Evaluation of serum progesterone on the day of human chorionic gonadotropin administration as a predictor of pregnancy rate in ICSI

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Abstract

Introduction: Increase in serum P4 levels alongside high estradiol (E2) levels may lead to endometrial gland stroma asynchrony, which can lead consequently to implantation failure. Aim: Is to investigate the role of serum progesterone level on the day of hCG administration as a predictor of pregnancy in ICSI.

Methods: a prospective observational clinical study included fifty infertile women undergoing ICSI. The main outcome of the study was to evaluate the role of serum progesterone on the day of hCG administration as a predictor of pregnancy rate in ICSI.

Results: serum progesterone level at the day of hCG administration is not a useful predictor of pregnancy in cases undergoing ICSI. Conclusion: Serum progesterone at the day of hCG is not a useful predictor of pregnancy outcome. Further studies with larger numbers are needed to confirm or refute this finding.

Key words: Serum progesterone; prediction; pregnancy.

Introduction

In gonadotropin-releasing hormone (GnRH) analogues protocol, small increases in serum progesterone (P4) levels beyond a certain threshold value is seen at late follicular phase in IVF cycles. This varies between 5 and 35% with GnRH agonist protocol and between 9 and 38% in GnRH antagonists protocols [1-4].

Increase in serum P4 levels alongside high estradiol (E2) levels may lead to endometrial gland stroma asynchrony, which can lead consequently to implantation failure as a result of luteal phase defect, without influencing oocyte or embryo development [5-8].

The aim of the current study was to investigate the role of serum progesterone level on the day of hCG administration as a predictor of pregnancy rate in ICSI.

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Patients & Methods

This is a prospective observational clinical study performed in the assisted reproduction unit of Air-Force Specialized hospital from jaunuary 2019 to December 2019 and was approved by the ethical committee of the hospital. The study included fifty infertile women undergoing ICSI with the following inclusion criteria age between 20 and 40 years, BMI < 35 kg/m2, basal FSH < 10 IU/ml and patients stimulated by the long protocol. While those who had previous history of low ovarian response to stimulation, previous failed ICSI, hydrosalpinx or any uterine pathology were excluded from the study. The main outcome of the study was to evaluate the role of serum progesterone on the day of hCG administration as a predictor of pregnancy rate in ICSI.

All cases were subjected to detailed history, general, abdominal and local examination, in addition to, investigations in the form of FSH, LH, PRL, E2 and thyroid functions in day 2 of the menstrual cycle before the induction protocol. Semen analysis and transvaginal ultrasound (TVS) were also done.

Induction protocol

Patients underwent controlled ovarian stimulation using the long GnRH agonist protocol for pituitary down-regulation. Ovarian stimulation was done by human menopausal gonadotropin (HMG)(Merional IBSA,Swittzerland). The initial dose of HMG was individualized for each patient according to age, FSH level, antral follicle count (AFC) and BMI. Dose adjustments was performed according to ovarian response, which was monitored according to TVS and E2 levels. Serum progesterone was performed on the day of hCG administration (Chorioumon ,IBSA,Swittzerland)which was given if 3 or more follicles reached 18 mm.

Ovum pick-up

TVS guided oocyte retrieval was performed 34-36 hours after hCG injection using 17-gauge needle under general anesthesia. The oocyte-corona complexes were denuded and ICSI performed 2 hours after incubation.

Embryo transfer

Two or three good quality embryo were transferred in day 3. B-hCG was performed 14 days after embryo transfer to define chemical pregnancy and TVS was performed at 5 weeks gestational age to define clinical pregnancy.

Progesterone measurement

Venous blood samples were collected in the day of hCG administration to measure serum progesterone. Samples were tested with a microparticle enzyme immunoassay Axsym System (Cobas e 411, Roche diagnostics. HITACHI), which has a sensitivity of 0.03 ng/ml.

Statistical analysis

Data were analysed using statistical program for social science (SPSS) version 18.0. Quantitative data were expressed as mean & standard deviation (SD). Qualitative data were expressed as frequency and percentage.

Independent-samples t-test of significance was used when comparing between two means. Spearman's rank correlation coefficient (rs) was used to assess the degree of association between two sets of variables if one or both of them were skewed, otherwise pearson correlation was used. P-value < 0.05 was considered significant, < 0.01 was considered highly significant and > 0.05 was considered insignificant.

Results

Nineteen cases out of fifty cases got pregnant. Comparison was done between non-pregnant and pregnant cases.

Table 1 shows comparison between pregnant & non-pregnant cases regards the basal characteristics

	Group A (n=31) mean & SD	Group B (n=19) mean & SD	P value
Age	28.37 +/- 4.38	29.03 +/- 3.09	0.569
BMI	27.68 +/- 5.83	28.52 +/- 2.79	0.560
FSH	6.35 +/- 1.86	5.91 +/- 1.74	0.409
AFC	10.60 +/- 4.46	11.11 +/- 4.36	0.694

Table 2 shows comparison between pregnant & non-pregnant cases regards No. of HMG ampoules, induction duration, E2 & P4 (day hCG), No. of retrieved oocytes. No. of MII, fertilized oocytes and No. of embryos transferred.

	Group A (n=31) mean & SD	Group B (n=19) mean & SD	P value
No. of HMG ampoules	3.42 +/- 1.05	3.42 +/- 0.86	0.961
Induction duration	11.85 +/- 1.53	11.39 +/- 1.35	0.2866
Oocyte	10.55 +/- 5.33	11.53 +/- 5.97	0.549
E2 (day hCG)	3898.77 +/- 1.948.1	4909.21 +/- 3567.7	0.426
P4 (day hCG)	1.67 +/- 1.54	1.39 +/- 0.92	0.477
No. of retrieved oocytes	12.58 +/- 8.65	14.55 +/- 7.62	0.418
No. of MII	8.68 +/- 7.00	9.89 +/- 4.71	0.509
Fertilized oocytes	6.67 +/- 5.15	7.29 +/- 3.24	0.641
No. of ETs	2.54+/- 0.50	2.63 +/- 0.49	0.572

Table 3 shows correlation between serum progesterone (day hCG) and E2 (day hCG), No. of retrieved oocytes, No of MII, fertilized ova, No. of good quality embryos, No. of E.Ts and expected oocytes in cases who got pregnant (n=19)

	P4 (day hCG)	
E2 (day hCG)	r	0.475
	P value	0.003
No. of retrieved oocytes	r	0.065
	P value	0.697
No. of MII	r	0.154
	P value	0.356
Fertilized ova	r	0.155
	P value	0.354
No. of good quality embryos	r	-0.033
	P value	0.855
No. of ETs	r	0.278
	P value	0.091
Expected oocytes	r	-0.204
	P value	0.219

Table 4 shows correlation between serum progesterone (day hCG) and E2 (day hCG), No. of retrieved oocytes, No of MII, fertilized ova, No. of good quality embryos, No. of E.Ts and expected oocytes in cases who didn't get pregnant (n=31)

	P4 (day hCG)	
E2 (day hCG)	r	0.280
	P value	0.031
No. of retrieved oocytes	r	0.163
	P value	0.212
No. of MII	r	0.217
	P value	0.096
Fertilized ova	r	0.144
	P value	0.271
No. of good quality embryos	r	-0.030
	P value	0.834
No. of ETs	r	0.012
	P value	0.930
Expected oocytes	r	-0.028
	P value	0.831

Discussion

The results of the effect of serum P4 level on day of hCG trigger as a predictor of pregnancy in IVF/ICSI cycles using either the GnRH agonist or antagonist protocol are variable. The Possible reasons for such discrepancies include the retrospective nature of most studies, differences in ovarian stimulation protocols, differences in cut-off values used for P4 aduring data analysis or inaccurate definitions in the references for elevated P4 levels in some cases. Other factors include variations in the statistical methods used for estimation of circulating P4 limit values and the precision of P4 measurements due to use of different immunoassays. Most investigators agreed that supraphysiological rise in P4 in late follicular phase has deleterious effect on pregnancy rates [9-16].

The results of the current study showed that serum progesterone level at the day of hCG administration is not a useful predictor of pregnancy in cases undergoing ICSI and a significant positive correlation between estradiol and serum progesterone levels measured at the day of hCG stimulation in both pregnant and non-pregnant cases, while there was no significant correlation between serum progesterone measured at the day of hCG administration and number of retrieved oocytes, number of MII oocytes, fertilized ova, number of good quality embryos, number of embryos transferred or expected oocytes.

The results of the current study partially agrees with the results of Sangisapu et al [17] who studied 306 cases of fresh IVF cycles and concluded that serum progesterone at the day of hCG trigger alone is not associated with IVF outcome; however, it differed from the results of the current study in that it found a significant association with the number of oocytes retrieved; however, Merviel et al [18] found that serum progesterone level on the night before and the day of hCG trigger predicted the likelihood of pregnancy.

Li et al [19], found that higher levels of serum estradiol and progesterone on the day of hCG trigger may affect endometrial receptivity and suggested the transfer of frozen embryos in a natural cycle to avoid this determintal effect of such high hormonal levels.

The current study has the advantage of being prospective, while the limitations of the current study include recruitment from a single center, small number of cases and lack of study of the effects of other hormones.

Conclusion

Serum progesterone at the day of hCG is not a useful predictor of pregnancy outcome.

Further studies with larger numbers are needed to confirm or refute this finding.

Conflict of interest & financial support:

None of authors has any conflict of interest to declare.

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References

1. Bosch E, Valencia I, Escudero E, Crespo J, Simón C, Remohí J et al. Premature luteinization during gonadotropin-releasing hormone antagonist cycles and its relationship with in vitro fertilization outcome. Fertil Steril. 2003;80(6):1444-9
2. Saleh HA, Omran MS, Draz M. Does subtle progesterone rise on the day of HCG affect pregnancy rate in long agonist ICSI cycles? Journal of Assisted Reproduction and Genetics. 2009;26(5):239-242.
3. Ochsenkühn R, Arzberger A, von Schönfeldt V, Gallwas J, Rogenhofer N, Crispin A, et al. Subtle progesterone rise on the day of human chorionic gonadotropin administration is associated with lower live birth rates in women undergoing assisted reproductive technology: a retrospective study with 2,555 fresh embryo transfers. Fertil Steril. 2012;98(2):347-54

4. Fleming R, Jenkins J. The source and implications of progesterone rise during the follicular phase of assisted reproduction cycles. Reprod Biomed Online. 2010;21(4):446-9.
5. Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Hum Reprod Update. 2006;12(6):731-46.
6. Coughlan C, Vitorino R, Melado L, Digma S, Sibal J, Patel R, et al. Evolution of serum progesterone levels in the very early luteal phase of stimulated IVF/ICSI cycles post hCG trigger: a proof of concept study. J Assist Reprod Genet. 2022;39(5):1095-1104.
7. Lahoud R, Kwik M, Ryan J, Al-Jefout M, Foley J, Illingworth P. Elevated progesterone in GnRH agonist down regulated in vitro fertilisation (IVFICSI) cycles reduces live birth rates but not embryo quality. Arch Gynecol Obstet. 2012;285(2):535-40.
8. Fanchin R, Righini C, Olivennes F, Ferreira AL, de Ziegler D, Frydman R. Consequences of premature progesterone elevation on the outcome of in vitro fertilization: insights into a controversy. Fertil Steril. 1997;68(5):799-805.
9. Van Vaerenbergh I, Fatemi HM, Blockeel C, Van Lommel L, In't Veld P, Schuit F, et al. Progesterone rise on HCG day in GnRH antagonist/rFSH stimulated cycles affects endometrial gene expression. Reprod Biomed Online. 2011;22(3):263-71
10. Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Jenkins 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.
11. Kolibianakis EM, Venetis CA, Bontis J, Tarlatzis BC. Significantly lower pregnancy rates in the presence of progesterone elevation in patients treated with GnRH antagonists and gonadotrophins: a systematic review and meta-analysis. Curr Pharm Biotechnol. 2012;13(3):464-70
12. Huang R, Fang C, Xu S, Yi Y, Liang X. Premature progesterone rise negatively correlated with live birth rate in IVF cycles with GnRH agonist: an analysis of 2,566 cycles. Fertil Steril. 2012;98(3):664-670
13. Xu B, Li Z, Zhang H, Jin L, Li Y, Ai J, Zhu G. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of more than 10,000 cycles. Fertil Steril. 2012;97(6):1321-7
14. Venetis CA, Kolibianakis EM, Bosdou JK, Lainas GT, Sfontouris IA, Tarlatzis BC et al. Basal serum progesterone and history of elevated progesterone on the day of hCG administration are significant predictors of late follicular progesterone elevation in GnRH antagonist IVF cycles. Hum Reprod. 2016;31(8):1859-65.
15. Demir B, Kahyaoglu I, Guvenir A, Yerebasmaz N, Altinbas S, Dilbaz B et al. Progesterone change in the late follicular phase affects pregnancy rates both agonist and antagonist protocols in normoresponders: a case-controlled study in ICSI cycles. Gynecol Endocrinol. 2016;32(5):361-5.
16. Wu Z, Dong Y, Ma Y, Li Y, Li L, Lin N et al. Progesterone elevation on the day of hCG trigger has detrimental effect on live birth rate in low and intermediate ovarian responders, but not in high responders. Sci Rep. 2019 26;9(1):5127
17. Sangisapu S, Karunakaran S. Comparative Study of Serum Progesterone Levels at the Time of Human Chorionic Gonadotropin Trigger and Ovum PickUp in Predicting Outcome in Fresh in vitro Fertilization Cycles. J Hum Reprod Sci. 2019;12(3):234-239.
18. Merviel P, Bouée S, Jacamon AS, Chabaud JJ, Le Martelot MT, Roche Set et al. Progesterone levels on the human chorionic gonadotropin trigger day affect the pregnancy rates for embryos transferred at different stages of development in both general and selected IVF/ICSI populations. BMC Pregnancy Childbirth. 2021 6;21(1):363.
19. Li R, Qiao J, Wang L, Zhen X, Lu Y. Serum progesterone concentration on day of HCG administration and IVF outcome. Reproductive Biomedicine Online 2008; 16(5):627-631.