocytes and the mean number of embryos transferred were not significantly different between the 2 groups. Some studies highlighted the relationship between PPE and the ovarian reserve of the patient. Fanchin et al. demonstrated that elevated P levels were not associated with lower PRs in the presence of an adequate response to COH [2]. However, when the response to COH was weak, premature P elevation led to lower PRs. Younis et al. defined PPE as the P: E_2 ratio >1 on the day of hCG administration, and it was suggested to be an important variable that could result in the manifestation of diminished ovarian reserve and poor pregnancy outcome [32]. However, this is not the case in high-responder patients requiring coasting. The present study demonstrates that PPE in patients treated with a GnRH-a protocol with a high response and with a short coasting interval (<4 days) does not have a significant detrimental effect on IR, clinical outcome, or live birth rates. Pregnancy outcome was not different between the 2 groups, with or without evidence of PPE.

Conclusions

Two limitations need to be acknowledged in the present study. Its retrospective nature and small sample size prevent us from drawing strong conclusions. Furthermore, clinical data in high-responder patients who exhibit PPE during the coasting period is lacking. We have shown that serum P concentrations ≥1.3 ng/ml on the day of hCG, designated in this study as PPE, does not appear to be related to an adverse effect in terms of clinical outcomes in high-responder patients undergoing coasting < 4 days due to their high risk of developing OHSS treated with a long-acting GnRH-a protocol in IVF-embryo transfer cycles.

References:

1. Fanchin R, de Ziegler D, Taieb J et al: Premature elevation of plasma progesterone alters pregnancy rates of *in vitro* fertilization and embryo transfer. Fertil Steril, 1993; 59: 1090–94

2. Fanchin R, Righini C, Olivennes F et al: Consequences of premature progesterone elevation on the outcome of *in vitro* fertilization: insights into a controversy. Fertil Steril, 1997; 68: 799–805

3. Ubaldi F, Camus M, Smitz J et al: Premature luteinization *in vitro* fertilization cycles using gonadotrophin releasing hormone agonist (GnRH-a) and recombinant follicle stimulating hormone (FSH) and GnRH-a and urinary FSH. Fertil Steril, 1996; 66: 275–80

4. Schoolcraft W, Sinton E, Schlenker T et al: Lower pregnancy rate with premature luteinization during pituitary suppression with leuprolide acetate. Fertil Steril, 1991; 55(3): 563–66

5. Martinez F, Barri PN, Coroleu B et al: Women with poor response to IVF have lowered circulating gonadotrophin surge-attenuating factor (GnSAF) bioactivity during spontaneous and stimulated cycles. Hum Reprod, 2002; 17(3): 634–40

6. Saleh HA, Omran MS, Draz M: Does subtle progesterone rise on the day of HCG affect pregnancy rate in long agonist ICSI cycles? J Assist Reprod Genet, 2009; 26(5): 239–42

7. Hofmann GE, Bentzien F, Bergh PA et al: Premature luteinization in controlled ovarian hyperstimulation has no adverse effect on oocyte and embryo quality. Fertil Steril, 1993; 60: 675–79

8. Bosch E, Valencia I, Escudero E et al: Premature luteinization during gonadotrophin-releasing hormone antagonist cycles and its relationship with *in vitro* fertilization outcome. Fertil Steril, 2003; 80: 1444–49

9. Smitz J, Andersen AN, Devroey P, Arce JC; MERIT Group: Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinant FSH in IVF patients. Hum Reprod, 2007; 22(3): 676–87

10. Venetis CA, Kolibianakis EM, Papanikolaou E et al: Is progesterone elevation on the day of human chorionic gonadotrophin administration associated with the probability of pregnancy in *in vitro* fertilization? A systematic review and meta-analysis. Hum Reprod Update, 2007; 13(4): 343–55

11. Papanikolaou EG, Kolibianakis EM, Pozzobon C et al: Progesterone rise on the day of human chorionic gonadotropin administration impairs pregnancy outcome in day 3 single-embryo transfer, while has no effect on day 5 single blastocyst transfer. Fertil Steril, 2009; 91(3): 949–52

12. Doldi N, Marsiglio E, Destefani A et al: Elevated serum progesterone on the day of HCG administration in IVF is associated with a higher pregnancy rate in polycystic ovary syndrome. Human Reproduction, 1999; 14: 601–5

13. Melo MA, Meseguer M, Garrido N et al: The significance of premature luteinization in an oocyte-donation programme. Human Reproduction, 2006; 21: 1503–7

14. Hofmann G, Khoury J, Johnson C et al: Premature luteinization during controlled ovarian hyperstimulation for *in vitro* fertilization-embryo transfer has no impact on pregnancy outcome. Fertil Steril, 1996; 66: 980–86

15. Elnashar AM: Progesterone rise on the day of HCG administration (premature luteinization) in IVF: an overdue update. J Assist Reprod Genet, 2010; 27(4): 149–55

16. Fatemi HM, Platteau P, Albano C et al: Rescue IVF and coasting with the use of GnRH antagonist after ovulation induction. Reproductive BioMedicine Online, 2002; 5: 273–75

17. Levinsohn-Tavor O, Friedler S, Schachter M et al: Coasting – what is the best formula? Human Reproduction, 2003; 18: 937–40

18. Sher G, Zouves C, Feinman M et al: Prolonged coasting: an effective method for preventing severe ovarian hyperstimulation syndrome in patients undergoing *in-vitro* fertilization. Human Reprod, 1995; 10: 3107–9

19. Ulug U, Bahceci M, Erden HF et al: The significance of coasting duration during ovarian stimulation for conception in assisted fertilization cycles. Human Reprod, 2002; 17: 310–13

20. Segal S, Glatstein I, McShane P et al: Premature luteinization and *in vitro* fertilization outcome in gonadotrophin/gonadotrophin-releasing hormone antagonist cycles in women with polycystic ovary syndrome. Fertil Steril, 2009; 91: 1755–59

21. Copperman AB, Horowitz GM, Kaplan P et al: Relationship between circulating human chorionic gonadotrophin levels and premature luteinization in cycles of controlled ovarian hyperstimulation. Fertil Steril, 1995; 63: 1267–71

22. Dumesic DA: Periovulatory serum progesterone levels as a predictor of pregnancy outcome during ovarian hyperstimulation for assisted reproductive technology. Fertil Steril, 1994; 62: 911–12

23. Peluso JJ: Role of the amplitude of the gonadotrophin surge in the rat. Fertil Steril, 1990; 53: 150–54

24. Ubaldi F, Smitz J, Wisanto A et al: Oocyte and embryo quality as well as pregnancy rate in intracytoplasmic sperm injection are not affected by high follicular phase serum progesterone. Human Reproduction, 1995; 10: 3091–96

25. Moreno L, Diaz I, Pacheco A et al: Extended coasting duration exerts a negative impact on IVF cycle outcome due to premature luteinization. Reproductive BioMedicine Online, 2004; 9: 500–4

26. Richards JS: New signalling pathways for hormones and cycle adenosine 3'-5'-monophosphate action in endocrine cells. Mol Endocrinol, 2002; 15: 209–18

27. Zhong YP, Zhou CQ, Zhuang GL et al: Impact of serum progesterone levels on clinical outcome of *in vitro* fertilization and embryo transfer. Academic Journal of Sun Yat-Sen University of Medical Sciences, 2002; 23: 124–26

28. Li R, Qiao J, Wang L et al: Serum progesterone concentration on day of HCG administration and IVF outcome. Reproductive BioMedicine Online, 2008; 16: 627–31

29. Bosch E, Labarta E, Crespo J et al: Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for *in vitro* fertilization: analysis of over 4000 cycles. Hum Reprod, 2010; 25(8): 2092–100

30. Edelstein MC, Seltman HJ, Cox BJ et al: Progesterone levels on the day of human chorionic gonadotrophin administration in cycles with gonadotrophin-releasing hormone agonist suppression are not predictive of pregnancy outcome. Fertil Steril, 1990; 54: 853–57

31. Givens C, Schirock E, Dandekar P et al: Elevated serum progesterone levels on the day of human chorionic gonadotrophin administration do not predict outcome in assisted reproduction cycles. Fertil Steril, 1994; 62: 1011–17

32. Younis JS, Matilsky M, Radin O et al: Increased progesterone/estradiol ratio in the late follicular phase could be related to low ovarian reserve in *in vitro* fertilization-embryo transfer cycles with a long gonadotrophin-releasing hormone agonist. Fertil Steril, 2001; 76: 294–99