Assessing predictors for the success of GnRH antagonist protocol in reproductive women in IVF/ICSI - in fresh cycles

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Abstract. The aim of the present study was to evaluate the factors that affect the success rate of gonadotropin-releasing hormone antagonist on *in vitro* fertilization/intracytoplasmic sperm injection cycles. Multivariate analysis was performed to assess the factors that influence the outcomes, such as oocytes retrieved, and the success of pregnancy. The results showed that E_2, P on human chorionic gonadotropin (HCG) day and body mass index (BMI) were positively correlated with the number of oocytes retrieved (P=0.001, P=0.024, P=0.017, respectively). The duration of infertility as well as the luteinizing hormone on HCG day were negatively correlated with the number of oocytes (P=0.048, P=0.002, respectively). The age of the women and P on HCG day were negatively correlated with successful pregnancy (P<0.001, P=0.022). In conclusion, some parameters, such as E_2, P, and LH on the HCG day, as well as age and BMI, may affect treatment outcomes.

Introduction

Gonadotropin-releasing hormone (GnRH) antagonist is used in controlled ovarian stimulation cycles, and is at least as safe as the long GnRH agonist protocol. Furthermore, the GnRH antagonist protocol requires less follicle stimulation, and has a lower risk for ovarian hyperstimulation syndrome (1). It has been shown that age, oocyte, quality of the embryo and endometrial receptivity are the most important factors in the success of *in vitro* fertilization (IVF), and the GnRH antagonist has an extrapituitary effect on the above factors (2).

The GnRH antagonist offers several advantages compared with the GnRH agonist protocol, including a reduction in the duration of the treatment and reduced doses of gonadotropins, as well as no risk of ovarian cyst formation (3). Qiao *et al* reported that the normal responders treated with the GnRH antagonist protocol exhibited the same high success rates as women treated with the long GnRH agonist protocol (4). However, in low responders, the ovaries are stimulated without pituitary suppression, which may induce asynchronous follicular development. Antral follicle size during the early follicular phase is markedly heterogeneous. As GnRH antagonists prevent the increase in luteinizing hormone (LH) levels, it has been reported that the GnRH antagonist causes more profound LH than follicle-stimulating hormone (FSH) blockage, thereby reducing the follicular fluid E_2 level compared to GnRH agonist protocols (5). Thus, whether the levels of LH and E_2 on human chorionic gonadotropin (HCG) day influence the outcomes of the antagonist protocol need to be elucidated.

As FSH is needed for ensuring follicular growth as well as endometrial development and LH is needed for achieving proper oocyte maturation, both FSH and LH are necessary for oocyte development. However, the role of baseline serum LH in predicting the success of IVF in terms of infertility outcomes remains controversial. Inconsistent results have been found, especially with regard to infertile women aged ≥35 years, regardless of whether they were using rLH supplementation during ovarian stimulation or not (6).

For the best results in IVF outcome, optimal follicular development should be achieved. It has been reported that good morphological quality of embryos is positively associated with conception after IVF (7) and endometrial characteristics, such as endometrial thickness (EM), have been evaluated as prognostic factors. However, the lack of consensus on EM is explained by the difficulty of an exact definition of a thin endometrium as assessed by transvaginal ultrasonography. Thus there is no clear conclusion on the clinical significance of EM as a predictive parameter for the chances of pregnancy after IVF.

Therefore, the aim of this retrospective study was to explore rFSH treatment without rLH supplementation and antagonist treatment and to evaluate the best predictors for the success of the GnRH antagonist protocol in reproductive women undergoing IVF/intracytoplasmic sperm injection (ICSI)-ET treatment in fresh cycles. Baseline serum FSH, LH, E_2, P level and LH, E_2, P level and EM on the HCG day as well as the number of quality embryos, were evaluated to determine the

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influence of these factors on the success of IVF in terms of clinical pregnancy.

Materials and methods

Patients. This was a retrospective, single-centre cohort study. The study included patients who underwent IVF/ICSI cycles with the GnRH antagonist protocol from January 1, 2014 to September 30, 2015. All the patients reached the ovum pick-up stage. Only women undergoing their first antagonist protocol were included. It has been shown that the two sources (IVF/ICSI) of embryos have no effect on their cultivation (8). The fecundity of all male partners of the patients was normal according to World Health Organization criteria (9). The present study was conducted at the Linyi People's Hospital (Shandong, China) and was approved by the Ethics Committee of Linyi People's Hospital. A written informed consent form was obtained from all patients.

Materials. The patients underwent COH using the flexible GnRH antagonist protocol, as reported in previous studies (10,11). The injection of rFSH (Gonal F®; Merck Serono S.A., Geneva, Switzerland) started on day 2 of the menstrual cycle, and the starting dose of rFSH was 75-300 IU daily and was individualized according to the patient's age, body mass index (BMI), antral follicle count, baseline E_2, P, FSH and LH concentration.

The GnRH antagonist used was cetrorelix acetate (Cetrotide; Merck-Serono Ltd., Aubonne, Switzerland). Treatment with rFSH and cetrorelix acetate was continued until the day of the final oocyte maturation trigger.

For the group, the final oocyte maturation trigger was injected with 250 μg human chorionic gonadotropin α (r-HCG), (Ovidrel, Merck-Serono Ltd., Aubonne, Switzerland). Thirty-six to 37 h after r-HCG injection, oocyte aspiration was performed, which was guided by transvaginal ultrasound. Embryo transfer was performed on day 3/5 following oocyte retrieval. All of the cycles received luteal phase support with progesterone in the form of vaginal suppositories of 90 mg once daily (Crinone, Fleet Laboratories Ltd., Watford, UK). Clinical pregnancy was defined as visualization of a gestational sac and foetal cardiac activity on transvaginal ultrasound after 4-5 weeks of IVF-ET.

Statistical analysis. SPSS 23.0 software for Windows was used for statistical treatment (SPSS, Chicago, IL, USA). In the present study, the data were reported as the mean ± standard deviation (SD). Linear regression was conducted to evaluate the effect of the different variables on the number of oocytes retrieved. Logistic regression was conducted to evaluate the different variables on the success of pregnancy. A $P<0.05$ was considered significant.

Results

Baseline characteristics. A total of 298 IVF/ICSI fresh cycles were evaluated in antagonist protocols. The serum gonadotropin (FSH and LH), E_2 and P levels were evaluated beyond the baseline, and the baseline characteristics are presented in Table I. The mean age was 35.46±5.22 (108 cases aged <35 years, 190 cases aged ≥35 years), and the mean BMI was 24.03±3.22. The mean duration of infertility was 4.25±3.09 years, and the mean basal hormone profile of FSH was 8.11±2.70, E_2 was 45.58±20.98, P was 0.48±0.28 and the mean LH was 3.80±2.04. The mean initial dose of rFSH administration was 204.82±47.61, and the mean total dose of rFSH was 1926.22±589.11. The mean duration of stimulation was 9.29±1.71. The total dose of antagonist administered was 1.01±0.39. The mean level of E_2 on HCG day was 1411.26±936.37, and the mean level of P on HCG day was 0.62±0.29. The mean level of LH on HCG day was 2.57±2.07, and the mean thickness of the EM on HCG day was 9.98±2.20. The mean number of total oocytes retrieved was 5.12±3.31, and the mean number of 2PN oocytes was 3.70±2.80. The mean number of embryos available was 2.28±1.31, the mean number of high quality embryos was 1.55±1.49, and the mean number of embryos transferred was 1.73±0.50. The clinical pregnancy rate was 38.93% (116/298), and the live birth rate was 26.85% (80/298) (Table I).

Table I. Baseline cycle characteristics of patients undergoing the GnRH antagonist protocol.

Characteristics	Mean ± SD
Age (years)	35.46±5.22
Duration of infertility (years)	4.25±3.09
BMI (kg/m^2)	24.03±3.22
Basal FSH level (UI/l)	8.11±2.70
Basal LH level (UI/l)	3.80±2.04
Basal E_2 (pg/ml)	45.58±20.98
Basal P (ng/ml)	0.48±0.28
Initial dose of rFSH administration (UI)	204.82±47.61
Total dose of rFSH (UI)	1926.22±589.11
Stimulation duration (days)	9.29±1.71
Total dose of antagonist administration (mg)	1.01±0.39
E_2 on HCG day (pg/ml)	1411.26±936.37
P on HCG day (ng/ml)	0.62±0.29
LH on HCG day (UI/l)	2.57±2.07
EM on HCG day (mm)	9.98±2.20
Mean no. of total oocytes retrieved	5.12±3.31
Mean no. of 2PN oocytes	3.70±2.80
Mean no. of embryos available	2.28±1.31
Mean no. of high quality embryo	1.55±1.49
Mean no. of embryos transferred	1.73±0.50

GnRH, gonadotropin-releasing hormone; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HCG, human chorionic gonadotropin; EM, endometrial thickness.

Linear regression for the number of total oocytes retrieved and logistic regression analysis for the success of clinical pregnancy. Table II shows the influence factors that affect the number of oocytes retrieved. The duration of infertility and the level of LH on HCG day was negatively correlated with the number of oocytes retrieved (P=0.048, P=0.002, respectively). By contrast, the level of E_2, P on HCG day and the BMI were

Table II. Linear regression analysis for the number of total oocytes retrieved.

Items	β	P-value
Age (years)	-0.070	0.087
Duration of infertility (years)	-0.078	0.048[a]
BMI (kg/m^2)	0.102	0.017[b]
Basal FSH (UI/l)	-0.083	0.055
Basal LH (UI/l)	0.025	0.555
Basal E_2 (pg/ml)	-0.034	0.396
Basal P (ng/ml)	0.005	0.888
Initial dose of rFSH administration (UI)	0.067	0.557
Total dose of rFSH (UI)	-0.072	0.650
Duration of rFSH stimulation (days)	-0.003	0.981
Total dose of antagonist (mg)	0.077	0.150
E_2 on HCG day (pg/ml)	0.667	<0.001[b]
P on HCG day (ng/ml)	0.096	0.024[b]
LH on HCG day (UI/l)	-0.122	0.002[a]
EM on HCG day (cm)	0.067	0.079

[a]Negatively and [b]Positively correlated with total oocytes retrieved. BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HCG, human chorionic gonadotropin; EM, endometrial thickness.

Table III. Logistic regression analysis for the success of clinical pregnancy.

Items	β	Exp (B)	P-value
Age (years)	-0.116	0.890	0.000[a]
Duration of infertility (years)	-0.020	0.980	0.660
BMI (kg/m^2)	-0.020	0.981	0.682
Basal FSH (UI/l)	0.046	1.047	0.423
Basal LH (UI/l)	-0.068	0.934	0.341
Basal E_2 (pg/ml)	-0.008	0.992	0.265
Basal P (ng/ml)	-0.012	0.988	0.980
Initial dose of rFSH administration (UI)	-0.007	0.993	0.413
Total dose of rFSH (UI)	0.001	1.001	0.468
Duration of rFSH stimulation (days)	-0.308	0.735	0.231
Total dose of antagonist administration (mg)	0.827	2.286	0.093
E_2 on HCG day (pg/ml)	0.000	1.000	0.594
P on HCG day (ng/ml)	-1.266	0.282	0.022[a]
LH on HCG day (UI/l)	0.033	1.034	0.603
EM on HCG day (cm)	0.020	1.021	0.742
Mean no. of total oocytes retrieved	-0.080	0.923	0.391
Mean no. of 2PN oocytes	0.155	1.167	0.142
Mean no. of embryos available	-0.206	0.814	0.417
Mean no. of high quality embryo	0.339	1.403	0.078
Mean no. of embryos transferred	0.507	1.660	0.114

[a]Negatively correlated with success of clinical pregnancy. BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HCG, human chorionic gonadotropin; EM, endometrial thickness.

positively correlated with the number of oocytes retrieved (P<0.001, P=0.024, P=0.017, respectively).

Table III shows that age was inversely correlated with the success of pregnancy (P<0.001), as well as the level of P on HCG day (P=0.022).

Discussion

In this retrospective study, we aimed to identify factors that affect the success of the antagonist protocol to improve clinical outcomes. Usually clinicians focus on factors such as the duration of rFSH and antagonist, E_2/P/LH levels on the HCG day, and EM on the HCG day when these protocols were used to treat patients.

In this study, we found that there were no significant correlated factors among the age of the women, basal FSH/LH/E_2/P levels, EM on HCG day, or duration of rFSH administration on the number of total oocytes retrieved.

There was noteworthy finding that the level of E_2, P on HCG day was positively correlated with the number of oocytes retrieved. Another finding in the study was the positive correlation between the BMI of the women and the number of oocytes retrieved. The duration of infertility was negatively correlated with the number of eggs retrieved.

It has been reported that clinical pregnancy rates increase with the increasing EM, and most studies have defined the minimal thickness at approximately 7 mm. When women fail to achieve minimal endometrial development, the embryos are often frozen (12-14). However, in the retrospective study, the mean EM on HCG day was 9.98±2.20 mm and exhibited no significant correlation with the success of pregnancy.

In controlled ovarian stimulation, the use of pituitary suppression agents to prevent premature LH surge is central. GnRH antagonists permit the immediate suppression of pituitary gonadotrophins by competitive inhibition of gonadotrophin receptors. However, low endogenous LH concentrations may induce negative effects that affect treatment outcomes. It has been reported that low LH levels increase early pregnancy loss rates (15,16), but the definition of the LH threshold remains controversial. Westergaard *et al* used an LH threshold of 0.5 mIU/ml to define the low LH group and found similar clinical pregnancy rates between the low LH group and the normal group (17). However, the low LH group was associated with a lower chance of live birth compared with the normal group. Chen *et al* used an LH cut-off value of 0.8 mIU/ml to define the two groups (≤0.8 mIU/ml and >0.8 mIU/ml) (18). Their study showed significantly increased early pregnancy loss rates in the low LH group (≤0.8 mIU/ml) compared with the group with normal LH concentrations (>0.8 mIU/ml). Although the implantation rates, clinical pregnancy rates and live birth rates were lower in the low LH group, the differences were not significant.

In the present study, the mean basal LH was 3.80±2.04, and the LH on HCG day was 2.57±2.07. Linear regression showed

that basal LH had no effect on the oocytes retrieved, but the LH on HCG day was inversely correlated with the number of eggs retrieved. Using logistic regression, neither the basal LH nor the LH on HCG day was significantly correlated with the success of clinical pregnancy.

In IVF/ICSI cycles, the endometrium and embryo are exposed to supraphysiological concentrations of E_2 and P, which may influence pregnancy outcomes. Whether the elevated E_2, and especially the P level, affect the clinical pregnancy is still controversial. Li *et al* reported that the P concentration on HCG day adversely affects IVF pregnancy outcomes (19). However, some findings have shown that elevated P levels have no effect on blastocyst embryo transfer in GnRH agonist/antagonist cycles (20,21). Some investigators have demonstrated that there is no correlation between P levels and pregnancy outcome (22-24). Yang *et al* demonstrated that the high P level on HCG day may affect the endometrial receptivity rather than the oocyte or embryo quality (25). For those patients, researchers have suggested frozen-thawed embryo transfer or blastocyst transfer. Li *et al* have demonstrated the effect of high progesterone levels on outcomes of *in vitro* fertilization-embryo transfer in patients with different ovarian responses (26). They defined a P cut-off value of 2.5 ng/ml in the high ovarian response group, 2.25 ng/ml in the moderate ovarian response group and 1.5 ng/ml in the low ovarian response group. Their results showed that in each group, the clinical pregnancy rate and embryo implantation rate were lower in the patients with an increased P level than those in which the P level did not increase. The increased level of P on the day of HCG may affect the treatment outcomes of IVF-ET. The phenomenon of the increased P level in women undergoing controlled ovarian stimulation still needs to be elucidated. It has been reported that for women with a low ovarian response and, a P level of >1.5 ng/ml, HCG given in advance reduces the negative effects of the elevated P on pregnancy outcomes. For PCOS patients with a high ovarian response, a small starting dose of FSH may reduce an elevated P level (27,28).

In the present study, the mean serum P level was 0.62±0.29, and the P level on HCG day was inversely correlated with the success of clinical pregnancy.

As the serum E_2 level reflects the maturity of the follicle and the quality of the oocytes, the E_2 level is regarded as one of the most important factors in predicting clinical outcomes during the course of IVF/ICSI cycles.

Peña *et al* reported that patients with E_2 >3,000 pg/ml on HCG days had a significantly higher number of oocytes retrieved than other groups with lower E_2 levels of 1,500-3,000 pg/ml and <1,500 pg/ml (29). Some researchers have concluded that E_2 >4,000 pg/ml or E_2 >5,000 pg/ml on the day of HCG had a significantly higher number of oocytes retrieved compared to other groups (30,31). Siddhartha *et al* (32) conducted a retrospective study on the association of supraphysiological E_2 level with the reproductive outcome of ICSI. The study subjects were grouped based on the serum E_2 level on the day of HCG: group 1, <1,000 pg/ml; group 2, 1,000-2,000 pg/ml; group 3, 2,000.1-3,000 pg/ml; group 4, 3,000.1-4,000 pg/ml; group 5, 4,000.1-5,000 pg/ml. Their results showed that group 5 had a significantly higher number of oocytes retrieved than groups 1 and 2. However, there were no significant differences in the pregnancy rates.

In our retrospective study, the E_2 on the day of HCG was positively correlated with oocytes retrieved, but the E_2 on the day of HCG was not correlated with pregnancy rates and could not be used to predict pregnancy in antagonist cycles, which is consistent with previous findings (29-33).

In the present study, the mean age was 35.46±5.22 and the mean number of oocytes retrieved was 5.12±3.31. Our results indicated that 63.76% of women (190/298) undergoing antagonist protocols were aged ≥35 years. This explains the results such as the low E_2 level on HCG day (1411.26±936.37) and low total oocytes retrieved (5.12±3.31).

The finding suggests, that age was negatively correlated with the success of pregnancy, is consistent with that of other clinicians (34).

In conclusion, further larger studies should be performed to elucidate the role of factors such as the EM, E_2 and P level on HCG day in predicting the number of embryos available and clinical outcomes. Additionally, we hope that an increased number of predictors may be identified to guide the use of GnRH antagonists to ensure good reproductive and clinical outcomes.

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