Saudi Journal of Biological Sciences 27 (2020) 1049–1056

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Original article

Establishment of predictive model for analyzing clinical pregnancy outcome based on IVF-ET and ICSI assisted reproductive technology

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ARTICLE INFO

Article history:
Received 16 October 2019
Revised 25 February 2020
Accepted 26 February 2020
Available online 4 March 2020

Keywords:
IVF-ET
Assisted reproductive technology
Prediction model
ICSI
Ovarian response

ABSTRACT

Objective: In order to explore the predictive model for analyzing clinical pregnancy outcomes based on IVF-ET (in vitro fertilization and embryo transfer) and ICSI (Intracytoplasmic sperm injection) assisted reproductive technology (ART). Methods: this study selected the embryo transfer (fresh) patients who received IVF-ET or ICSI treatment in the First Affiliated Hospital of Guangxi Medical University as the subjects. Moreover, the controlled ovarian stimulation (COS) and follow-up were conducted to collect relevant data for analysis, and finally a prediction model was established. Results: The results showed that the patients were divided into different ovarian response groups at first. The age, bFSH and bFSH/bLH were the highest in the poor ovarian response group (POR), followed by the normal ovarian response group (NOR) and the lowest in the high ovarian response group (HOR). The area under the ROC curve was 0.669 according to the predictive model of pregnancy-related factors. The confidence interval of 94% was 0.629–0.697, with statistical significance (P = 0.000, P < 0.01). Conclusion: it can be concluded that in clinical pregnancy, for many related factors, regression equation can be used to establish a prediction model to diagnose the success rate of pregnancy. In conclusion, a prediction model can be built based on the relevant experimental results, to provide experimental reference ideas for increasing the success rate of ART in late clinical pregnancy, which is of great research significance.

1. Introduction

In today's social development, people's living standards are constantly improving, but there are still diseases that danger people's daily life. Among the diseases, infertility occurs constantly in married couples, with a probability of more than 15%, which has a great impact on patients and families (Singh et al., 2016). Infertility refers to the situation in which a man and a woman live together for no less than 12 months without contraception and the woman is not pregnant. In this process, the male condition is called infertility (Zhao et al., 2017). In the current situation, there are many factors leading to female infertility symptoms, but for these reasons, there are still nearly 10–20% of the infertility factors are unknown. At the current level of medical care, it is still unable to accurately detect and analyze them (Benaglia et al., 2016; Wang et al., 2016). Therefore, the exploration of infertility has once become the focus of attention.

Assisted reproductive technology (ART), as a way to solve couples' infertility, rebuilds a new hope for them to gestate offspring so that they can be freed from the shadow of previous infertility (Wang et al., 2016). Since Louis Brown, the world's first test-tube baby, was born in Britain, the development of reproductive medicine has entered a new era. With the development of science and technology, the assistant means in reproductive field become more and more mature, and the methods are also increasing. In vitro fertilization-embryo transfer (IVF-ET), also "test-tube infant" (Jeon et al., 2016; Basirat et al., 2016), refers to the technology of IVF after the oocyte is taken out from the female body and the sperm is taken out from the male body. After the formation of the fertilized egg, the embryo is developed and then transferred into the uterus of the oocyte-providing mother, so that the female can get fertilized. After 14 days of pregnancy test, the pregnancy can be determined by urine test or blood test. Human IVF or ET technology is relatively late, but it develops rapidly (Feng et al.,

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2020.02.021
1319-562X/

2018; Lai et al., 2017). In order to further increase the success rate of IVF and maternal conception, it is very important to predict pregnancy outcomes in advance. Ross et al. (2018) investigated the prevalence of neural tube defects (NTD) in twin pregnancy and the incidence of pregnancy complications in the past 10 years, and summarized the incidence of potential complications and related factors in unaffected in vitro infants (Ross et al., 2018); Özel et al. (2019) detected and analyzed the heavy metals in 21 pregnant women with middle and late NTD, and finally found that the high level of blood lead and manganese in pregnant women in the middle stage of pregnancy was related to the NTDs of newborns (Özel et al., 2019). Therefore, the continuing research on it has become the focus of the current scientific research.

In summary, although many scholars have discussed IVF, there is no unified method for evaluating the ovarian response of women. In order to understand the pregnancy outcomes more quickly and improve the success rate of test tube baby, embryo transfer patients treated with IVF-ET or ICSI in XX Maternal and Child Health Hospital were chosen, and the related data were counted and analyzed. Finally, the predictive model was established for the data obtained in order to increase the success rate for assistant biotechnology for later clinical pregnancy.

2. Materials and methods

2.1. Research objects

In this study, 220 cases of embryo transfer (fresh) patients treated with IVF-ET or ICSI from March 2016 to March 2018 at the Reproductive Genetics Center of The First Affiliated Hospital of Guangxi Medical University were selected. Among them, 113 cycles were transplanted. Others canceled the transplantation or cycle due to some factors, resulting in only 126 cases finally conforming to the requirements. The patients were 21–44 years old, with an average age of 31.04 ± 5.11; the infertility was 1–12 years, average 3.24 ± 2.61 years, and BMI was 21.17 ± 3.22 kg/m^2. All the experiments were approved by the patients and their families, and by the ethics committee of the First Affiliated Hospital of Guangxi Medical University.

Inclusion criteria: The follow-up records of all patients were complete; they were performed with embryo transfer (fresh) for the first time; all patients were diagnosed by gynecological or endometrial conditions greater than or equal to two times; no chromosomal abnormalities; no mental disorders.

Exclusion criteria: patients lost visits; those who failed to transfer fresh embryos due to multiple or single factors; those who had or were undergoing frozen embryo transplantation; those who suffered from medical complications such as hypertension, diabetes and nephropathy; and those who cannot provide complete information.

2.2. Grouping

According to the different number of eggs, the patients whose number of eggs was less than 3 were classified as poor ovarian response group (POR) according to the European Bologna Consensus (Zhang et al., 2017). According to the literature (Yuan et al., 2016), patients with more than 15 eggs were classified as high ovarian response group (HOR). Those with low and high ovarian response were excluded and classified as normal ovarian response group (NOR).

In 113 transplantation cycles, there were 53 cases (pregnancy group) and 60 cases (no pregnancy group) according to the success of pregnancy.

2.3. Controlled stimulation of ovarian response

Long-term luteal regimen. This is a routinely clinical controlled ovarian stimulation (COS) program for patients with normal ovarian reserve. Firstly, the regulation of menstrual cycle was lowered. In the luteal mid-term of 7 days after ovulation, the patients were injected with gonadotropin-releasing hormone agonist (GnRH-a) (Tianjin Taize Xingye Biotechnology Co., Ltd., China) to regulate the menstrual cycle. For long-acting agents, 0.8–1.3 mg was injected once, and for short-acting agents, 0.05–0.1 mg was injected daily to HCG day. For those with irregular menstrual cycles, they were given short-acting oral contraceptives (OC) on the 3rd to 5th day of the first month's menstrual cycle before COS, one pill a day, and GnRH-a was lowered in the hospital when they took the remaining 6 pills. After 14 days of descending regulation, B- ultrasound was performed. If the diameter of ovarian cyst was more than 20 mm, the puncture of ovarian cyst could be performed on that day. The levels of FSH, LH and E2 in blood were detected. The pituitary descending regulation status in vivo was understood. If the descending regulation was achieved, Gn was activated. If the descending regulation standard was not reached, the subjects were observed until the descending regulation standard was reached, then the following steps were carried out.

Extra-long scheme. This scheme is mostly suitable for patients with adenomyosis, endometriosis and uterine leiomyoma. The implementation method is to inject long-acting GnRH-a (3.75 mg) on the 3rd day of menstruation. Twenty-eight days later, the second long-acting GnRH-a is injected twice. The dosage is unchanged and it can be injected 2–3 times continuously. After the last injection, 23.75 mg can be injected 2–3 times. B-ultrasound can be conducted within 28 days after the last injection. Then, the levels of FSH, LH and E2 of the blood samples are sampled and checked and Gn is started in time. Because of the inhibition of serum LH level in this scheme, drugs containing LH level are often needed to assist, such as HMG. The dosage selection method, follicular monitoring and HCG day determination are the same as those of the long scheme.

Long follicular phase. There are many applicants of this scheme. Only those aged over 40 years old and AMH < 0.5 ng/mL are not suitable, and all other patients can adopt this scheme. Firstly, 3.75 mg of long-acting drug was injected on the 2nd to 3rd day of menstrual cycle. B-mode ultrasound was carried out within 28 days after injection. Then, the levels of FSH, LH and E2 were investigated by blood sampling.

The above scheme designs all started after the pituitary hypophysis is completely down-regulated, and the growth of follicles was monitored by vaginal B-ultrasound, then recorded, and Gn was initiated at the appropriate time. At the same time, the number of mature follicles with 16–22 mm diameter in both ovaries of women on HCG day was recorded, and the follicle output rate was calculated.

2.4. Luteal support

After egg retrieval, the luteal support was made. First, there are injections, oral preparations, vaginal suppositories etc., and then injected with progesterone needle 20–60 mg/d, or in the vaginal, giving progesterone gel 90 mg/d, or these two kinds of medicine were taken orally, and continued for 14 days after the day of egg collection.

2.5. Determination of postoperative pregnancy

For all subjects, blood β-HCG test was performed in hospital after 11 weeks of operation. If blood HCG (+) was found, then vaginal B-ultrasound was performed 4–5 weeks after blood β-hCG test.

At this time, if the primitive cardiac pulsation in intrauterine gestational sac or embryo was found, the clinical pregnancy would be successful, and then the corpus luteum would continue to be given some support until about 8–10 weeks to stop the supply of drugs.

2.6. Establishment of prediction model and statistical analysis

The data were analyzed by SPSS 22.0 software. 2IST method was used for single factor analysis and logistic regression analysis for multi-factor analysis. $P < 0.05$ indicated significant statistical difference. A full-variable prediction model of pregnancy-related factors was established. The data were analyzed by regression analysis, and the meaningful correlative factors were introduced into the model established in this study. Then, the success rate of pregnancy after simulation and the success probability of the prediction model were calculated according to the equation of the prediction model, and the ROC curve was made between the predicted probability of pregnancy success calculated and the clinical pregnancy data measured. The equation was verified by calculating the graphic area, so as to test its effect and performance.

Table 1
Comparison and analysis of patients' general condition and related indicators in different ovarian response groups (A. determination of clinical indicators; B. COS data analysis).

	Groups	POR group	NOR group	HOR group
A	Case	15	76	35
	Age	33.84 ± 3.87*	32.18 ± 5.19*	30.97 ± 4.21#
	Infertility duration	4.11 ± 2.69	3.71 ± 2.88	3.43 ± 2.51
	BMI	21.91 ± 3.55	21.33 ± 3.10	21.15 ± 3.08
	AFC	9.63 ± 5.19*	12.87 ± 5.04#*	17.08 ± 4.93#
	bFSH	9.79 ± 5.13*	7.48 ± 2.14#	6.93 ± 1.92#
	bFSH/bLH	2.14 ± 1.33*	1.87 ± 0.79*	1.28 ± 0.53#
	bE2	43.19 ± 42.08	71.09 ± 73.11	77.98 ± 105.34
	AMH	1.66 ± 1.39*	2.93 ± 1.88#*	4.69 ± 2.37#
B	Total Gn	3298.51 ± 725.19*	2893.19 ± 918.07*	2279.08 ± 978.11#
	Average Gn	282.47 ± 52.11*	239.31 ± 62.19#*	179.08 ± 69.05#
	Gn start-up dose	278.12 ± 50.09*	229.28 ± 71.95#*	188.35 ± 59.07#
	Gn days	11.09 ± 1.54	12.31 ± 2.18	12.29 ± 2.43
	HCG day E2	1892.29 ± 1279.68*	3618.52 ± 1779.44#*	6479.08 ± 2417.37#
	FORT	48.52 ± 23.19*	93.03 ± 101.33#*	99.08 ± 47.52#
	Number of eggs obtained	2.58 ± 0.51*	9.19 ± 3.18#*	20.07 ± 4.31#
	Number of high-quality embryos	0.92 ± 0.96*	2.53 ± 2.18#*	4.53 ± 3.19#

Note: #, compared with POR group, $P < 0.05$; *, compared with HOR group, $P < 0.05$.

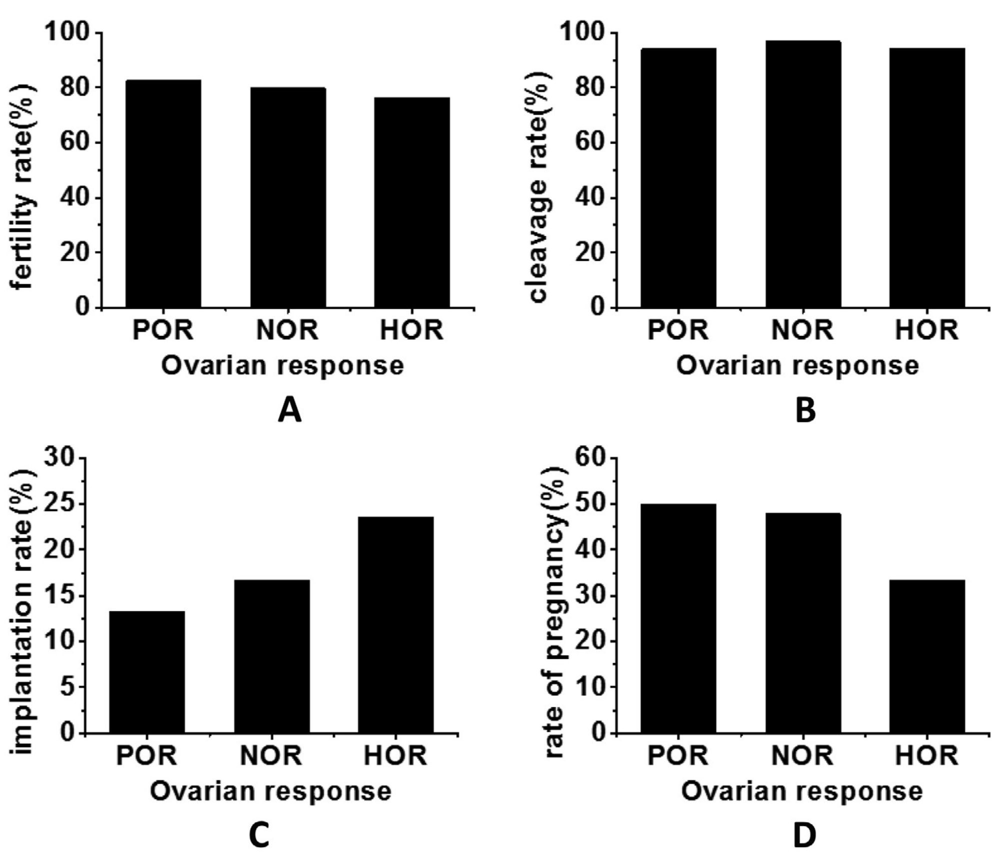

Fig. 1. Comparative analysis of outcomes in different ovarian response groups (A: fertilization rate; B: cleavage rate; C: implantation rate; D: pregnancy rate).

3. Results

3.1. Comparison of general situation and determination of clinical detection indexes in different ovarian response groups

As shown in Table 1A, through collecting and analyzing the relevant information of the subjects, it was found that in the detection of age, bFSH and bFSH/bLH, the results were as follows: POR group > NOR group > HOR group. The age of HOR group is significantly different from that of POR group and NOR group ($P < 0.05$). The index of bFSH of POR group was apparently different from that of NOR group and HOR group ($P < 0.05$). For AFC and AMH, the results were as follows: POR group < NOR group < HOR group, and the two-two comparisons results were different ($P < 0.01$). The infertility duration, BMI and bE2 had small differences among the three groups (P greater than 0.05).

Table 2
Analysis of basic indicators of patients grouped according to success of pregnancy.

Groups	Pregnancy group	No pregnancy group	P
Case	53	60	
Age	32.18 ± 5.37	3.96 ± 4.39	0.731
Infertility duration	3.34 ± 2.08	4.21 ± 3.09	0.325

3.2. Controlled ovarian stimulation data analysis and outcome analysis in different ovarian response groups

Table 1B suggested that the demand for Gn was the highest in the POR group, followed by NOR group, and then HOR group. The total amount of Gn of the HOR group was obviously different from that of the other two groups ($P < 0.05$). For E2, FORT, number of eggs and high-quality embryos on HCG day, the lowest was found

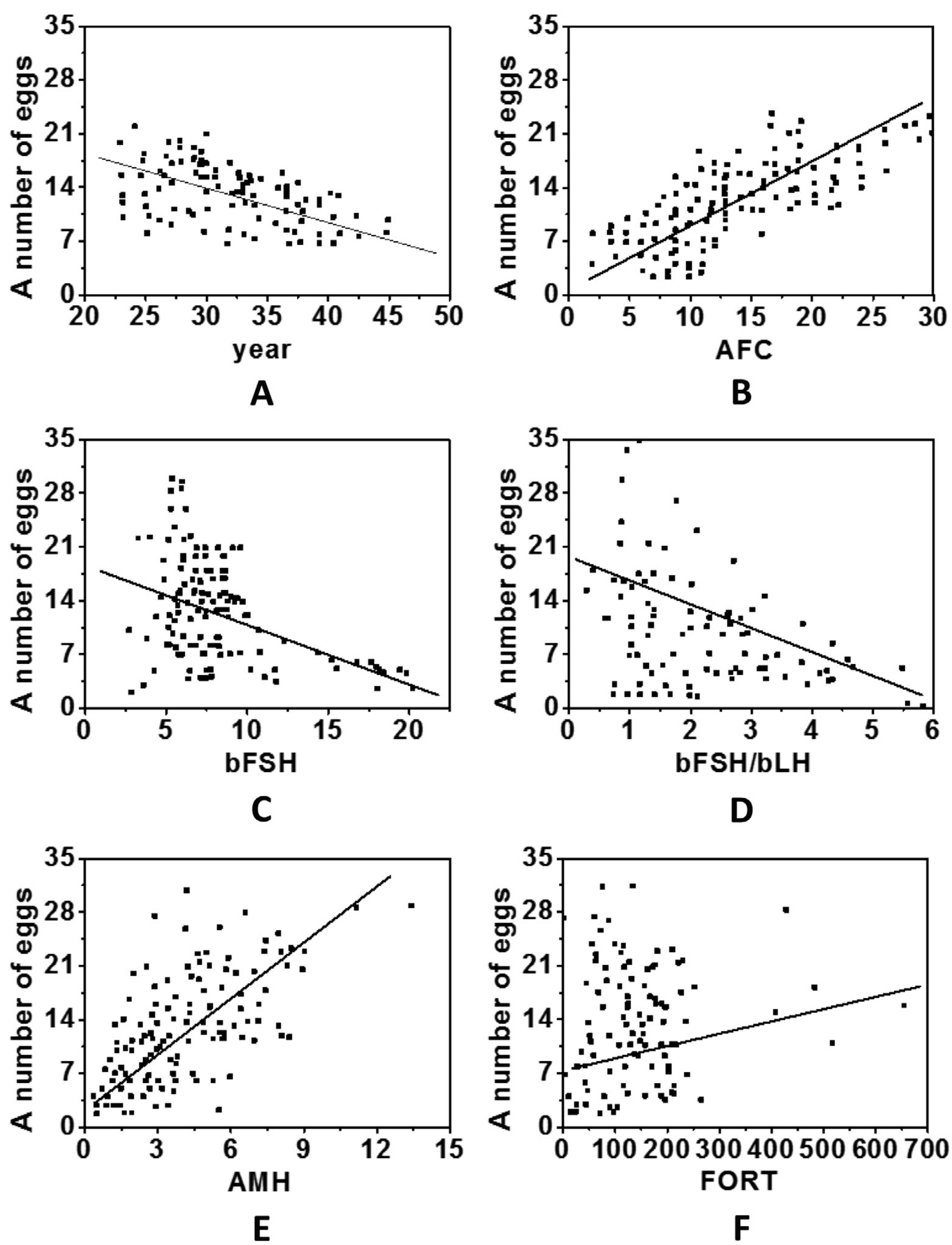

Fig. 2. Correlation analysis of the number of eggs obtained and multiple factors (A: correlation analysis with age; B: correlation analysis with AFC; C. correlation analysis with bFSH; D. correlation analysis with bFSH/bLH; E. correlation analysis with AMH; F. correlation analysis with FORT).

in the POR group, while the highest was in the HOR group, and the middle was in the NOR group. Therefore, the comparison between the two groups had significant statistical significance ($P < 0.01$). Other indicators, such as total days of Gn, fertilization rate, cleavage rate, implantation rate, and pregnancy rate had small difference ($P > 0.05$) (Fig. 1).

3.3. Analysis of the correlation between the number of eggs obtained and age, AFC, bFSH, bFSH/bLH, AMH, and FORT

From Fig. 2, it was known that the number of eggs obtained by patients was correlated with age, AFC, bFSH, bFSH/bLH, AMH and FORT ($P < 0.01$). Among them, the number of eggs obtained was negatively correlated with age, bFSH and bFSH/OLH, and positively correlated with AFC, AMH and FORT. It was found that among the factors, it had the most significant correlation with AMH, while FORT had the weakest correlation.

3.4. Comparative analysis of general situation and clinical examination between pregnancy group and no-pregnancy group

From Table 2, the age and infertility duration of the two groups were slightly different. From Fig. 3, it was found that the pregnancy group had higher BMI, AFC, bE2 and AMH, while the no-pregnancy

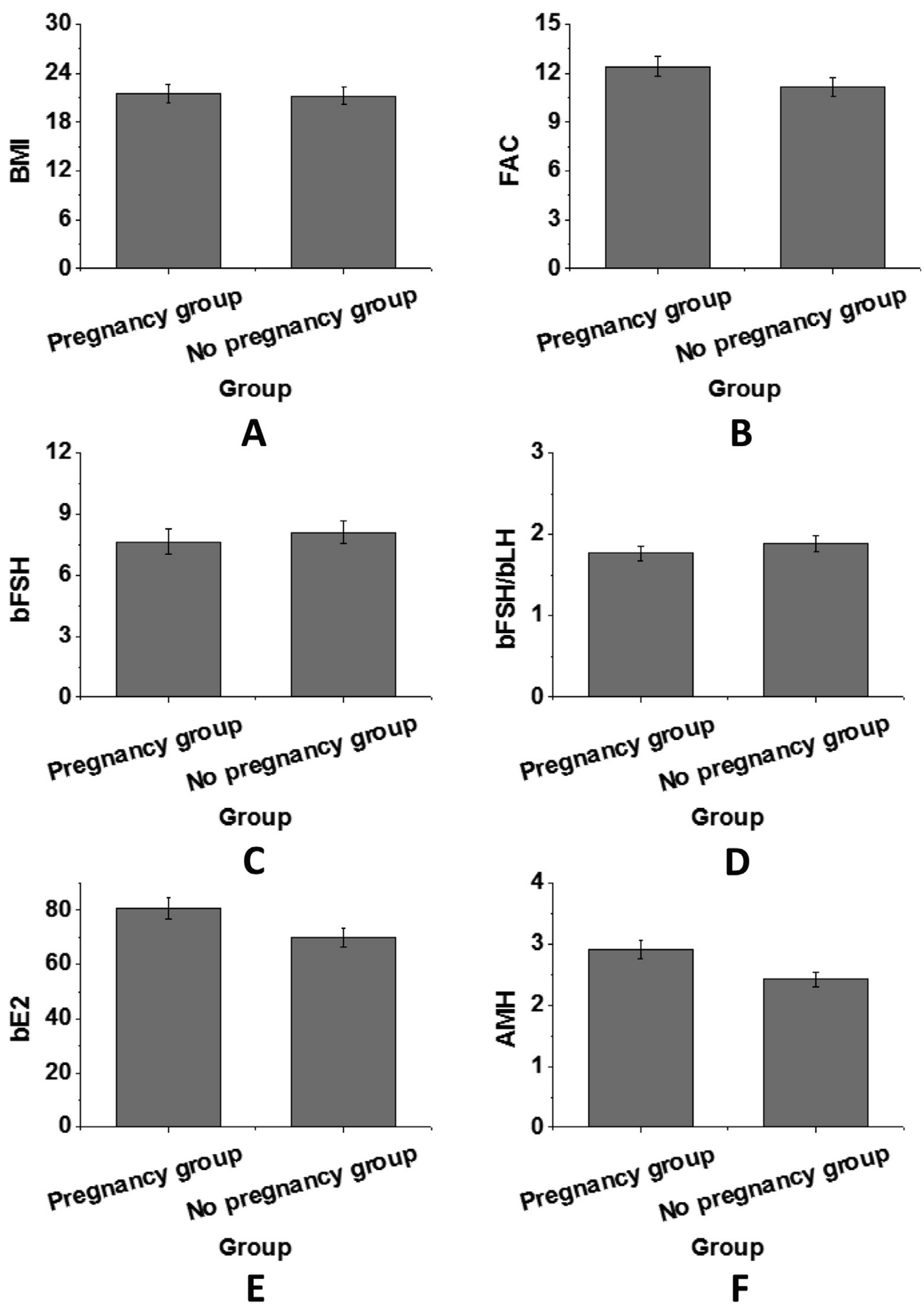

Fig. 3. Analysis of clinical detection indicators of patients grouped according to pregnancy success (A: BMI; B: AFC; C. bFSH; D. bFSH/bLH; E. bE2; F. AMH).

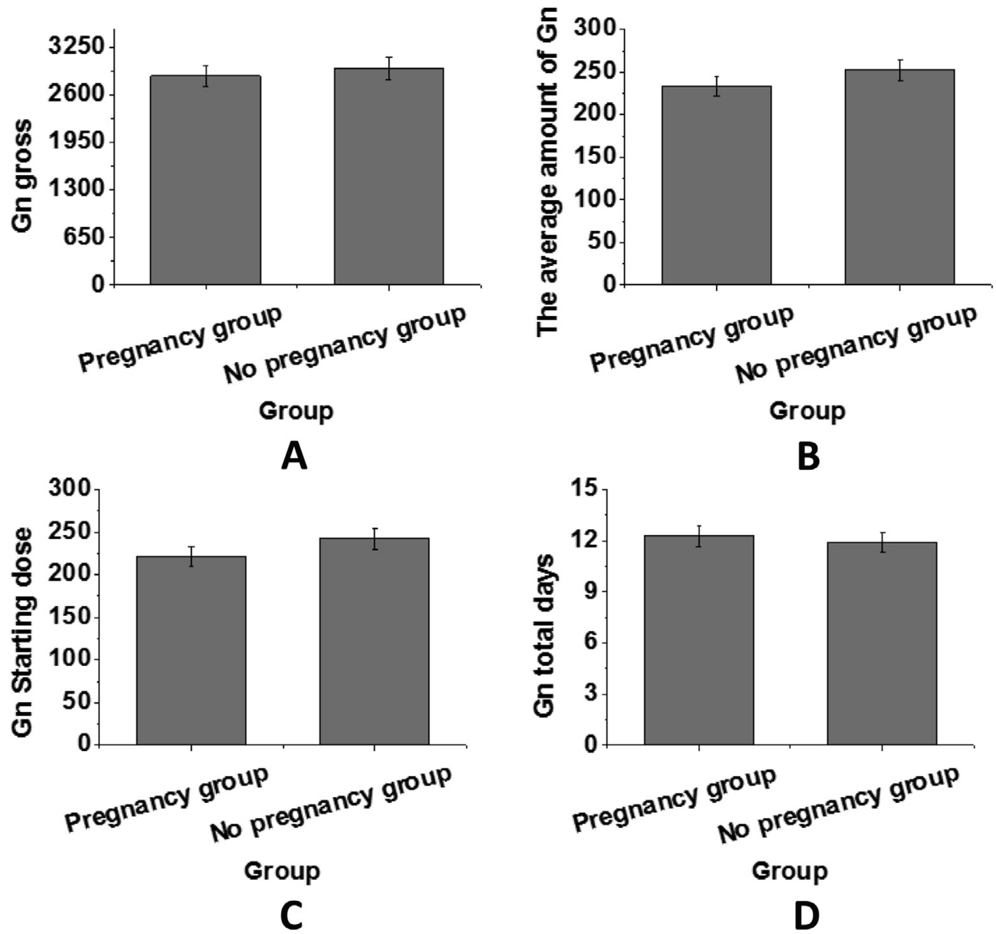

Fig. 4. COS analysis of two groups of patients (A: total amount of Gn; B: average dose of Gn; C. Gn start-up dose; D. total days of Gn).

group had higher bFSH and bFSH/bLH, and the related clinical indexes were not obviously different.

3.5. COS data analysis of two groups of patients

Fig. 4 indicted that pregnancy group had lower total amount of Gn, the average dose of Gn, and the Gn start-up dose, but had higher total days of Gn. The indexes in two groups were slightly different.

4. Comparative analysis of pregnancy outcomes between the two groups

Table 3 and Fig. 5 showed that the pregnancy group had higher E2, FORT and the number of eggs obtained on HCG day, but smaller number of pregnant embryos and lower fertilization rate and cleavage rate, and the pregnancy outcome was slightly different.

Table 3
COS data and outcomes of pregnancy group and no pregnancy group.

Group	Pregnancy group	No pregnancy group	P
HCG day E2	3035.81 ± 1123.52	2932.41 ± 1304.15	0.691
FORT	85.63 ± 51.08	81.19 ± 90.32	0.319
Number of eggs obtained	9.84 ± 4.31	8.92 ± 3.97	0.274
Number of eugenic embryos	2.18 ± 1.49	2.23 ± 2.15	0.675

4.1. Establishment and analysis of predictive model of multiple factors related to pregnancy in clinic

Fig. 6 shows the ROC curve of prediction probability and clinical pregnancy data in the total regression model. The area under ROC curve was 0.669, and the confidence interval of 94% was 0.629–0.697, with statistical significance ($P = 0.000$, $P < 0.01$). Therefore, it can be concluded that in clinical pregnancy, for many related factors, regression equation can be used to establish a prediction model to diagnose the success rate of pregnancy.

5. Discussion

As an assisted reproductive technology, IVF-ET can accurately evaluate ovarian response, and can make an optimal and characteristic ovulation promotion program from the most effective way. In this assisted reproductive program, it can reduce the abolition or disorder of menstrual cycle caused by POR, and finally get a complete result. The implementation of this measure is the key to the successful implementation of COS technology, and is also one of the difficult problems that need to be overcome in medicine at present (Bounartzi et al., 2016). Divide the patients into three groups: POR, NOR, and HOR. By comparing the general situation of each group with the clinical detection indicators, it was found that in the detection of age, bFSH and bFSH/bLH, the results were as follows: POR group > NOR group > HOR group. The age and bFSH/bLH of the HOR group were obviously different from those of other two groups ($P < 0.05$). The index of bFSH of the POR group

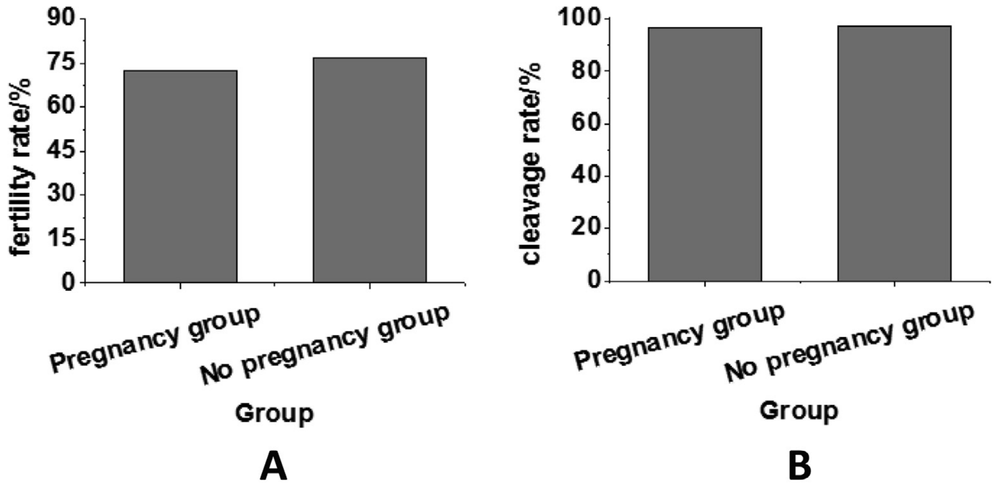

Fig. 5. Pregnancy outcomes of pregnancy group and no pregnancy group (A: fertilization rate; B: cleavage rate).

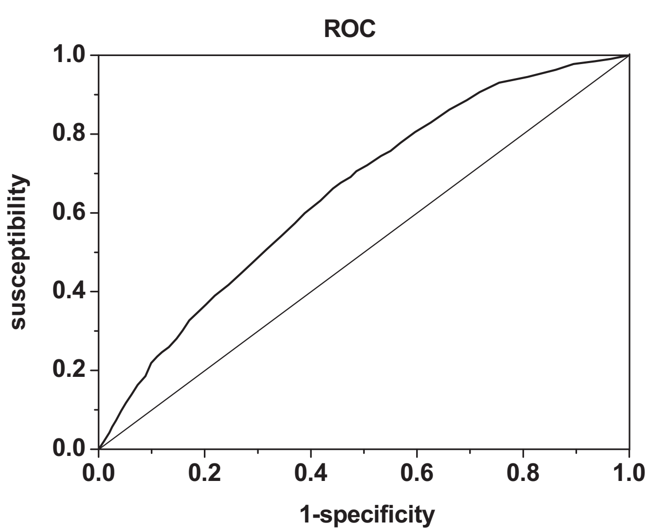

Fig. 6. ROC of predictive model for clinical pregnancy-related influencing factors.

was apparently different from the other two groups ($P < 0.05$). For AFC and AMH, the results were as follows: POR group < NOR group < HOR group, and there was significant difference in the two-two group comparisons ($P < 0.01$). The infertility duration, BMI and bE2 were slightly different among the three groups ($P > 0.05$). In the analysis of the correlation between the number of eggs obtained and age, AFC, bFSH, bFSH/bLH, AMH and FORT, it was found that the number of eggs obtained was correlated with age, AFC, bFSH, bFSH/bLH, AMH and FORT ($P < 0.01$), which is consistent with the study of Bounartzi et al. (Bounartzi et al., 2016).

At present, many evaluations of COS assisted reproductive technology are still a non-consensus predictor, and there is no statistical explanation for the results obtained in clinical trials or for the same subject and different parts. There was no significant difference between the pregnancy group and no pregnancy group and each index by analyzing the general situation and clinical detection, COS data and results, which is consistent with the study results of Zhang et al. (2016). Some studies have found that abnormal BMI can reduce the clinical pregnancy rate during ATR treatment (Bai et al., 2017; Shi et al., 2016). The area under ROC curve was 0.669 in the analysis of predictive model based on the related factors of clinical pregnancy. The confidence interval of 94% was 0.629–0.697, which had obviously statistical difference ($P = 0.000$, $P < 0.01$). Therefore, it can be concluded that in clinical pregnancy, for many related factors, regression equation can be used to establish a prediction model to diagnose the success rate of pregnancy.

To sum up, this paper explores the establishment of predictive model based on IVF-ET and ICSI assisted reproductive technology to analyze clinical pregnancy outcomes, and establishes predictive model based on the relevant experimental results, to provide experimental basis for increasing the success rate of assisted reproductive technology in late clinical pregnancy. However, there are some shortcomings. For example, this study only selects two years' patients as the research object, and only selects samples in our hospital. Therefore, in the follow-up study, the sample selection amount and sample points should be further increased, so that the research in this field is more reliable and rigorous.

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