

Low-level Progesterone on the Day of hCG Injection Has No Detrimental Effect on the Pregnancy Outcome after IVF with GnRH-a Protocol: A Retrospective Study

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Abstract

Objective: To investigate the effect of low progesterone (P) level on the day of human chorionic gonadotropin (hCG) injection on the outcome of *in vitro* fertilization (IVF) with GnRH- agonist (GnRH-a) long protocol.

Methods: A retrospective study was conducted in a reproductive medicine center of University-affiliated teaching hospital. 1115 women included were divided into two groups according to the P level: Group 1 (233 women with P level ≤ 0.5 ng/ml, and Group 2 (882 women with P level $>0.5, \leq 1.5$ ng/ml). No. of oocyte retrieved, fertilization rate, implantation rate, and clinical pregnancy rate were compared between the two groups.

Results: Compared with Group 2, Group 1 had significantly decreased number of oocyte retrieved (9.84 ± 4.01 vs. 11.83 ± 4.06 , $P=0.000$) and significantly increased implantation rate (39.4% vs. 34.1%, $P=0.037$). Group 1 had an increased trend of clinical pregnancy rate (55.8% vs. 49.9%, $P=0.109$) compared with that of Group 2. However, the fertilization rates were similar between Group 1 and Group 2 (76.6% vs. 77.0%, $P=0.725$).

Conclusions: Low P level on the day of hCG injection may have a trend towards higher implantation and clinical pregnancy rates after IVF cycles with GnRH-a long protocol. Therefore, we should not worry about the low P on hCG injection day.

Keywords: Progesterone, *In vitro* fertilization, Pregnancy outcome

Introduction

Progesterone (P) can be synthesized and secreted by the ovary and the adrenal glands. In the women ovary, granulosa cells and theca cells produce P. In the later stage of follicular, P is produced by mature granulosa cells before the luteinizing hormone (LH) peak [1], and plays a key role in the regulation ovulation [2].

During the process of controlled ovarian stimulation (COS), the premature LH surge could be avoidable with GnRH- agonist (GnRH-a) / GnRH-ant [3]. So the elevation of P level would be avoided in most COS cycles because of the reduced LH level. However, P elevation during late follicular phase still occurs in about 38% of all *in vitro* fertilization cycles [4-5].

Until now, many studies have attempted to explore the impact of late follicular high-level P on the pregnancy outcome after IVF, and suggested that a higher P level

have detrimental effect on the endometrial receptivity and negatively affect the pregnancy rate following IVF [6-14]. So during the clinical practice, embryo transfer would be cancelled if the P level is higher than a threshold.

The above researches seem to finally answer the question on whether a high P level have negative effect on the pregnancy outcome after COS or not. However, few studies have assessed the influence of low P level on IVF outcome.

In addition, animal experiments have indicated that the P level during the late follicular phase is important for the maturation of oocyte [15], fertilization of oocyte [16], and luteinization of theca / granulosa [17,18]. Additionally, P is important to support the endometrium in the luteal phase. Therefore, we suppose that low level P in the phase of late follicular may compromise pregnancy outcome after IVF cycles.

Until now, two clinical trails [19,20] have assessed the impact of low P level on the pregnancy outcome after IVF. One study included 254 women undergoing COS with GnRH-a protocol, and showed significant lower clinical pregnancy rate in infertile women with low level P (<0.7 ng/ml) [19]. The other study compared pregnancy outcome of IVF among women with low P level, normal P level and high P level, and similarly demonstrated that low P level on the day of hCG injection impair live birth in patients with GnRH-ant protocol followed fresh embryo transfer [20]. Considering the studies, which assess the association between low P level and pregnancy outcome after COS, were limited. So, the present study was aimed to study whether low P level on the day of hCG injection has detrimental effect on the pregnancy outcome after IVF with GnRH-a protocol.

Materials and Methods

Study population and design

The present study was reviewed and approved by the Institutional Review Board and the Ethics Committee of Xiangya Hospital, Changsha, China. The study was based on the Declaration of Helsinki, as revised in 1983. All participants in the study have obtained informed consent.

This was a retrospective cohort study, which was conducted at the Reproductive Medicine Center of Xiangya hospital, Central South University (Changsha, China). Women undergoing fresh IVF-ET with GnRH-a protocol between January of 2014 and May of 2015 were included in the present study. The inclusion criteria including: (1) 20-35 years old; (2) the first COS for IVF; (3) GnRH-a long protocol; (4) tubal factor infertility; (5) P level was ≤ 1.5 ng/ml on the day of HCG injection. Exclusion criteria including: (1) endometrial polyp; (2) uterine anomaly; (3) donor oocytes or cryopreserved embryos. The included women were divided into two groups according to the concentration of P: Group 1: ≤ 0.5 ng/ml; Group 2: >0.5 ng/ml to ≤ 1.5 ng/ml.

Ovulation induction and IVF-ET procedures

All women used the long protocol with GnRH-a down regulation. GnRH-a (Triptorelin, sc 0.1 mg/day) was used beginning on the 21st day of the cycle prior to stimulation. Gn (FSH/HMG) and reduced dose of GnRH-a (Triptorelin, sc 0.05 mg/day) were given on the 2nd day of menstruation or later, and at this moment the serum estradiol concentration (E₂) level should be ≤ 50 pg/ml, LH <5 mIU/ml, all follicle <9 mm. The dosage of Gn (FSH/HMG) ranged from 150 to 225 IU, according to the women age, AMH, and the number of total antral follicle. Oocytes were triggered with 10000 IU of hCG when the largest two follicles ≥ 18 mm. Oocytes were retrieved 36 hours after hCG injection, and followed by conventional IVF. No more than two high-

quality embryos were transferred 3 days after oocyte retrieval. The luteal phase was supported using 80 mg progesterone on oil intramuscular injection daily lasting 60 days. The presence of a gestational sac with heart activity via ultrasound 28-35 days after embryo transfer was considered to be clinical pregnancy.

P assessment immunoassay

Electrochemiluminescence immunoassay was used to measure the P levels on the day of hCG injection, with the measured sensitivity and total imprecision of 0.03 ng /ml and $<5\%$, respectively.

Statistical analysis

Continuous data were recorded as Mean \pm SD, and the Student's *t*-test/ One-Way ANOVA were selected to conduct the statistics. Categorical data was reported as numbers and the Chi-Square test was used to compare the percentage. The women recruited in the present study were divided into 2 groups according to the level of P on the hCG injection day. SPSS16.0 (SPSS Inc, USA) was implied to carry out the statistical analysis, and the difference was considered to be significance when the $P < 0.05$.

Results

A total of 1115 IVF cycles (1115 women) were included in the present study. The average clinical pregnancy rate (PR) per transfer cycle was 51.1%. The average P level on the day of hCG injection was 0.78 ng/ml with a range from 0.03 ng/ml to 1.50 ng/ml. Other demographic date, such as age, infertile duration, BMI, COS days, E₂ level, LH level on the day of hCG injection, the number of oocyte retrieved were summarized in Table 1.

Characteristics	Mean \pm SD
Age (years)	29.81 \pm 3.13
Infertility (years)	4.28 \pm 2.94
BMI (kg/m ²)	21.73 \pm 2.88
Length of stimulation (days)	11.05 \pm 2.01
Total dose of Gn (IU)	1975.30 \pm 684.34
Endometrial thickness on HCG day (mm)	10.91 \pm 2.16
E ₂ on HCG day (pg/ml)	3557.45 \pm 1935.64
LH on HCG day (IU/L)	1.67 \pm 1.01
P on HCG day (ng/mL)	0.78 \pm 0.31

No. of oocyte retrieved	11.42 ± 4.13
No. of MII oocyte	8.46 ± 3.01
No. of embryos	8.78 ± 3.81
No. of high quality embryos	5.57 ± 3.30
No. of embryos transferred	1.99 ± 0.09
No. of gestational sac	0.70 ± 0.77
Kind of infertility	
Primary infertility	38.6% (430/1115)
Secondary infertility	61.4% (685/1115)

Table 1: Characteristics of study group (n=1115).

As hypothesized before, BMI, the number of oocyte/ MII oocyte obtained, the number of embryo/ high quality embryo, E₂ level, LH levels on the day of hCG injection were different between Group 1 and Group 2 (Table 2). Nonetheless, our analysis still showed that there was no significantly difference in the oocyte maturation rates (74.4% vs. 74.1%, P=0.708), fertilization rates (76.6% vs. 77.0%, P=0.725,) and clinical pregnancy rates (55.8% vs. 49.9%, P=0.109) between the Group 1 and the Group 2. However, Group 1 has a significantly higher embryo implantation rate compared with that of the Groups 2 (39.4% vs. 34.1%, P=0.037) (Table 3).

In order to evaluate the effect of P level on the day of hCG injection on the pregnancy outcome of IVF-ET, the effect was further valuated at a threshold increment of 0.1 ng/ml. There was no significantly difference in the oocyte maturation rate, oocyte fertilization rate, embryo implantation rate, and clinical pregnancy rate amongst groups (Table 4).

Characteristics	Group 1 (n=233)	Group2 (n=882)	P
Age (years)	29.75 ± 3.40	29.84 ± 3.08	0.714
Infertility (years)	4.63 ± 3.35	4.19 ± 2.82	0.067
BMI (kg/m ²)	22.12 ± 3.20	21.63 ± 2.79	0.032
Length of stimulation (days)	11.10 ± 2.56	11.03 ± 1.84	0.700
Total dose of Gn (IU)	1940.02 ± 760.31	1984.62 ± 662.97	0.377
Endometrial thickness on HCG day (mm)	10.97 ± 2.06	10.89 ± 2.19	0.644
E ₂ on HCG day (pg/ml)	2447.85 ± 1401.10	3850.58 ± 1951.67	0.000
LH on HCG day (IU/L)	1.43 ± 0.76	1.73 ± 1.05	0.000
No. of oocyte retrieved	9.84 ± 4.01	11.83 ± 4.06	0.000
No. of MII oocyte	7.32 ± 3.00	8.76 ± 2.95	0.000
No. of embryos	7.54 ± 3.58	9.11 ± 3.80	0.000
No. of high quality embryos	4.96 ± 3.09	5.73 ± 3.33	0.001
No. of embryos transferred	1.98 ± 0.13	1.99 ± 0.08	0.197
No. of gestational sac	0.78 ± 0.79	0.68 ± 0.76	0.072

Table 2: Characteristics of group 1 and group 2.

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Group	Oocyte Maturation rate	Fertilization rate	Implantation rate	Clinical Pregnancy rate
Group 1 (n=233)	74.4%	76.6%	39.4%	55.8%
Group 2 (n=882)	74.1%	77.0%	34.1%	49.9%
<i>P</i>	0.708	0.725	0.037	0.109

Table 3: Comparison of IVF outcome between group 1 and group 2.

Progesterone (ng/ml)	Samples (n)	Oocyte maturation rate [% (n)]	Fertilization rate [% (n)]	Implantation rates [% (n)]	Clinical pregnancy rate [% (n)]
≤ 0.2	27	77.7 (199/256)	84.4 (216/256)	45.3 (24/53)	59.3 (16/27)
>0.2 to ≤ 0.3	46	75.2 (319/424)	73.8 (313/424)	41.8 (38/91)	58.7 (27/46)
>0.3 to ≤ 0.4	72	74.2 (520/701)	75.3 (528/701)	41.0 (59/144)	59.7 (43/72)
>0.4 to ≤ 0.5	88	73.3 (668/911)	76.7 (699/911)	35.1 (61/174)	50.0 (44/88)
>0.5 to ≤ 0.6	113	74.5 (905/1215)	77.0 (936/1215)	36.0 (81/225)	51.3 (58/113)
>0.6 to ≤ 0.7	131	74.1 (1072/1447)	76.0 (1100/1447)	32.7 (85/260)	47.3 (62/131)
>0.7 to ≤ 0.8	136	74.9 (1155/1542)	77.4 (1193/1542)	33.6 (91/271)	51.5 (70/136)
>0.8 to ≤ 0.9	130	74.4 (1143/1537)	77.5 (1191/1537)	37.7 (98/260)	53.8 (70/130)
>0.9 to ≤ 1.0	93	73.6 (886/1203)	76.6 (921/1203)	35.5 (66/186)	53.8 (50/93)
>1.0 to ≤ 1.1	100	73.6 (913/1240)	76.4 (947/1240)	38.0 (76/200)	55.0 (55/100)
>1.1 to ≤ 1.2	65	72.2 (559/774)	75.6 (585/774)	33.1 (43/130)	44.6 (29/65)
>1.2 to ≤ 1.3	56	73.1 (538/736)	77.4 (570/736)	25.9 (29/112)	41.1 (23/56)
>1.3 to ≤ 1.5	58	75.1 (558/743)	79.3 (589/743)	26.1 (30/115)	39.7 (23/58)
χ^2		5.468	15.957	17.381	12.375
<i>P</i>		0.941	0.193	0.136	0.416

Table 4: Clinical outcome and progesterone on the day of hCG injection.

Binary logistic regression analysis was implied to evaluate the effect of women age, duration of infertility, BMI, endometrial thickness, E₂, LH, P levels on the day of hCG injection, number of oocyte/MII oocyte retrieved, and the number of embryos/ high quality embryo on clinical pregnancy. The analysis indicated that duration of infertility, P level were negatively correlated with clinical pregnancy, and that increased length of stimulation, endometrial thickness and the number of high quality embryo were associated with improved clinical pregnancy rates (Table 5).

Independent variable	R ^b	P ^c
Duration of infertility	-0.035	0.097
Length of stimulation	-0.080	0.027
Total dose of Gn	0.000	0.019
Endometrial thickness	0.082	0.004
P on hCG day	-0.439	0.029
No. of good quality embryos	0.063	0.001

^aClinical pregnancy served as dependent variable; Method = Backward stepwise (Likelihood Ratio)

^bPartial coefficients

^cP values. R values were considered statistically non-significant unless $P < 0.05$.

Table 5: Binary logistic regression (model R² = 0.099, $P < 0.001$).

Discussion

So far, two studies have referred to the effect of low P level on the day of hCG injection on the pregnancy outcome after IVF cycles [19,20]. One included 254 women undergoing 296 IVF cycles with GnRH-ant protocol, and the other was with GnRH-ant protocol. To the best of our knowledge, this study is the largest with respect to sample size with 1115 IVF cycles, aiming to assess the effect of low P level on the hCG injection day on pregnancy outcome during COS in a long protocol with GnRH-a suppression.

As we all known, high P level on the day of hCG injection have detrimental effect on the embryo implantation via impairing endometrial receptivity. In our reproductive medicine center, we mostly cancelled embryo transfer if the P was higher than 1.5 ng/ml on the day of hCG injection.

By comparing the pregnancy outcome of these two groups, our results indicated that low P level may have no effect on the oocyte maturation, fertilization and clinical pregnancy. However, Group 1 had higher embryo implantation rate ($P < 0.05$) and showed a trend towards higher clinical pregnancy rate ($P > 0.05$) than Group 2, even the women in Group 1 have higher BMI, less number oocytes retrieved and embryos than that of women in Group 2. Our study showed obviously contrary results with two previous researches, one done by Santos-Ribeiro et al., which indicated that low P level on the day of hCG injection has detrimental impact on the pregnancy outcome of IVF using GnRH-ant for pituitary down-regulation [10]; another study, which including 254 women undergoing COS with GnRH-a pituitary suppression, also came to the same conclusion that low P range (< 0.7 ng/ml) results in a lower pregnancy rate [19].

Additionally, the present study further evaluated the effect of P level on the day of hCG injection at a threshold increment of 0.1 ng/ml on IVF outcome, and the results did not find any significantly difference in the oocyte maturation rate, oocyte fertilization rate, embryo implantation rate and clinical pregnancy rate amongst groups. In a binary logistic regression model, P level on the day of hCG injection was an independent predictive factor for clinical pregnancy. The present study demonstrated an increased trend in pregnancy rate when P level decreased.

We analyzed the possible explanations for the above results as below: (i) Total dose of exogenous Gn, length of stimulation, stimulation protocol, oocyte maturation rate, and fertilization rate were same between Group 1 and Group 2. So, the difference in embryo implantation rate and clinical pregnancy rate would not be associated with oocyte quality and oocyte fertilization competence. (ii) E₂ level of Group 2 was significantly higher compared with that of Group 1. Previous studies believed supraphysiologic E₂ level have detrimental effect on the endometrial receptivity and resulted in impairment of embryo implantation [20-22]. In the present study, the higher E₂ level may impair the endometrial receptivity even if the endometrial thickness is similar between the two groups. (iii) Previous researches including clinical trials and basic animal experiments all indicated that P is critical and necessary for the oocyte maturation and fertilization. Our present study found low P level on the day of hCG injection was associated with increased embryo implantation rate and increased clinical pregnancy rate. So, we suppose that the low P level in the IVF cycle is still above the lowest threshold of oocyte development, maturation and fertilization. (iv) The women in the present study were all undergone ovary stimulation with GnRH-a long protocol, whereas two previous trails

used GnRH-ant protocol, which may contribute to the difference of the results.

This study has some limitations, one is that the sample size was not large enough, and another limitation is that the evaluation index is the fertilization rate, implantation rate and clinical pregnancy rate rather than the live birth rate, which may be a better observation. In spite of the limitations, the present study is of interest in that few studies have reported with contrary results.

Conclusion

In general, the present study demonstrated that low P level on the day of hCG injection have a trend towards a higher embryo implantation and clinical pregnancy after IVF cycles with GnRH-a long protocol. Therefore, we should not worry about the low P level on the day of hCG injection.

Competing Interest

The authors declare that they have no conflict of interest.

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Authors' Contribution

Zhao Jing designed the study, performed the analyses and wrote the initial draft of the manuscript; Hao Jie, Wang Yonggang and Xu Bin collected the data of patients; Li Yanping performed the quality assessment of included studies; All authors contributed to the design, interpretation of the results and critical revision of the manuscript.

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