Predictive Value of Decreased Serum Estradiol Levels Following Human Chorionic Gonadotropin Trigger For Unexpected Ovulation During *In Vitro* Fertilization Cycle of Patients With Poor Ovarian Response

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Research

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Abstract

Background

Unexpected spontaneous ovulation typically occurs in patients with poor ovarian response (POR); however, reliable predictors are lacking. We analyzed explore the predictive value of decreased serum estradiol (E2) levels on the day after human chorionic gonadotropin (hCG) trigger during *in vitro* fertilization (IVF) cycles.

Methods

We retrospectively analyzed clinical data ($n = 978$) in IVF cycles between 2017 and 2020. According to decreased ratios of E2 levels ($\Delta E2\%$) between day 1 and day 0 of hCG trigger, patients were divided into: $\leq 10\%$ (group A), $10\text{--}20\%$ (group B), and $\geq 20\%$ (group C). Basic characteristics and laboratory data were compared using analysis of variance or Mann–Whitney U-test. Logistic regression and receiver operating characteristic (ROC) curve analyses were used to assess the relationship between $\Delta E2\%$ and spontaneous unexpected ovulation. Fresh embryo transfer cycles in groups A, B, and C were subgrouped as A1, B1, and C1, respectively; clinical outcomes were compared.

Results

Mean E2 and luteinizing hormone (LH) levels, ratio of premature LH peak and high progesterone levels, time interval between hCG trigger and oocyte retrieval, number of follicles ≥ 11 mm in diameter, and dose regimen of gonadotropin among the three groups showed significant differences ($P < 0.05$). After adjusting for relevant confounders, likelihood ratios of unexpected ovulation in groups B and C were 2.96 (95 % confidence interval [CI]: 0.64–13.70), and 11.74 (95 % CI: 3.09–44.62), respectively, compared with that in group A. The test for trend was significant before and after correction (P for trend < 0.05). On combining premature LH peak (> 10 mIU/mL) or high progesterone level (> 1.0 ng/mL) on the day of hCG, area under ROC curve (AUC) was 0.849 (95 % CI, 0.764–0.934, $P < 0.05$). However, when we only considered $\Delta E2\%$, AUC was 0.738 (95 % CI, 0.562–0.914, $P < 0.05$). Rates of embryo implantation, clinical pregnancy, live birth in fresh embryo transfer cycle, and early abortion among the three subgroups did not differ significantly ($P > 0.05$).

Conclusions

E2 levels on the day after hCG trigger are valuable for predicting unexpected ovulation. However, their decreased levels do not directly affect clinical pregnancy outcomes.

Background

Obtaining an optimal number of high-quality oocytes through controlled ovarian stimulation (COS) without increasing the incidence of complications is critical for successful assisted pregnancy using *in vitro* fertilization-embryo transfer (IVF-ET) or intracytoplasmic sperm injection (ICSI) treatment cycles [1, 2]. However, few low-quality oocytes often occur in patients with poor ovarian response (POR). Improving the clinical pregnancy outcomes of patients with POR has always been a challenge in reproductive medicine. In such cases, selecting an appropriate COS protocol is an important factor.

Recently, with further understanding of the ovary stimulating drugs, the advantages of using gonadotropin releasing hormone-antagonists (GnRH-A), such as rapid action and small dosage of gonadotropin, have been highlighted [3, 4]. Currently, it is considered that GnRH-A can be used in patients with both low- and high-ovarian responses [3]. The addition of GnRH-A can effectively inhibit the endogenous luteinizing hormone (LH) peak to prevent uncontrolled spontaneous ovulation during the COS process. However, there are approximately 2–5% POR patients with premature LH peaks, which lead to unexpected ovulation and luteinization [5]. Therefore, it is important to identify reliable indicators for predicting unexpected ovulation. The level of serum estradiol (E2) level is an important index for evaluating follicular development during ovulation induction. When using gonadotropin to stimulate the ovaries, the serum E2 levels continue to increase with follicular growth. A slow increase or a decrease in serum E2 levels may indicate abnormal follicular growth. Therefore, considering the E2 levels at different time points of COS is particularly important. Previous studies [6–8] have focused on the relationship between E2 levels on the day of human chorionic gonadotropin (hCG) trigger and clinical pregnancy outcomes, but the data are inconclusive. Moreover, whether the change in serum E2 levels on the day after hCG trigger affects the occurrence of unexpected ovulation in patients with POR remains unclear.

We conducted this retrospective study to assess the predictive value of decreased serum E2 levels on the day after hCG trigger for unexpected ovulation and clinical outcomes during the GnRH-A protocol in patients with POR.

Methods

Study subjects

The clinical data of 978 patients who underwent IVF/ICSI treatment were collected from the Department of Reproductive Health and Infertility, Guangdong Women and Children Hospital from January 2017 to June 2020. Among them, 295 were fresh embryo transfer cycles. The inclusion criteria for study subjects were as follows: (1) stimulation using the GnRH-A protocol, (2) patients with anti-Müllerian hormone (AMH) levels <1.2 ng/mL and/or the number of antral follicle count (AFC) <5, defined as POR, in accordance with the 2016 Poseidon criteria [9], and (3) decrease in E2 levels one day after hCG administration compared with that on the day of hCG administration. The exclusion criteria were as follows: (1) patients whose serum E2 levels had not been tested for various reasons, and (2) E2 level exceeding the upper limit of the instrument detection because in such a case the specific value of E2 displayed was incorrect.

Grouping method

The subjects were divided into three groups according to the different decline rate of serum E2 level ($\Delta E2\%$), which was calculated as follows: (decreased ratio of E2 levels between day 1 and day 0 of hCG trigger / E2 level on day 0 of hCG trigger) $\times 100\%$. Subjects with $\Delta E2\% \leq 10\%$ were defined as group A, those with $\Delta E2\%$ between 10 and 20 % were defined as group B, and those with $\Delta E2\% \geq 20\%$ were defined as group C. The fresh embryo transfer cycles were divided into three subgroups: fresh embryo transfer in group A (group A1), group B (group B1), and group C (group C1).

Process of assisted pregnancy

Using the GnRH-A protocol, on days 2–3 of menstruation, gonadotropin, along with either recombinant follicle-stimulating hormone (r-FSH) or urinary FSH was administered at an initial dose ranging from 200 to 300 U. Thereafter, the gonadotropin doses were adjusted according to follicular growth until the day of hCG trigger. GnRH-A was added at 0.125–0.5 mg/day on day 5 of gonadotropin administration or added variably according to follicular growth and hormone levels. When the dominant follicles were at least 18 mm in diameter, urinary hCG (6,000–10,000 IU) or recombinant hCG (250 μ g) was injected as the triggering agent.

After 34–36 h of the hCG trigger, oocyte retrieval was performed. The oocytes were inseminated by IVF or ICSI according to the quality of the sperm and the clinical indication. If there were no contraindications to fresh embryo transfer, not more than two embryos were transferred on day 3 (cleavage stage) or day 5 (blastocyst stage). After transplantation, luteal support with progesterone was provided until 10 weeks after conception. Non-transferred embryos were cryopreserved using vitrification.

Hormone level determination

The blood samples of patients were collected between 7:30–9:00 AM on the start day of COS, day 0 and day 1 of hCG trigger to determine FSH, LH, E2, and progesterone levels using specific commercial kits (Roche Diagnostic Products Shanghai Co., Ltd.). The coefficient of variation between and within the batches was less than 5 %.

Statistical indicators

Unexpected ovulation rate was defined as the number of spontaneous ovulation cycles prior to oocyte retrieval/the total number of cycles. The rate of formation of oocyte-cumulus complexes (OCCs) was calculated as the number of oocytes retrieved divided by the number of follicles ≥ 11 mm in diameter on the day of hCG trigger. Clinical pregnancy was confirmed by an ultrasound evidence of a gestational sac. Clinical pregnancy rate was defined as the number of clinical pregnancy cycles divided by the number of transferred cycles. The live birth rate was defined as the number of liveborn-infant cycles divided by the number of transferred cycles.

Statistical analyses

Statistical analyses were performed using SPSS for Windows (version 26.0). Continuous variables with normal distribution are presented as the mean $\pm$ standard deviation (SD); non-normal variables as median (interquartile range). Comparisons between groups for continuous normally distributed variables were performed using ANOVA, whereas those for nonparametric data were conducted using the Mann–Whitney U-test. The countable data are expressed as rate (%) and were compared using the chi-square or Fisher’s exact test. Statistical significance was set at $P < 0.05$. Logistic regression analysis was used to assess the relationship between $\Delta E2\%$ and spontaneous unexpected ovulation, expressed as odds ratios with 95% confidence intervals (95% CIs). Receiver operating characteristic (ROC) curve analysis was used to calculate the area under the ROC curve (AUC), cut-off values, sensitivity, and specificity.

Results

Baseline characteristics of the three groups

No significant differences in the mean age, body mass index (BMI), baseline FSH level, AFC, and year of infertility were observed among groups A, B, and C ($P > 0.05$). The hormone levels of the three groups on the day of hCG trigger were compared, and the results revealed no significant difference in the mean progesterone levels ($P > 0.05$); however, the mean E2 and LH levels, ratio of premature LH peak (> 10 mIU/ml), and ratio of high progesterone levels (> 1.0 ng/ml) showed significant differences ($P < 0.05$). Significant differences in the time interval between oocyte retrieval and hCG trigger, number of follicles ≥ 11 mm in diameter, and dosage regimen of Gn were observed among the three groups in comparison with those in group C ($P < 0.05$) (Table 1).

Table 1
Comparison of general basic data among groups A, B, and C.

Characteristics	Group A (n = 585)	Group B (n = 235)	Group C (n = 158)	P value
Age(year)	37.77 ± 5.10	37.79 ± 5.21	38.25 ± 4.96	0.563
Infertility year (year)	4.56 ± 4.36	4.17 ± 3.79	4.14 ± 2.04	0.294
BMI (Kg/m ²)	22.07 ± 2.85	21.88 ± 2.85	21.82 ± 2.85	0.518
Baseline FSH (IU/L)	10.25 ± 5.60	10.20 ± 5.17	10.43 ± 4.95	0.915
AFC count(n)	3.92 ± 2.01	4.15 ± 1.94	3.87 ± 2.23	0.287
The total dosages of Gn (IU)	1991.62 ± 1115.07	1990.48 ± 1014.74	1560.36 ± 1162.72	0.000
The total days of Gn (days)	7.95 ± 3.15	7.99 ± 3.06	6.53 ± 4.11	0.000
Number of ≥ 11 mm follicles (n)	3(2,4)	3(1,6)	4(2,7)	0.000
E2 levels on the day of hCG (ng/ml)	1026.5(615.85,1636.25)	1005(632.5,1773.50)	800(439.9,1582)	0.047
LH levels on the day of hCG (IU/l)	3.84(2.39,5.66)	4.27(2.47,7.81)	8.08(3.78,14.29)	0.000
P levels on the day of hCG (ng/ml)	0.54(0.33,0.8)	0.60(0.32,0.8)	0.56(0.31,0.96)	0.352
The ratio of premature LH peak (%)	6.2(36/585)	17(40/235)	39.2(62/158)	0.000
The ratio of progesterone levels > 1.0ng/ml (%)	14(82/585)	21.3(50/235)	22.8(36/158)	0.006
The time interval (h)	35.40 ± 3.15	34.92 ± 4.21	33.11 ± 7.56	0.000
Gn: gonadotropin; The time interval (h): the time interval between the hCG trigger and oocyte retrieval.				

Laboratory Data Of The Three Groups

The number of oocytes retrieved, OCCs rate, unexpected ovulation rate, rate of non-retrieved oocytes, mature oocyte rate, fertilization rate, and rate of obtaining high-quality embryos showed significant differences among the three groups ($P < 0.05$). With increasing $\Delta E2\%$, the unexpected ovulation rate of group C (8.9 %) was higher than that of group A (0.9%) and B (2.6 %) ($P < 0.05$, Table 2).

Table 2
Comparison of laboratory data of the three groups

Factors	Group A (n = 585)	Group B (n = 235)	Group C (n = 158)	P-value
The number of oocytes retrieved (n)	3(2,6)	3(2,5)	2(1,3)	0.000
The OCCs rate(%)	84.32 ± 24.30	82.78 ± 27.10	71.89 ± 37.55	0.000
The premature ovulation rate (%)	0.9(5/585)	2.6(6/235)	8.9(14/158)	0.000
The oocytes non-retrieved rate (%)	3.6(21/585)	5.5(13/235)	16.5(26/158)	0.000
The mature oocyte rate (%)	85.24 ± 26.34	83.37 ± 29.69	72.34 ± 40.66	0.000
The fertilization rate (%)	66.35 ± 32.87	67.11 ± 34.79	56.21 ± 42.03	0.003
The utilizable embryos rate (%)	72.99 ± 38.88	72.79 ± 39.84	55.78 ± 46.60	0.000
The high-quality embryo rate (%)	63.34 ± 40.43	63.02 ± 40.96	45.11 ± 44.64	0.000

Logistic regression analysis of relation between Δ E2% and unexpected ovulation

Group A was considered the reference group. The likelihood ratio of unexpected ovulation rate in groups B and C was 3.36 (95% CI: 0.75–5.13) and 18.86 % (95% CI, 5.35–66.51), respectively, in comparison with that in group A. After adjusting for age; basal FSH level; AFC; gonadotropin dosage regimen; and levels of E2, LH, and progesterone on the day of hCG trigger, and the time interval between hCG trigger and oocyte retrieval, the likelihood ratio of unexpected ovulation rate in groups B and C was 2.96 (95% CI: 0.64–13.70) and 11.74% (95% CI: 3.09–44.62), respectively. The test for trend was statistically significant before and after correction ($P < 0.05$).

Moreover, it was concluded that the risk of unexpected ovulation increased by 2.27 times for one standard deviation (SD) (approximately 10%) increase in Δ E2% (95 % CI: 1.76–2.94). After adjusting relevant confounders, the risk of unexpected ovulation increased by 2.22 times (95% CI: 1.72–2.87) (Table 3).

Table 3
Logistic regression analysis of relation between $\Delta E2\%$ and unexpected ovulation

Factors	Odds ratio (95% CI)	Odds ratio-adjusted (95% CI)
Group A($\Delta E2\% < 10\%$)	Ref	Ref
Group B($10\% > \Delta E2\% > 20\%$)	3.36(0.75–15.13)	2.96(0.64–13.70)
Group C($\Delta E2\% \geq 20\%$)	18.86(5.35–66.51)	11.74(3.09–44.62)
<i>P</i> for trend	0.000	0.000
Per 10% (1 SD) decrement	2.27(1.76–2.94)	2.22(1.72–2.87)

ROC curve analysis of predictive value of $\Delta E2\%$ for unexpected ovulation

To assess the predictive value of $\Delta E2\%$ for unexpected ovulation, ROC curves were generated. When we combined premature LH peak (> 10 mIU/ml) or high progesterone level (> 1.0 ng/ml) on the day of hCG trigger, the AUC was 0.849 (95% CI: 0.764–0.934, $P < 0.05$), and the maximum Youden Index was 0.610, with a cut-off of 0.260 (Fig. 1). However, when we considered only $\Delta E2\%$, the AUC was 0.738 (95% CI: 0.562–0.914, $P < 0.05$), and the maximum Youden Index was 0.380, with a cut-off of 0.072 (Fig. 2). Therefore, the results suggest that the $\Delta E2\% > 26\%$ in cycles with premature LH peak and high progesterone levels on the day of hCG trigger is a valuable predictor of unexpected ovulation.

Clinical Data Of Subgroups A1,b1, And C1

A total of 295 cases of fresh embryo transfer were performed in the study data, comprising 189 cases of fresh embryo transfer cycle in group A (marked as group A1), 79 cases in group B (marked as group B1), and 27 cases in group C (marked as group C1). Comparison of the baseline characteristics and clinical outcomes of the three subgroups showed no significant difference in mean age, years of infertility, BMI, baseline FSH level, AFC counts, and the total dosages of gonadotropin ($P > 0.05$). The three subgroups were balanced and comparable. There was no significant difference in the rates of embryo implantation, clinical pregnancy, live birth in fresh embryo transfer cycle, and early abortion among the three subgroups ($P > 0.05$) (Table 4).

Table 4

Comparison of baseline characteristics and clinical outcomes among subgroups A1, B1, and C1.

Factors	Group A1 (n = 189)	Group B1 (n = 79)	Group C1 (n = 27)	P-value
Age(year)	36.73 ± 5.06	35.65 ± 5.26	36.85 ± 5.05	0.262
Infertility year (year)	4.40 ± 3.90	3.74 ± 2.97	4.30 ± 2.51	0.389
BMI (Kg/m ²)	21.83 ± 2.60	21.10 ± 2.52	21.84 ± 3.01	0.107
Baseline FSH (IU/L)	8.76 ± 3.70	8.79 ± 3.34	8.75 ± 3.58	0.959
AFC count(n)	4.49 ± 1.88	4.77 ± 1.98	4.26 ± 2.18	0.396
The total dosages of Gn (IU)	2621.30 ± 877.70	2572.78 ± 715.20	2217.11 ± 891.91	0.088
Endometrium thickness on day of ET (mm)	9.83 ± 2.10	9.72 ± 2.10	9.38 ± 1.65	0.571
Embryo transfer number (n)	1.83 ± 0.42	1.80 ± 0.46	1.82 ± 0.42	0.783
Embryo implantation rate (%)	27.8(97/349)	33.1(47/142)	26.0(13/50)	0.444
Clinical Pregnancy rate (%)	42.3(80/189)	43.0(34/79)	37.0(10/27)	0.854
The early abortion rate (%)	21.3(17/80)	17.6(6/34)	30.0(3/10)	0.697
Live birth rate (%)	29.1(55/189)	32.9(26/79)	18.5(5/27)	0.364
ET: embryo transfer.				

Discussion

Serum E2 levels play a vital role in follicular growth, oocyte maturation, embryonic development, and endometrial receptivity. In the present study, we selected subjects who demonstrated POR. The primary concern was the availability of sufficient and high-quality oocytes and embryos. The results showed that the decrease in E2 levels on the day after hCG trigger was a valuable predictor of unexpected ovulation in patients with POR. However, the decline in E2 levels may not directly affect the clinical outcomes of fresh embryo transfer in IVF/ICSI.

Although previous studies [10–12] have focused on the effect of serum E2 levels or progesterone / E2 ratios on the day of hCG trigger on clinical outcomes, there was a lack of consensus in this regard. Two high-quality studies [6, 13] concluded that the E2 levels on the day of hCG trigger had no significant predictive value for the occurrence of premature ovulation in the natural cycle; however, the ratio of E2 change between the day 0 and 1 of hCG administration was significant. Another study [14] found that decreased E2 levels on the day after hCG trigger was an effective prediction index for premature ovulation in the natural cycle. Similar to the literature, the present study not only focused on E2 levels on the day of

hCG, but also on the change in the ratio of E2 levels between day 0 and 1 of hCG trigger. However, the novelty of this study is that it focuses on the decreased ratios of E2 levels on the day after hCG trigger, helping us to predict the occurrence of unexpected spontaneous ovulation. The decrease in E2 levels at any time point will make clinicians vigilant, but the corresponding measures to be realized are still based on clinical experience. In the present study, it was observed that the higher the ratio of decreased E2 levels on the day after hCG trigger, the higher the incidence rate of unexpected ovulation and lower the number of oocytes, OCCs, mature oocytes, fertilization, and high-quality embryos obtained. We further explored the relationship between the different decreased rates of E2 level following hCG trigger and the incidence of premature ovulation. After adjusting for relevant confounders, the risk of unexpected ovulation by a 30% decrease in E2 level was 11.72 times higher than that of a 10 % decrease; and the trend was statistically significant. Moreover, when the decreased ratios of E2 were standardized, it was found that the risk of unexpected ovulation increased by 2.22 times for each SD (approximately 10%) of decreased E2 on the day after hCG administration. Therefore, the decrease in E2 levels on the day after hCG trigger is an effective indicator for predicting premature ovulation.

Increase in the LH peak and/or increased progesterone levels on the day of hCG trigger are currently effective indicators for predicting premature ovulation. However, these studies are not unified in their conclusions. Most studies [15–17] suggest that with LH level ≥ 10 mIU/mL and progesterone levels > 1.0 ng/mL on the day of hCG trigger, the probability of premature ovulation increases. Effect of the GnRH-A protocol is similar to that of the GnRH agonist protocol in controlling the early onset of the LH peak [18, 19]. However, in the elderly and patients with POR, the LH peak is still likely to occur, resulting in early ovulation. This is because the secretion of gonadotrophin peak-attenuating factor (GnSAF), the key factor for controlling the LH peak to prevent unexpected ovulation, is reduced in patients with POR and in elderly women. The results of this study showed that higher the decreased ratio of E2 level on the day after hCG trigger, higher the LH levels on the day of hCG trigger and thus, higher the ratio of early LH peak and early rise in progesterone levels. The ROC curve analysis suggested that combination of LH and progesterone levels on the day of hCG trigger, and the decreased E2 levels were more valuable in predicting unexpected ovulation.

Previous studies on whether the fluctuation of E2 level influenced the clinical outcomes were discordant. Some studies [6, 7, 13] suggested that the E2 level on the day of hCG trigger affected clinical pregnancy rates. However, most studies [20–22] suggested that E2 levels before oocyte retrieval cannot be used as the sole predictor of clinical outcomes. The different conclusions of these studies could also be related to the different research groups and COS protocols. In this study, we focused on whether the clinical outcomes of patients with POR were affected by the different decline rates of E2 levels on the day after the hCG trigger in the GnRH-A protocol. Our results showed that there was no significant difference in the clinical or live birth rates. The main reason for this is the stringent assessment of the appropriate conditions for fresh embryo transfer. If observations such as abnormal progesterone levels, endometrial abnormalities, or abnormal uterine environment are conducted, the whole embryo freezing method will be opted. We also found that the basic characteristics of the three subgroups were balanced, which is one of the reasons for the lack of significant differences in clinical outcomes. Therefore, these results further

support the idea that the decrease in E2 level on the day after hCG trigger cannot be used as the sole predictor of clinical outcome.

Lu et al. [14] found that when E2 decreased after hCG administration, emergency oocyte retrieval could effectively reduce the incidence of premature ovulation and the cancelation rate; in particular, emergency oocyte retrieval did not reduce the rate of mature oocytes and implantation rate. As shown in Table 1, it is suggested that more the level of E2 decreased, shorter the time interval between hCG trigger and oocyte retrieval. This is related to active emergency oocyte retrieval to improve the oocyte retrieval rate in clinical practice. Nevertheless, there are a few limitations to this study. Briefly, we failed to further explore the exact relationship between the rate of E2 decline on the next day of hCG trigger and the timing of oocyte retrieval, and, currently, there is not enough literature on the same. Therefore, further randomized controlled studies are required to provide valuable information for clinical practice.

Conclusions

In summary, we explored the predictive value of E2 decline on the day after hCG trigger in unexpected spontaneous ovulation, and found that the higher the E2 decline, the greater was the incidence of premature ovulation. Moreover, combination of the LH or progesterone levels on the day of hCG trigger, and the E2 level decrease on the day after hCG trigger can better predict unexpected spontaneous ovulation, to ensure effective intervention measures and guide clinical work. However, the decreased ratios of E2 levels on the day after hCG trigger did not directly affect the clinical pregnancy outcome.

List Of Abbreviations

Δ E2% - decline rate of serum E2 level

AFC - antral follicle count

AMH - anti-Mullerian hormone

AUC - area under the ROC curve

BMI - body mass index

CI - confidence intervals

COS - controlled ovarian stimulation

E2 - estradiol

FSH - follicle-stimulating hormone

GnRH-A - gonadotropin-releasing hormone antagonist

hCG - human chorionic gonadotropin

ICSI - intracytoplasmic sperm injection

IVF-ET - in vitro fertilization-embryo transfer

LH - luteinizing hormone

ROC - Receiver operating characteristic

SD - standard deviation

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangdong Women and Children Hospital and has been performed in accordance with the principles of Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

None declared.

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Authors' contributions

Q.H, Q.Z and L. S were responsible for experiment conception, collection, and analysis of data. W.L, T. T and J. Z were responsible for experiment design, experiment conception and manuscript writing. F.L. designed the work, provided technical guidance and final approval of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

ROC curve analysis of predictive value of $\Delta E2\%$ for unexpected ovulation, which combined premature LH peak (>10 mIU/ml) or the high P level (>1.0 ng/ml) on the day of hCG.

Figure 2

ROC curve analysis of predictive value of $\Delta E2\%$ for unexpected ovulation.