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ORIGINAL RESEARCH

The Influencing Factors and Predictive Algorithm of Pregnancy Outcomes in IVF/ICSI-ET Patients

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Purpose: To explore the influencing factors of clinical pregnancy outcomes for in vitro fertilization/intracytoplasmic single sperm injection and embryo transfer (IVF/ICSI-ET) patients, and to establish a predictive algorithm to predict the rate of clinical pregnancy.

Patients and Methods: A single-center retrospective analysis was performed on 1183 treatment cycles of patients undergoing IVF/ICSI-ET at Hangzhou Women's Hospital, covering the period from April 2018 to March 2023. All cases were categorized into clinical pregnancy and non-pregnant groups. Totally 24 clinical and laboratory indicators were analyzed by logistic regression model to analyze the factors affecting clinical pregnancy outcome in IVF/ICSI-ET treated couples. Furthermore, by stratifying the influencing factors and quantitatively assigning scores, a predictive algorithm was established to predict the clinical pregnancy outcomes by calculating the total score.

Results: The results of multivariate logistic regression analysis showed that the male age (OR=0.965, 95% CI: 0.949~0.980) and progesterone (P) level on hCG day (OR=0.687, 95% CI: 0.500~0.944) were negatively correlated with clinical pregnancy in IVF/ICSI-ET couples, and that AMH (OR=1.085, 95% CI: 1.022~1.151), the number of high-quality embryos (OR=1.094, 95% CI: 1.039~1.152), and the number of transferred embryos (OR=2.218, 95% CI: 1.684~2.922) were positively associated with clinical pregnancy. Our multivariate logistic regression model reached a sensitivity of 64.55%, a specificity of 58.42%, and an AUC of 0.644 (95% CI: 0.614–0.673). A simple predictive algorithm of clinical pregnancy outcome was then developed using the five variables, both internal and external validations have been taken. The total score of the algorithm is between 0 and 23, and couples with total score of 10 or higher are highly likely to achieve clinical pregnancy.

Conclusion: Factors affecting clinical pregnancy in infertile couples mainly included male age, AMH, P level on hCG day, number of high-quality embryos, and number of embryos transferred. Clinicians can use predictive algorithms to predict clinical pregnancy outcomes more simpler and convenient, and develop personalized embryo transfer strategies more precisely.

Keywords: infertility, clinical pregnancy, *in vitro* fertilization/intracytoplasmic sperm injection, fresh embryo transfer

Introduction

In recent years, the incidence of infertility among couples of childbearing age in China has increased annually. With the postponement of childbearing age, more couples seek pregnancy through assisted reproductive technology (ART). Clinicians choose different treatment options, fertilization methods, and the number of embryos to be transferred according to the infertile couple's age, infertility factors, and underlying endocrine conditions.[1,2]

Despite the increasing sophistication of ART technology, gestational failure is still inevitable The age, pre-pregnancy body mass index (BMI), anti-Müllerian hormone (AMH), luteinizing hormone (LH), estradiol (E_2), progesterone (P), and other female clinical features[3,4] all affects the clinical pregnancy rate in infertile couples. Abnormal male factors, including oligospermia, asthenozoospermia, teratozoospermia, or a combination thereof, are closely related to the decrease in fertilization rate and live birth rate in IVF cycles.[5] These semen parameter abnormalities arise from a multitude of etiologies, including genetic factors, environmental exposures, lifestyle factors, and idiopathic causes, which collectively contribute to the heterogeneity of male factor infertility.[6,7] In addition, laboratory parameters such as

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the number of oocytes acquired, and the stage of transferred embryos have also been shown to be associated with clinical pregnancy outcomes.[1,8]

At present, a growing body of research has analyzed the influencing factors of pregnancy and live birth outcomes.[9–13] Multivariate Logistic regression models are commonly adopted analytical tools, while the integration of artificial intelligence has further diversified the construction of predictive models.[14] However, normal multivariate Logistic regression models are more difficult to generalise in clinical applications, and are not conducive to patient understanding; machine learning models are not suitable for application in small-scale medical centers or developing countries due to their poor generalizability.

Therefore, this study retrospectively compiled clinical medical records of IVF/ICSI-ET assisted couples and comprehensively analyzed the relationship between 24 clinical and laboratory indicators and pregnancy outcomes after fresh embryo transfer. Based on the logistic regression model, we established a predictive algorithm of pregnancy outcomes that calculates the total scores of influencing factors. The aim of this study was to improve the clinical pregnancy rates in infertile couples, and in particular to inform clinicians in developing individualised fresh embryo transfer strategies and easily predicting clinical pregnancy outcomes in IVF/ICSI-ET patients.

Materials and Methods

Study Subjects and Ethics Statement

Infertility couples who underwent IVF/ICSI-ET at a single-center (Hangzhou Women's Hospital) between April 2018 and March 2023 were recruited in our study. Inclusion criteria: patients who underwent fresh embryo transfer and for whom clinical data were available. Exclusion criteria: patients with previous history of autoimmune disease, hypertension, diabetes, or tuberculosis were excluded. Blood hCG was checked 14 days after embryo transfer to determine whether pregnancy was present or not, and those who saw gestational sacs on ultrasound after 28 days were considered as clinical pregnant. Totally 1183 assisted couples were categorized into clinical pregnant and non-pregnant group based on clinical pregnancy outcomes.

The study was granted ethical approval by the Ethics Committee of the Faculty of Hangzhou Women's Hospital (2023 Medical Ethics Review A No. 058). In view of the retrospective nature of the study, the Institutional Review Board (IRB) waived the requirement for informed consent. The complete details of the entire study design and procedures involved were in accordance with the Declaration of Helsinki. All patient data were kept confidential.

Collection of Clinical Features

The medical records of the study subjects were retrieved through the hospital's electronic medical record system, and the relevant factors that might affect the clinical pregnancy outcome were organized, such as the female age, male age, BMI, AMH, and the infertility years, etc. The type of infertility was categorized into primary and secondary infertility; infertility factors were categorized into fallopian tube factor, endometriosis, ovulation disorders, unknown reasons, male factors, and bilateral factors; and stimulation protocols were categorized into long protocol, prolonged protocol, antagonist, and others (natural cycles, etc). In addition, information on the number of gonadotropin (GN) days, total GN, and serum LH, E_2, and P levels on hCG days during the ovulation promotion cycle was also collected. Semen parameters are also collected simultaneously.

Collection of Laboratory Features

Laboratory features included fertilization methods (IVF and ICSI), source of sperm, number of oocytes obtained, fertilization rate (IVF: number of 2PN fertilized/number of oocytes obtained; ICSI: number of 2PN fertilized/number of oocytes fertilized by ICSI), number of high-quality embryos, rate of high-quality embryos (number of high-quality embryos/total number of embryos), number of transferred embryos, stage of transferred embryos, and quality of transferred embryos. The specific evaluation criteria for good-quality embryos are applied differently, depending on the embryo stage. The scoring criteria for embryos at the cleavage stage[15] are as follows: Grade I, the size of the cleavage sphere is uniform and regular, with a more complete zona pellucida, and the content of non-nuclear debris is <10%;

Grade II, the size of the cleavage sphere is slightly uneven and slightly irregular, and the content of non-nuclear debris is 10%-30%; Grade III, the size of the cleavage sphere is slightly uneven and slightly irregular, and the content of non-nuclear debris is 30%-50%; and Grade IV, the size of the cleavage sphere is obviously uneven and irregular, and the content of nuclear debris is >50%. Grade I and II cleavage embryos with more than 6 cells were regarded as high-quality cleavage embryos. Mulberry embryos with partial fusion were used as the standard for good quality embryos. Blastocyst stage embryos were evaluated according to morphological grading, and high-quality blastocysts included 3~6AA, 3~6AB, 3~6BA and 3~6BB.

Multivariate Logistic Regression Analysis

All data were collected by two researchers and performed by double-blind method. IVF/ICSI-ET patients with incomplete data were excluded. Our sample size estimation based on $n \geq 10p$, where p is the sum of the potential indicators. The sum of the indicators in this study is 24, so the sample size needs to be greater than 240. Regarding the handling of missing values, our analysis revealed that only 4.56% of the dataset contained missing data, and since the missing rate was below 10%, no imputation was performed for these missing values.

We used binary logistic regression to screen the variables while using the last category as the reference group for the count data. A preliminary logistic regression model was further developed using the Forward method, and the odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. An OR value of 1 indicated that the factor did not play a role in the clinical pregnancy outcome; an OR value of >1 indicated that the factor was a positive influencing factor in clinical pregnancies; and an OR value of <1 indicated that the factor had a negative influence on clinical pregnancy.

Predictive Algorithm of Pregnancy Outcomes

The male age was divided into five strata with 25 and 40 years as cut-off points,[16] and every 5 years as an age group. The AMH data was divided into four strata with a stratum of 2.00 ng/mL, groups set as <2.00, 2.00–3.99, 4.00–5.99, ≥6.00 ng/mL. P level on hCG day data were divided into five strata with≥2.00 ng/mL as the diagnostic cut-off point,[17] and every remaining 0.5 ng/mL as a group. The number of high-quality embryos was divided into three strata: less than 5 embryos, 5–9 embryos, and more than 10 embryos. The number of transferred embryos ranged from 1–2, divided into two groups according to the specific number. The middle value of each group was chosen as the reference value (W_{ij}), and the semi-closed interval was taken as the middle value of the 1st and 99th percentiles. The group of male aged ≥40 years, AMH<2.00 ng/mL, P level on hCG day ≥2.00 ng/mL, number of high-quality embryo <5, and the number of embryo transferred = 1, were used as baseline risk reference values (W_{iREF}). The intercept of the reference value was calculated by combining the coefficients in the logistic regression model with the distance $(D)=(W_{ij}-W_{iREF}) *\beta$ coefficient. We set a score of 1 point for 2.00 ng/mL increase in the AMH, the constant B was calculated as 2.00 * coefficient of the AMH (0.081) = 0.162. The score for each classification was calculated using the following formula: score = D/constant B, and the data were rounded to the nearest whole number. The predicted probability of pregnancy corresponding to each score was calculated using a logistic regression model.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 16.0). The count data is described as frequency (percentage), and the chi-square test was used to compare the data between groups. The measurement data in this study did not follow a normal distribution measured by Kolmogorov–Smirnov method. So the measurement data is described as median (25th percentile, 75th percentile) [M (Q1, Q3)]; and Mann–Whitney *U*-test was used for comparison between groups. The collinearity among multiple independent variables is determined by the correlation coefficient r and the variance inflation factor (VIF) index, with the thresholds of r<0.8 and VIF<5. Trend test is conducted through Linear-by-Linear Association (LLA) test. Differences were considered statistically significant at $P<0.05$.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Results

General Information of Infertile Couples

In 1183 IVF/ICSI-ET treatment cycles, the age of the female partner ranged from 20 to 44 years, with a mean of 32.00 (29.00, 34.00) years; the age of the male partner ranged from 22 to 60 years, with a mean of 33.00 (29.00, 35.00) years; the infertility years ranged from 0 to 18 years, with a mean of 2.00 (1.50, 4.00) years. Given that multiple pregnancies are associated with an increased risk of maternal pregnancy complications, our center performs single embryo transfer for patients with the following conditions: uterine malformations (eg, uterine scar), cervical insufficiency, height below 150 cm, and high risk of ovarian hyperstimulation syndrome (OHSS). Two embryos may be transferred for the remaining patients. A total of 754 clinical pregnancies were observed in our dataset, with a clinical pregnancy rate of 63.74% (754/1183).

Among 1183 cycles, 1154 cases used ejaculated sperm, 17 cases used sperm obtained through testicular sperm aspiration (TESA), and the remaining 12 cases used frozen sperm. Although patients using TESA or cryopreserved sperm accounted for only a small proportion of our study population (2.45%), we still included sperm source as a factor in the influencing factor analysis.

Comparison of Clinical Features

Female age, male age, and total dosage of GN in the clinical pregnant group were lower than those in the non-pregnant group (all $P<0.001$), meanwhile the AMH was higher ($P=0.001$). The distribution of infertility types and infertility factors also differed between two groups (all $P=0.008$). BMI, infertility years, stimulation protocols, LH, E_2, P on hCG day, semen parameters, and duration of GN in the different pregnancy outcome groups were not statistically different (Table 1, $P>0.05$).

Table 1 Comparison of Clinical Features with Different Pregnancy Outcomes in IVF/ICSI-ET Couples

Factor	Clinical Pregnant Group (n=754)	Non-Pregnant Group (n=429)	Z/χ^2 value	*P* value
Female age	31.00 (29.00, 34.00)	32.00 (29.00, 35.00)	−4.15	<0.001***
Male age	33.00 (30.00, 36.00)	34.00 (31.00, 37.00)	−3.95	<0.001***
BMI (kg/m^2)	21.87 (20.15, 24.09)	21.48 (19.77, 24.00)	−1.80	0.072
AMH (ng/mL)	3.29 (2.23, 4.77)	2.91 (2.01, 4.30)	−3.23	0.001**
Infertility years	2.00 (1.50, 4.00)	2.50 (1.50, 4.00)	−0.36	0.721
Infertility type (%)				
Primary	50.93 (384/754)	42.89 (184/429)	7.08	0.008**
Secondary	49.07 (370/754)	57.11 (245/429)		
Infertility factors (%)				
Fallopian tube factors	53.18 (401/754)	58.74 (252/429)	15.76	0.008**
Endometriosis	4.24 (32/754)	4.66 (20/429)		
Ovulation disorders	11.94 (90/754)	7.46 (32/429)		
Unknown reasons	14.19 (107/754)	12.12 (52/429)		
Male factors	14.19 (107/754)	11.89 (51/429)		
Bilateral factors	2.26 (17/754)	5.13 (22/429)		
Stimulation protocols (%)				
Long protocol	90.32 (681/754)	86.48 (371/429)	4.51	0.212
Prolonged protocol	8.09 (61/754)	10.72 (46/429)		
Antagonist	0.53 (4/754)	0.93 (4/429)		
Other	1.06 (8/754)	1.87 (8/429)		
Hormone levels on hCG day				
LH (IU/L)	2.00 (1.43, 2.77)	1.97 (1.33, 2.70)	−1.50	0.135
E_2 (pg/mL)	2414.00 (1687.00, 3502.00)	2397.68 (1570.00, 3420.68)	−0.81	0.416
P (ng/mL)	0.84 (0.62, 1.13)	0.90 (0.67, 1.19)	−1.79	0.074

(*Continued*)

Table 1 (Continued).

Factor	Clinical Pregnant Group (n=754)	Non-Pregnant Group (n=429)	Z/χ^2 value	*P* value
Duration of GN	10.00 (9.00, 12.00)	10.00 (9.00, 12.00)	−0.97	0.333
Total dosage of GN (U)	1837.50 (1462.50, 2287.50)	1950.00 (1512.50, 2565.00)	−3.50	<0.001***
Semen parameters				
Sperm concentration (×10^6/mL)	47.00 (27.00, 72.00	48.90 (27.00, 76.25)	−0.80	0.425
Progressive (PR) motility (%)	44.00 (30.63, 56.00)	45.00 (32.00, 55.00)	−0.58	0.563
Normal morphology percentage (%)	5.00 (3.00, 8.00)	5.00 (3.00, 8.00)	−0.14	0.888

Notes: Count data is described using [frequency (positive/total)] and compared using chi-square test, while measurement data is described using [M (Q1, Q3)] and compared using Mann–Whitney *U*-test. **$P < 0.01$; and ***$P < 0.001$.

Abbreviations: BMI, body mass index; AMH, anti-Müllerian hormone; LH, luteinizing hormone; E_2, estradiol; P, progesterone; GN, gonadotropin; hCG, human chorionic gonadotropion.

Comparison of Laboratory Features

The number and rate of high-quality embryos, and the number of transferred embryos were higher in the clinical pregnant group than in the non-pregnant group ($P<0.001$, $P=0.012$, $P<0.001$; respectively), and the distribution of the quality of the transferred embryos differed from that of the non-pregnant group ($P<0.001$). The fertilization method, sperm source, number of oocytes obtained, fertilization rate, and stage of transferred embryos were not statistically different in different pregnancy outcome groups (Table 2, $P>0.05$).

Table 2 Comparison of Laboratory Indicators with Different Pregnancy Outcomes in IVF/ICSI-ET Couples

Factor	Clinical Pregnant Group (n=754)	Non-Pregnant Group (n=429)	Z/χ^2 value	P value
Fertilization method (%)				
IVF	81.56 (615/754)	80.19 (344/429)	0.34	0.561
ICSI	18.44 (139/754)	19.81 (85/429)		
Sperm source (%)				
Ejaculated sperm	97.48 (735/754)	97.66 (419/429)	0.50	0.780
TESA sperm	1.59 (12/754)	1.17 (5/429)		
Frozen sperm	0.93 (7/754)	1.17 (5/429)		
Number of oocytes obtained	10.00 (7.00, 12.00)	9.00 (7.00, 12.00)	−1.32	0.189
Fertilization rate (%)	75.00 (60.00, 86.67)	75.00 (57.14, 87.50)	−0.73	0.466
Number of high-quality embryos	4.00 (2.00, 6.00)	4.00 (2.00, 5.00)	−4.26	<0.001***
Rate of high-quality embryo (%)	69.38 (50.00, 88.89)	66.67 (40.00, 85.71)	−2.52	0.012*
Number of transferred embryos	2.00 (2.00, 2.00)	2.00 (1.00, 2.00)	−4.80	<0.001***
Stage of transferred embryos (%)				
Cleavage embryo	77.72 (586/754)	76.92 (300/429)	1.72	0.423
Mulberry embryo	17.51 (132/754)	16.55 (71/429)		
Blastula	4.77 (36/754)	6.53 (28/429)		
Quality of transfered embryo (%)				
All high-quality	92.84 (700/754)	86.71 (372/429)	13.90	<0.001***
Single high-quality	5.57 (42/754)	8.86 (38/429)		
Non high-quality	1.59 (12/754)	4.43 (19/429)		

Notes: Count data is described using [frequency (positive/total)] and compared using chi-square test, while measurement data is described using [M (Q1, Q3)] and compared using Mann–Whitney *U*-test. *$P < 0.05$; and ***$P < 0.001$.

Abbreviations: IVF, in vitro fertilization; ICSI, intracytoplasmic single sperm injection; TESA, testicular sperm aspiration.

Results of Multivariate Logistic Regression

With $P<0.20$ as the variable screening criterion, the female age, the male age, BMI, AMH, infertility type, infertility factors, LH, P on hCG day, total dosage of GN, the number of oocytes obtained, the number of high-quality embryos, the rate of high-quality embryos, the number of transferred embryos, and the quality of the transferred embryos were used as the independent variables. And according to the literature reports, the stage of transferred embryos had a certain effect on clinical pregnancy outcome,[15] so the stage of transferred embryos were also included as an independent variable; with pregnancy outcome as the dependent variable (0=non-pregnant group, 1=clinical pregnancy group), a multivariate logistic regression analysis was performed. The results showed that the male age, AMH, P level on hCG day, number of high-quality embryos, and number of transferred embryos were independent factors affecting clinical pregnancy in couples with IVF/ICSI-ET (Table 3). The age of the male partner ($\beta=-0.036$, $P<0.001$) and P level on hCG day ($\beta=-0.376$, $P=0.020$) were negatively correlated with clinical pregnancy, whereas the AMH ($\beta=0.081$, $P=0.007$), number of high-quality embryos ($\beta=0.090$, $P=0.001$) and number of transferred embryos ($\beta=0.797$, $P<0.001$) were positively correlated with clinical pregnancy. There is no collinearity among the 5 variables, and except for the P level on hCG day, the other four variables all had a linear trend with pregnancy outcomes. Our multivariate logistic regression model reached a sensitivity of 64.55%, a specificity of 58.42%, and an AUC of 0.644 (95% CI: 0.614–0.673; Figure 1). Internal classification validation of this model has a sensitivity of 91.74% and a specificity of 19.68% with whole 65.44% accuracy.

Logistic Regression Model-Based Predictive Algorithm

The male age was divided into five strata with an age range of 5 years old; the AMH data was divided into four strata with a stratum of 2.00 ng/mL; the P on hCG day data was divided into five strata with a stratum of 0.50 ng/mL; the number of high-quality embryos was divided into three strata according to a stratum of 5 embryos; and the number of transferred embryos was divided into two strata according to a specific number of embryos. The stratification reference value (W_{ij}), base risk reference value (W_{iREF}), distance, and assignment scores for each group are listed in Table 4. The total score of the summation for each influencing factor was a minimum of 0 and a maximum of 23. According to the equations of the logistic regression model, the clinical probability of pregnancy corresponding to the scores of 0–23 was calculated, and the range was 18.47–90.39% (Table 5).

Algorithm Validation and Application Comparison

To verify the accuracy of the predictive algorithm and thereby enhance its potential for clinical translation, we optimized the embryo transfer strategy based on the clinical status of patient couples prior to transplantation. From July 2023 to June 2025, the selection of the number of embryos for transfer was guided by the algorithm, with a score of over 10 points indicating a higher likelihood of clinical pregnancy. The predictive algorithm achieved an overall accuracy of 61.48% (249/405), with a sensitivity of 78.35% (181/231) for predicting clinical pregnancy. During this period, the multiple pregnancy rate at our center decreased from 32.49% (245/754) to 20.00% (46/230), while the clinical pregnancy rate was stably maintained at 56.93%. In addition, we also compared IVF prediction models over the past 5 years[9–12,18–26] (Table 6). Most existing

Table 3 Multivariate Regression Analysis of IVF/ICSI-ET Pregnancy Outcomes

Factor	*β*	*S.E.*	*Wald*	*P*	OR	95% CI
Male age	−0.036	0.008	18.943	<0.001	0.965	0.949~0.980
AMH	0.081	0.030	7.199	0.007	1.085	1.022~1.151
P on hCG day	−0.376	0.162	5.369	0.020	0.687	0.500~0.944
Number of high quality embryos	0.090	0.026	11.555	0.001	1.094	1.039~1.152
Number of transferred embryos	0.797	0.141	32.095	<0.001	2.218	1.684~2.922

Abbreviations: AMH, anti-Müllerian hormone; P, progesterone; OR, odds ratio; CI, confidence interval; hCG, human chorionic gonadotropion.

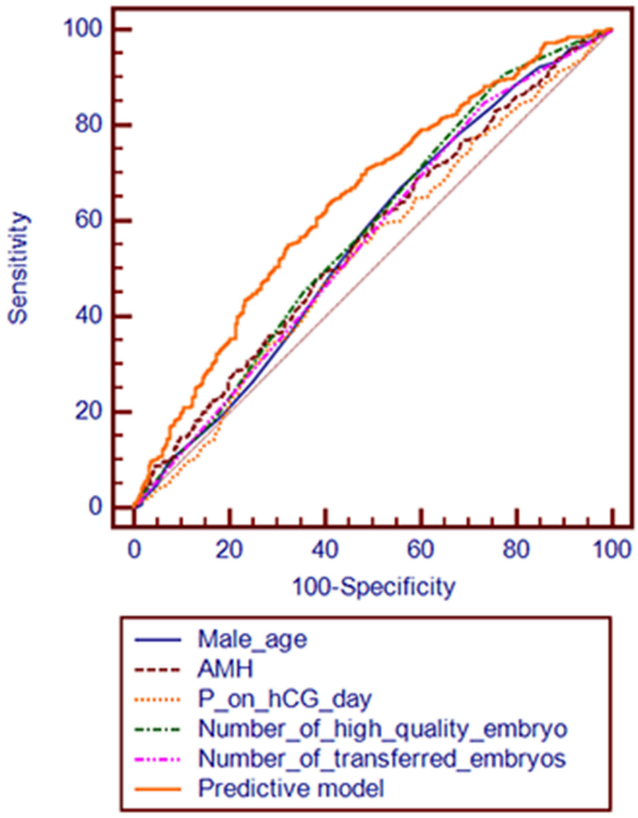

Figure 1 ROC curves analysis of male age, AMH, P on hCG day, number of high quality embryo, number of transferred embryos, and combination to discriminate clinical pregnancy.
Abbreviations: ROC, Receiver operation characteristics; AMH, anti-Müllerian hormone; P, progesterone; hCG, human chorionic gonadotropion.

predictive models lack subsequent application validation and involve overly complex algorithms, which impairs effective communication with patients.

Discussion

Globally, approximately 10.0% to 15.0% of couples suffer from infertility, and approximately 74.7% of infertility is primary infertility. Female tubal obstruction, ovulation disorders, and abnormal semen parameters in men may lead to infertility. IVF/ICSI-ET is a mature treatment for infertility, but its outcome is affected by a variety of factors, and the selection of

Table 4 Stratification and Scoring of the Influencing Factors Categories

		W_{ij}	β	D	Score
Male age	<25	23	−0.041	0.828	5
	25-29	27		0.684	4
	30-34	32		0.204	3
	35-39	37		0.324	2
	≥40	**W_{iREF}=46**		0.000	0
AMH	**<2.00**	**W_{iREF}=1.56**	0.081	0.000	0
	2.00–3.99	3.00		0.117	1
	4.00–5.99	5.00		0.279	2
	≥6.00	7.62		0.491	3

(*Continued*)

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Table 4 (Continued).

		W_{ij}	β	D	Score
P on hCG day	<0.50	0.15	−0.376	0.876	5
	0.50–0.99	0.75		0.650	4
	1.00–1.49	1.25		0.462	3
	1.50–1.99	1.75		0.274	2
	≥2.00	**W_{iREF}=2.48**		0.000	0
Number of high quality embryo	**<5**	**W_{iREF}=2**	0.090	0.000	0
	5-9	7		0.450	3
	≥10	11		0.810	5
Number of transferred embryos	**1**	**W_{iREF}=1**	0.797	0.000	0
	2	2		0.797	5

Notes: Bold text: The median value of each group is set as the reference value (W_{ij}), and the baseline risk reference values were marked as W_{iREF}. D: distance = (W_{ij}-W_{iREF}) *β coefficient. We set a score of 1 point for 2.00 ng/mL increase in the AMH, so the constant B was the 2.00 * coefficient of the AMH (0.081) = 0.162. The score for each classification was calculated using the following formula: score=D/constant B, and the data were rounded to the nearest whole number.

Abbreviations: AMH, anti-Müllerian hormone; P, progesterone; hCG, human chorionic gonadotropion.

Table 5 Score Sheet for IVF/ICSI-ET Couples Using Our Predictive Algorithm

Total Score	Pregnancy Rate (%)	Total Score	Pregnancy Rate (%)	Total Score	Pregnancy Rate (%)
0	18.47	8	45.29	16	75.15
1	21.03	9	49.32	17	78.06
2	23.85	10	53.37	18	80.70
3	26.91	11	57.37	19	83.10
4	30.21	12	61.27	20	85.26
5	33.74	13	65.04	21	87.18
6	37.45	14	68.63	22	88.88
7	41.31	15	72.01	23	90.39

Table 6 The Performance Comparison of Prediction Models for IVF Pregnancy Outcomes

	Cases	Method	Incorporate Influencing Factors	AUC
Bai et al[9]	2625	Machine learning (XGBoost)	Age, BMI, years of infertility, and other relevant 30 factors	0.999
Yang et al[18]	367	Random Forest	Embryonic morphokinetics	0.910
Li et al[19]	840	Machine learning (LightGBM)	Infertility duration, BMI, Trigger Day E_2, Endometrial thickness on trigger day	0.904
Chen et al[20]	338	Random Forest	Cumulus cell methylation profile	0.880
Chen et al[21]	86	Logistic Regression	AMH, E_2, Age, Sperm DFI, hsa-miR-199a-3p, hsa-miR-199a-5p, hsa-miR-99a-5p	0.853
Yang et al[10]	369	Multivariate Logistic regression	Age, BMI, Number of Cycles, Hematocrit, LH, P, FSH, Endometrial thickness	0.817
Wen et al[11]	1507	Machine learning (XGBoost)	Female age, Male age, BMI, Infertility duration, Number of spontaneous abortion, and other relevant 20 factors	0.787
Zhu et al[22]	969	Logistic Regression	Age, BMI, AFC, AMH, Number of mature oocytes, Number of transferred embryos, Quality of transferred embryos	0.752

(*Continued*)

Table 6 (Continued).

	Cases	Method	Incorporate Influencing Factors	AUC
Wang et al[23]	17288	Random Forest	Age, Cause of infertility, Duration of infertility, Ovarian stimulation protocol, Protocol for total number of frozen embryos, Total number of frozen embryos	0.721
Enatsu et al[24]	19342	Neural Network	Embryo image, Embryo data	0.710
Jiang et al[12]	113	Multivariate Logistic regression	Age, AFC, AMH, Number of high-quality embryos, and other relevant 17 factors	0.669
Sun et al[25]	1239	Logistic Regression	Progesterone to number of mature oocytes index	0.621
Ueno et al[26]	3018	Machine learning	Age, Embryo grading	>0.600

Abbreviations: AUC, area under the curve; AMH, anti-Müllerian hormone; AFC, antral follicle count; BMI, body mass index; E_2, estradiol; LH, luteinizing hormone; P, progesterone; FSH, follicle-stimulating hormone; DFI, DNA Fragmentation Index.

transplantation protocols is mostly dependent on the experience of clinicians. We conducted a retrospective multivariate regression analysis of the relationship between 24 clinical and laboratory features and clinical pregnancy outcomes after fresh embryo transfer and found that male age, P level on hCG day, rate of high-quality embryo, and number of transferred embryos were statistically associated with clinical pregnancy outcomes after IVF/ICSI-ET treatment.

There is growing evidence that men also have an optimal childbearing age. Datta et al[27] demonstrated that livebirth rates are influenced by an interaction between male and female partners' age, by an analysis of 59951 fresh IVF/ICSI cycles. Specificly, male partner's age significantly associated with livebirth rates in the female age-group of 35–39 years. Meanwhile, West et al[28] connected elevated male age with the rate of biochemical pregnancy. Our study also confirmed that the effect of advanced age on the male partner was more severe than that on the female partner in fresh embryo transfer cycles. We believe that this may be due to the fact that fresh embryo transfer has excluded the majority of patients with low ovarian reserve (undergoing PPOS protocol), which is mostly in the female partner's senior age group, and therefore the female partner's age has not been an independent influence on the clinical pregnancy outcome of fresh embryo transfer.

Meanwhile, the association between female AMH and pregnancy outcomes has been reconfirmed by our study. Due to the fact that our study population consisted of fresh embryo transplant recipients, a significant portion of individuals with low ovarian reserve or polycystic ovary syndrome (PCOS) were excluded. So in this study, clinical AMH values were positively correlated with clinical pregnancy. Similar to our results, Ye et al's study on the IVF/ICSI-ET patients under 35 years old also confirmed that higher AHM leads to better pregnancy outcomes.[29]

We found that lower P levels on hCG day were statistically associated with clinical pregnancy. Former studies[30,31] have indicated that elevated levels of P on hCG day reduce clinical pregnancy rates in IVF/ICSI-ET cycles, which is consistent with our results. Theoretically, the level of serum P on hCG day may be related to the quality of oocytes, with low levels of P suggesting poor oocyte maturation and high levels indicating premature luteinization of the follicle. Liu et al[32] also suggested that high levels of P may prevent embryo implantation by affecting the endometrial morphology and altering endometrial tolerance, which ultimately affects the pregnancy outcome. It has also been suggested that P levels on hCG day were closely related with clinical pregnancy rate of blastocyst transfer.[33]

Laboratory indicators suggest that higher number of high-quality embryos may increase the likelihood of clinical pregnancy in infertile couples. The embryo quality is largely associated with the developmental potential of patient embryos. As we mentioned before, elevated P on hCG day also has a detrimental effect on the development of quality embryos.[34] In addition to the effect of female sex hormone levels, the number of high-quality embryos was also significantly negatively correlated with the male sperm DNA fragmentation rate.[35,36] That is, the higher the sperm DNA fragmentation rate, the lower the number of high-quality embryos. Therefore, we believe that both men and women can influence the developmental potential of embryos in IVF/ICSI-ET cycles, and that the male partner's publicity and education can be strengthened to improve cooperation in assisted reproductive treatment.

We found no significant differences in fertilization method, sperm source, and semen parameters (sperm concentration, PR motility, and normal morphology percentage; Table 1) between the pregnant and non-pregnant groups. Cutting et al[37] also concluded that in couples with normal total sperm count and motility, there were no significant differences in clinical pregnancy, live birth, and miscarriage rate between IVF and ICSI techniques. In contrast, Jiang et al[5] demonstrated that patients with severe asthenozoospermia had lower clinical pregnancy rates and live birth rates, while the outcomes of the mild-to-moderate male factor group and the azoospermia group (using TESA sperm) were no different from those of normal sperm males. We propose that sperm selection prior to IVF largely reduces the impact of semen parameters on pregnancy, and the application of ICSI further weakens the influence of sperm concentration/motility on pregnancy outcomes.

The number of transferred embryos is a more controllable indicator of the assisted conception cycle, and increasing the number of transferred embryos can increase the clinical pregnancy rate. However, at the same time, an increase in the number of transferred embryos increases the likelihood of multiple births, gestational diabetes, eclampsia, miscarriage, and other perinatal morbidity.[36] Reducing the incidence of multiple pregnancies without decreasing the clinical pregnancy rate is the goal pursued by assisted reproductive technology. They suggested that a single embryo should be transferred for patients of all ages and ≤ 2 blastocysts could be transferred during IVF treatments for women ≥ 40 years.[38] Single blastocyst transfers do not reduce clinical pregnancy rates compared with cleavage embryo transfers,[39] and blastocyst transfers have a lower risk of pregnancy loss, and higher live birth rate per fresh transfer.[40] In the present study, the stage of transferred embryos had no effect on clinical pregnancy outcomes (P=0.423). Therefore, we recommended couples with high-quality blastocyst can transfer blastocyst first, and the number of transferred embryos at the cleavage stage should not exceed two. For patients with good condition, single-embryo (cleavage/blastocyst) transfer can be considered, which can ensure that the clinical pregnancy and live birth rates do not decrease and can effectively control the multiple pregnancy rate.

In this study, the logistic regression model we established has high sensitivity. And, we drew inspiration from the prediction tool reported in the Framingham Heart Study[41] and developed a simpler prediction algorithm based on the logistic regression model. Prediction tool reported in the Framingham Heart Study is a simple prediction algorithm developed using categorical variables, which allows clinicians to predict multivariate coronary heart disease risk in patients without overt coronary heart disease. For every IVF/ICSI-ET couple, clinical pregnancy is the desired outcome. So, we developed a predictive algorithm for every IVF/ICSI-ET couple before fresh embryo transfer. The present predictive algorithm of pregnancy outcomes can predict the probability of clinical pregnancy in different cycles for each IVF/ICSI-ET couple, and is more comprehensible to patients than the multivariate regression model, which makes subsequent replication easier. Prior to clinical application, this algorithm still requires extrapolation validation and adaptive reconstruction through multicenter studies. Other centres may also establish predictive algorithms and total score thresholds more suited to their own institutions based on their patient features.

Given that logistic regression itself struggles to capture the non-linear and interactive effects among influencing factors, the predictive model cannot fully identify confounding factors and is subject to potential biases. Established on a specific patient cohort from a single center, our algorithms' generalizability and external validity require further clarification. And, the current model demonstrates moderate predictive performance, and its value is mainly hypothesis-generating rather than ready for direct clinical decision-making. Incorporating additional variables may help to further improve model performance before the predictive algorithm can be applied in clinical practice. Finally, since the predictive algorithm is constructed based on historical data, it needs to be updated in tandem with advances in IVF protocols and new technologies.

Conclusions

In conclusion, the factors affecting the pregnancy outcome of fresh embryo transfer mainly included the male age, AMH, P on hCG day, number of high-quality embryos, and number of transferred embryos. Clinicians can use predictive algorithms to predict clinical pregnancy outcomes more simpler and convenient, and develop personalized embryo transfer strategies more precisely.

Consent for Publication

All authors have reviewed and endorsed the contents of this manuscript and provided their consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that this study was conducted without any business or financial relationships that could be perceived as a potential conflict of interest.

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