The development of using nomogram to predict pregnancy outcomes of emergency oocyte freeze-thaw cycles

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Research

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Abstract

Background: To study which characteristics of a pre-oocyte-retrieval patient can affect the pregnancy outcomes of emergency oocyte freeze-thaw cycles.

Methods: Nomogram model performance was assessed by examining the discrimination and calibration in the development and validation cohorts. Discriminatory ability was assessed using the area under the receiver operating characteristic curve (AUC), and calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and calibration plots. Data was collected from the Reproductive Center, Peking University Third Hospital of China. Nomogram model performance was assessed by examining the discrimination and calibration in the development and validation cohorts. Discriminatory ability was assessed using the area under the receiver operating characteristic curve (AUC), and calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and calibration plots.

Results: The predictors in the model of 'no embryo to transfer' are female age (OR= 1.099, 95% CI=1.003-1.205, P=0.044), duration of infertility (OR= 1.140, 95% CI=1.018-1.276, P=0.024), basal FSH level (OR= 1.205, 95% CI=1.051-1.382, P=0.0084), basal E2 level (OR=1.006, 95% CI=1.001-1.010, P=0.012) and sperm from MESA (OR=7.741, 95% CI=2.905-20.632, P<0.001). Upon assessing predictive ability, the AUC for this model was 0.799 (95% CI: 0.722–0.875, p=0.001). The Hosmer-Lemeshow test (p=0.721) and calibration curve showed good calibration. The predictors in the cumulative live birth were the number of follicles on the day of hCG administration (OR= 1.088, 95% CI=1.030-1.149, P=0.002) and endometriosis (OR= 0.172, 95% CI=0.035-0.853, P=0.031). The AUC for this model was 0.724 (95% CI: 0.647–0.801, p=0.001). The Hosmer-Lemeshow test (p=0.562) and calibration curve showed good calibration for the prediction of cumulative live birth.

Conclusion: The predictors in the final multivariate logistic regression models found to be significantly associated with poor pregnancy outcomes were increasing female age, duration of infertility, basal FSH and E2 level, the number of follicles with a diameter greater than 10 mm on the day of hCG administration, endometriosis and sperm from microdissection testicular sperm extraction (MESA).

Background

As early as 1986, researchers had applied frozen oocytes for in vitro fertilization (IVF) and achieved a successful pregnancy [1]. With the development of intracytoplasmic sperm injection (ICSI) and the improvement of cryogenic freezing technology, the recovery rate, fertilization rate and pregnancy rate of oocytes frozen cycle were significantly improved. The American society for reproductive medicine also proposed in 2013 that the freezing of mature oocytes could be widely applied in clinical practice without being confined to the experimental stage [2].

At present, the international clinical research on oocyte cryopreservation mainly focuses on the social and economic benefit analysis or the fertility preservation of malignant tumor patients. We have identified another common scenario during our daily clinical practice: patients who planned to receive assisted

reproductive technology (ART) on the day of oocyte retrieval where there is an unexpected sperm collection failure, such as the donor is unable to get to the hospital for sperm collection due to sudden illness or accident, the donor fails to perform masturbation or operation, or due to other various and sundry reasons. If these patients give up oocyte retrieval, the cost and time of treatment in previous ovulation induction process would be wasted, and the risk of ovarian hyperstimulation syndrome would be significantly increased due to the excessive physiological dose of estrogen in the body. However, if the oocytes are harvested as planned, the damage caused by freezing and thawing, and the risk of injury caused by the operation itself will also cause physical and psychological damage to the patients. As there is no unified evaluation framework or reference standard for this scenario to guide doctors in their daily clinical work, doctors often advise patients to give up oocyte retrieval or oocyte cryopreservation based on their own experience, or leave patients to choose completely by themselves.

IVF cannot guarantee 100% success; between 38% and 49% of couples who start IVF will remain childless, even after undergoing up to 6 IVF cycles [3]. To manage the expectations of the infertile couples, several clinical prediction models for IVF have been developed over the last three decades [4, 5]. However, all of those models are based on fresh oocyte cycles, and no prediction model exists to evaluate the recovery effect of freeze-thaw mature oocytes. Our reproductive center, in 2007, began to develop mature oocyte cryopreservation. 80% of them are emergency oocyte frozen because the sperm donor cannot come to the hospital on the day of oocyte retrieval. In this study, clinical data of emergency oocyte cryopreservation because of male reason from 2007 to 2019 were retrospectively analyzed.

According to the clinical characteristic and laboratory indexes, the prediction model of pregnancy outcomes of oocyte cryopreservation was established and validated. We hope this model could provide individualized and targeted suggestions to patients when they made the decision.

Methods

Study design and participants

From August 2007 to December 2019, 418 women who had undergone oocyte cryopreservation in the Reproductive Center, Peking University Third Hospital, China, were prospectively identified. Infertile couples who received IVF and conducted emergency oocyte cryopreservation due to issues with the sperm donor were enrolled (Figure 1). Issues with the sperm donor on the day of oocyte retrieval includes: the sperm donor cannot come to the hospital for sperm collection due to sudden illness or accident, fails to perform masturbation or operation (MESA, TESA), or fails to obtain enough sperm, as well as other unexpected sperm collection failures. Data used in the investigation data includes: female age, BMI, duration of infertility, primary/secondary infertility, causes of infertility, previous history of gestation, basal hormone levels, semen quality, gonadotropin (Gn) dosage and duration totally applied, number of follicles with a diameter greater than 10 mm and hormone levels on the day of hCG administration, oocyte storage duration and et al. The final date of follow-up was May 31, 2020. The study utilized the TRIPOD score [6] to establish and validate the models.

Procedures

The initial dose of gonadotropin (Gn) applied to ovulation promotion was selected according to the age of the patients, the level of basal hormone and other ovarian reserve situation. And the Gn was adjusted based on the growth of follicles. The trigger time was decided based on the diameter of follicles and the level of serum hormone. When the diameter of two or more follicles is $\geq 18\text{mm}$, recombinant human chorionic gonadotropin (r-hCG, Ezer, 250ug) was administered to the patients. The oocyte retrieval would be conducted 34-38 hours later.

Mature oocytes were vitrified and thawed as previously described [7]. Briefly, oocytes were firstly equilibrated in a 7.5% (v/v) EG + 7.5% (v/v) DMSO solution for 5 minutes at room temperature. These oocytes were then transferred into the vitrification solutions composed of 15% (v/v) EG +15% (v/v) DMSO + 0.5 M sucrose for less than 1 minute at room temperature. Finally, these oocytes were loaded on the sterile iVetri straw immediately and transferred directly into liquid nitrogen for storage. Thawing of the frozen oocytes was carried out step by step using different concentrations of sucrose solution. After recovery, only an oocyte with intact membrane and uniform cytoplasm was considered as having survived. Following ICSI, all embryos were further cultured for 3 days; the quality of the embryo was evaluated by experienced embryologists. The embryo which could be transferred was then transferred back to the uterus or freeze. Patients with regular menstruation and normal ovulation were grouped in natural cycles, while artificial cycles to prepare for endometrium was applied to those with irregular menstruation or anovulation used. Luteal support was given to them after embryo transfer.

Outcomes

‘No embryo to transfer’ and ‘cumulative live birth’ are the two key outcomes. ‘No embryo to transfer’ means after thawing the oocyte and formation of the embryo by ICIS, there was no available embryo to transfer back to the uterus. Cumulative live birth was defined as at least one live birth from the oocyte cryopreservation cycle as of May 2020 due to either the thawing fresh embryo transfer cycle or the following frozen embryo transfer cycle.

Statistical analysis

Primary statistical analysis

For the quantitative data, the Kolmogorov-Smirnov was used to test the normality distribution. The quantitative elements were expressed as mean $\pm$ std or median(p25, p75) according to whether it conformed to the normal distribution. For the qualitative data, the n (%) was used to express the data. Statistical tests were done with R software (version 3.6.0) and SPSS (version 25.0). Statistical significance was set at two-sided p values less than 0.05.

Model development

Univariable logistic regression analyses were performed to assess the association of each of the predictive factors with cumulative live birth and no embryo to transfer. A multivariable logistic regression model was used to derive the nomogram. The predictors included in the multivariable model were selected based on the result of univariable logistic regression analyses ($P \leq 0.1$). The backward procedure for variable selection was applied for the multivariable logistic regression model. Regression coefficients were used to generate a nomogram.

Missing Data

The entire dataset contained 211 women, and data entry was complete for all variables. There is no missing data.

Predictive ability

Nomogram model performance was assessed by examining discrimination and calibration in the development and validation cohorts. The discrimination was assessed by the area under the receiver-operator characteristic (ROC) and area under the curve (AUC) and its 95% CI. The calibration was constructed to examine the agreement between the predicted probabilities with the observed outcome, which was assessed by the Hosmer-Lemeshow goodness-of-fit test and calibration plots. The calibration plot was calculated by the 400 repetitions Bootstrap resampling.

Ethical approval

Ethical approval for this study was provided by the Ethics Committee of Peking University Third Hospital (Approval reference No:2019SZ-092; date of approval 16 December 2019). Patients provided written consent for the information to be used in the analyses, editing and publications.

Results

Basic characters

A total of 211 patients with 215 cycles of freeze-thaw oocytes participated in this study. Among them, four patients received two freeze-thaw oocytes cycles. 40 patients with 43 cycles did not have embryos to transfer. 7 patients conducted oocyte thawed and had embryo to transfer but they did not transfer yet. 164 patients received IVF-ET/FET. Figure 1 shows how we established the eligible cohort of oocyte freeze-thaw treatment cycles. Table 1 shows the baseline characteristics of the cohort. In total, there were 2546 oocytes that were thawed. The average recovery rate of oocytes was $75.42 \pm 24.04\%$, the fertilization rate was $69.54 \pm 26.07\%$ and the cleavage rate was $95.05 \pm 12.53\%$. The overall rate of cumulative live birth from the whole dataset was 39.63% (65/164), the rate of no embryo to transfer was 20.00% (43/215) and the live birth rate per frozen oocyte was 2.55% (65/2546).

Development and validation of a nomogram for predicting no embryo to transfer

The univariate associations of the potential predictors and multivariable logistic regression model for no embryo to transfer are shown in Table 2. Predictors included in the multivariable logistic regression were as follows: female age, antral follicle count (AFC), basal LH level, gonadotropin (Gn) dosage, number of follicles on the day of hCG administration, endometriosis, semen quality, sperm source, and storage duration of oocytes. The variables which showed a statistically significant increment in odds ratio of no embryo to transfer in the final model were: female age (OR= 1.099, 95% CI=1.003-1.205, P=0.044), duration of infertility (OR= 1.140, 95% CI=1.018-1.276, P=0.024), basal FSH (OR= 1.205, 95% CI=1.051-1.382, P=0.0084) and E2 (OR= 1.006, 95% CI=1.001-1.010, P=0.012) level. As for the source of sperm, compared with masturbation and PESA, sperm from MESA significantly increased the risk of no embryo to transfer (OR= 7.741, 95% CI=2.905-20.632, P<0.001).

The nomogram was derived from a multivariable logistic regression model. The model showed an AUC of 0.799 (95% CI: 0.722–0.875, $p=0.001$), which denotes a good performance. The Hosmer-Lemeshow goodness-of-fit test, and the calibration curve showed good discrimination and calibration of nomogram in the internal validation cohort (Figure2).

Development and validation of a nomogram for predicting cumulative live birth

The univariate associations of the potential predictors and multivariable logistic regression model for the cumulative live birth of freeze-thaw oocytes are shown in Table 3. Predictors included in the multivariable logistic regression were as follows: age of female and male, duration of infertility, basal FSH and E2 level, Gn dosage, number of follicles on the day of hCG administration, poor ovarian response and sperm source. The model shows that the odds ratio of a successful live birth decreases with the number of follicles on the day of hCG administration (OR= 1.088, 95% CI=1.030-1.149, P=0.002) and endometriosis (OR= 0.172, 95% CI=0.035-0.853, P=0.031).

The nomogram was derived from the multivariable logistic regression model. The model showed an AUC of 0.724 (95% CI: 0.647–0.801, $p=0.001$). The Hosmer-Lemeshow goodness-of-fit test, and the calibration curve showed good discrimination and calibration of nomogram in the internal validation cohort (Figure3).

Discussion

In the early 20th century, scientists began to preserve gametes and embryos at low temperatures. In 1999, Kuleshova [8] first reported the case of successful pregnancy and delivery after oocyte cryopreservation, which marked a breakthrough in oocyte cryopreservation. Presently thousands of children are born and benefited from this technique. Although new techniques are emerging and existing ones are always evolving, the freeze-thaw process can cause damage and changes of spindles, genetic materials, organelles and epigenetic in the oocyte [9]. Whether or not these alterations may produce a long-term negative health effect remains unclear. Existing studies have shown that the clinical pregnancy rate and

live birth rate of mature oocytes after freezing and thawing are similar to those of fresh oocytes, with evidence from oocyte donation cycles. However, for patients with poor ovarian reserve function or less expected number of oocytes, doctors and patients are still worried that no embryo could be transferred after thawing the oocytes. The data from our center indicates that nearly one-fifth of the patients (40/211, 18.96%) have no embryos to transfer after thawing the oocytes. For those patients, if we can inform them of the possibility of no embryos to transfer before oocyte retrieval, it may reduce the economic loss and the risks of the operation.

Main findings

At present, there is no predictive model of pregnancy outcome after emergency cryopreservation of oocytes. Based on the clinical data and laboratory results of emergency oocyte cryopreservation, prediction models of pregnancy outcomes were developed to fill the gap. All the indicators in the model are available before oocyte retrieval. The internal verification of the model was also conducted. The key predictors which had significant effects on the result of the model of no embryo to transfer are: female age, duration of infertility, basal FSH, basal E2 and the source of semen. While for the model of live birth, the key predictors are: the number of follicles which diameter greater than 10mm and endometriosis.

Strengths and weaknesses

Ratna [10] suggested that a high-quality prediction model article should meet the following three criteria: 1) a TRIPOD [6] score greater than 80%. 2) external validation and 3) the model had acceptable discrimination (c-statistic >0.7)[11]. 35 prediction models of IVF success have been published across 23 articles. These 35 models met between 29 to 95% of the items included in the TRIPOD checklist [12, 13]. Only 21% of studies met at least 80% of the checklist items, and the highest achieved a TRIPOD score of 95%. Only four models [14-17] had conducted external validation (4/23 = 17.39%), and almost all of the indicators in the models have missing values or do not describe missing values. The range of c-statistic was between 0.55 and 0.77.

From research design to manuscript drafting, we strictly followed the TRIPOD list. The self-evaluation TRIPOD score is 90.91%. The AUC of the 'no embryo to transfer' model is 0.799 (95% CI: 0.722–0.875, $p < 0.001$), and the AUC of the 'live birth' model is 0.724 (95% CI: 0.647–0.801, $p < 0.001$), which are greater than 0.7. The accuracy of the prediction model is at the forefront of the existing models. On the one hand, it benefits from the guidance of TRIPOD, but on the other hand, it is closely related to the fact that this study covers almost all the prediction indicators related to the pregnancy outcome of IVF and there is no missing value.

The main categories of predictors included in developed models are as follow: couple factors, gender, embryo and treatment. At present, several better prediction models recommended in the field of reproductive medicine mostly come from multicenter or national databases. Although the sample size is large, the number of prediction indicators included is limited [13]. The median number of predictors included in the existing models was 7 (range 3–14). Our model includes 26 forecast indicators. In

addition to the most frequently used predictors such as female age, duration of infertility, endometriosis, et al [18], we also included basic hormone levels, AFC, male age and semen quality and hormone levels on the day of hCG injection. The information about the embryos could not be obtained due to the pretreatment model. However, compared with other pretreatment models, the numbers of oocytes were estimated through the number of follicles with a diameter of more than 10 mm on hCG administration day. Moreover, the sources of the semen were also taken into consideration to further improve the accuracy of the model prediction.

One of the greatest strengths of our model is that it has highlighted the semen source as a key predictor for IVF success. Semen source is a factor that has never been used in any previous prediction models. Studies have indicated that NOA (non-azoospermia) patients could produce increased numbers of cytogenetically abnormal testicular spermatozoa despite their normal somatic karyotype, and were at increased risk to produce aneuploid gametes and of transmitting chromosome aneuploidy to the zygote [19, 20], which may lead to a reduced developmental potential of embryos. An [21] had compared 150 NOA patients who underwent micro-TESE with 174 OA patients who underwent TESA and found that developmental competence of the embryo was greatest among couples using sperm obtained by TESA rather than micro-TESE, and was not dependent on whether vitrified or fresh oocytes were utilized. Capello [22] showed that the quality and source of sperm did not affect the clinical pregnancy rate and live birth rate in vitrified oocyte donation IVF model. On the contrary, the results of our study suggest that the source of semen is an important factor leading to no embryo to transfer in freeze-thaw oocyte cycles. If the sperm comes from MESA, the risk of no embryo to transfer will be increased by 7.74 times.

Female age and duration of infertility are two important predictors applied to predict the pregnancy/live birth chances after IVF [18]. They both have negative associations with treatment outcomes. Our results suggest that in terms of pregnancy outcome of oocyte cryopreservation, female age and duration of infertility also play a negative role. For every 1-year increase in female age, the risk of no embryo to transfer increases by 1.099 times. The risk of no embryo to transfer increases by 1.14 times for every 1-year extension of infertility years.

Basal FSH and E2 levels are important indexes for the evaluation of ovarian reserve function. A high level reflects a reduced ovarian reserve and is associated with poor IVF treatment outcome [23]. Some studies also suggested that the FSH level on cycle day 3 was a better indicator of IVF outcome than female age [24]. High levels of basal E2 level were associated with low oocyte yields, low pregnancy rates and higher cancellation rate independent of FSH levels [25, 26]. Our results are consistent with the above studies. In the multiple logistic regression equation, the effect of basal FSH and basal E2 on the adverse outcome of no embryo to transfer is even beyond the female age.

Endometriosis is one of the important factors leading to female infertility. 57% (20/35) of the prediction models take endometriosis as one of the important indicators to evaluate the success rate of IVF. After balancing many other prediction indicators, only the number of follicles larger than 10 mm on the day of

hCG administration and endometriosis entered the final equation, which shows that the expected number of retrieved oocytes and endometriosis are closely related to the outcome of oocytes cryopreservation.

One of the weaknesses of our model is insufficient external validation. This is because there are a limited numbers of patients which require emergency oocyte cryopreservation. In one of the largest assisted reproductive centers in China, in over 10 years only 211 patients received emergency oocyte cryopreservation and returned to the hospital for follow-up treatment. The number is expected to be lower in other relatively smaller scale assisted reproductive centers. Therefore, it is difficult to carry out external verification at this moment. In addition, the sample size used to derive this prediction model is small, and all of them are from a single center. Whether the research results can be extended to other races and regions remains to be further verified.

Given the complexities of assisted reproductive technology, many other confounders can have an effect at different points in time. Although we can use the expected retrieved number of eggs and sperm sources to make a preliminary assessment of the embryo, our model is for pretreatment counseling only. We appreciate that IVF success rates depend on more than the factors in this model alone. Therefore, when using the model, it is important for clinicians to ensure that their patients understand the probability of having a successful outcome will invariably change as they progress through their treatment and thus should be interpreted as a baseline prediction only.

Comparison to existing models

The existing prediction models of IVF success rate are all for fresh oocyte; there is no available model for frozen oocyte. Therefore, there is no comparability of clinical indicators and prediction accuracy between this model and existing models. Different from the published clinical model of assisted reproduction, a nomogram was applied in this research to display the prediction model, which is more practical and intuitive. The nomogram makes it convenient for clinicians and patients to calculate the benefits of oocytes cryopreservation in each treatment cycle according to their own conditions. This can help reduce psychological pressure on both doctors and patients and make the decision easier under certain expectations. It may also reduce the economic and psychological pressure on patients when facing no embryo to transfer. We believe this prediction tool is an important and valuable addition in the counseling process for patients at this critical decision-making point in their journey.

Conclusions

Our results show that, as fresh oocyte cycle, for the oocyte cryopreservation cycle, with the increase of age, the prolongation of infertility, the decrease of ovarian reserve function and endometriosis, the risk of no embryo to transfer could be increased and the live birth rate could be decreased. We have illustrated not only the clinical use of this model but also how a couple's characteristics might affect their prognosis. This model provides a personalized approach to counseling and estimates the chances of success based on individual information. This can be applied by clinicians when counseling couples before emergency oocyte cryopreservation.

For example, take the case of an infertile patient and sperm donor where the woman is 32 years old with three years of infertile history, basal FSH, 7.5MIU/ml, basal E2:131mmol/L. Their IVF indicators are involved: endometriosis and severe oligozoospermia. The number of follicles with a diameter greater than 10 mm on the day of hCG administration is 8. The sperm donor could not come to the hospital due to an emergency on the day of oocyte retrieval. If the man can obtain sperm by masturbation, the possibility of no embryo to transfer is 25.30%. If it is necessary to extract sperm by MESA, the possibility of no embryo to transfer is 48.9%, and the possibility of live birth is 39.39%. The results from our model might assist the couples to decide whether to freeze or give up oocyte retrieval.

The next step for this model is to further validate the research findings by performing external validation in other assisted reproduction centers in China and worldwide. Furthermore, this model may be developed into both a user-friendly web-based decision aid platform and as a mobile application to assist both clinicians and patients.

Abbreviations

IVF: in vitro fertilization

ICSI: intracytoplasmic sperm injection

ART: assisted reproductive technology

MESA: Microsurgical Epididymal Sperm Aspiration

TESA: Testicular Sperm Aspiration

Gn: gonadotropin

Hcg: human chorionic gonadotropin

ROC: receiver-operator characteristic

AUC: area under the curve

AFC: antral follicle count

Declarations

Ethics approval and consent to participate

Ethical approval for this study was provided by the Ethics Committee of Peking University Third Hospital (Approval reference No:2019SZ-092; date of approval 16 December 2019). Patients provided written consent for the information to be used in the analyses, editing and publications.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yang Wang and Rong Li design the study. Yang Wang and Ziru Niu collected the data and drafted the manuscript. Liyuan Tao conducted the statistical analysis. Xiaoying zheng and Yifeng yuan conducted the oocyte frozen and thawing. Ping Liu and Rong Li revised the manuscript.

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Tables

Table 1. Baseline characteristics of the cohort		
	'no embryo to transfer' cohort(N=215)	Live birth rate(N=164)
Female age (years) Mean±SD	29.91±4.95	29.41±4.85
BMI(kg/m ²) Mean±SD	22.32±3.56	22.41±3.61
Duration of infertility (years) Mean±SD	3.44±3.24	3.13±2.68
Types of infertility		
Primary infertility n(%)	174(80.93%)	131(79.88%)
Secondary infertility n(%)	41(19.07%)	33(20.12%)
Gravidity (times) Median(min,max)	0.00(0, 5)	0.00(0, 5)
Delivery (times) Median(min,max)	0.00(0, 2)	0.00(0, 2)
Endometriosis n(%)	17(7.91%)	14(8.54%)
PCOS n(%)	24(11.16%)	18(10.98%)
POR n(%)a	22(10.23%)	13(7.93%)
Tubal factor n(%)	28(13.02%)	22(13.41%)
IVF failure history n(%)	21(9.77%)	16(9.76%)
basal FSH (MIU/ml) Mean±SD	6.11±2.82	5.86±2.38
basal LH (MIU/ml) Mean±SD	3.64±1.99	3.64±1.95
basal E2 (mmol/L) Mean±SD	164.58±88.24	157.86±58.30
AFC	14.55±6.86	14.85±6.69
Duration of Gn applied (Days) Mean±SD	11.47±2.59	11.47±2.53
total Gn applied units Mean±SD	2505.62±1140.04	2428.80±1106.91
LH on the day of hCG (MIU/ml) Mean±SD	1.73±2.40	1.63±2.17
E2 on the day of hCG (mmol/L) Mean±SD	11036.42±7532.33	11622.27±7552.50
P on the day of hCG (pmol/L) Mean±SD	2.85±1.86	2.89±1.59
The number of follicles with a diameter greater than 10 mm on the day of hCG(number) (Mean±SD)	16.08±6.88	16.76±6.81
Male age (years) Mean±SD	31.20±6.21	30.70±5.99
Semen quality		

Azoospermia	158(73.49%)	123(75.00%)
Oligozoospermia	21(9.77%)	14(8.54%)
Normal semen	36(16.74%)	27(16.46%)
Semen source		
AID	104(48.37%)	90(54.88%)
TESA/PESA	10(4.65%)	7(4.27%)
MESA	42(19.53%)	22(13.41%)
Masturbation	59(27.44%)	45(27.44%)
Duration of oocyte frozen (month)Mean±SD	8.23±8.94	8.51±9.12
Oocyte retrieval time grouped by year		
2007-2011	24(11.16%)	23(14.02%)
2012-2015	76(35.35%)	54(32.93%)
2016-2019	115(53.49%)	87(53.05%)
BMI:body mass index; AFC:antral follicle count; PCOS: polycystic ovary syndrome;		
POR-poor ovarian response diagnosis according to Bologna dianosis criteria		
AID:artificial insemination by donor; TESA:testicular sperm aspiration;		
PESA-percutaneous epididymal sperm aspiration; MESA-microdissection testicular sperm extraction.		

Table 2. Potential predictors and multivariable logistic regression model for no embryo to transfer				
Predictor	univariate analysis		multivariable analysis	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
Female age (years)	1.098(1.028–1.172)	0.005*	1.099(1.003,1.205)	0.044*
BMI(kg/㎡)	0.975(0.885–1.075)	0.616		
Duration of infertility (years)	1.149(1.047–1.262)	0.004*	1.140(1.018,1.276)	0.024*
Secondary infertility	1.575 (0.616, 4.029)	0.343		
Gravidity (times)	0.881 (0.568,1.367)	0.573		
Delivery (times)	0.842 (0.126,5.603)	0.859		
Endometriosis	1.181(0.324,4.310)	0.801		
PCOS	0.944(0.331,2.690)	0.914		
POR	0.309(0.122,0.781)	0.013*		
Tubal factor	1.518(0.518–4.825)	0.421		
IVF failure history	1.069(0.341,3.358)	0.909		
basal FSH (MIU/ml)	1.156(1.029–1.299)	0.014*	1.205(1.051,1.382)	0.008*
basal LH (MIU/ml)	1.014(0.858,1.198)	0.871		
basal E2 (mmol/L)	1.003(1.000–1.007)	0.059	1.006(1.001,1.010)	0.012*
AFC	0.960(0.912–1.010)	0.115		
Duration of Gn applied (Days)	0.994(0.873–1.131)	0.926		
total Gn applied units	1.003(1.000–1.001)	0.095		
LH on the day of hCG (MIU/ml)	1.066(0.944,1.203)	0.302		
E2 on the day of hCG (mmol/L)	1.000(1.000–1.000)	0.204		
P on the day of hCG (pmol/L)	0.972(0.804–1.174)	0.765		
The number of follicles with a diameter greater than 10 mm on the day of hCG(number)	0.950(0.901–1.001)	0.056		
Male age (years)	1.066(1.014–1.121)	0.012*		
Semen quality				
Azoospermia	1	0.516		
Oligozoospermia	1.779(0.636,4.978)	0.272		

Normal semen	1.271(0.526,3.073)	0.595		
Semen source				
AID	1	0.001*	1	0.001*
TESA/PESA	4.029(0.898,18.081)	0.069	2.180(0.383,12.403)	0.380
MESA	6.392(2.607,15.675)	0.001*	7.741(2.905,20.632)	0.001*
Masturbation	2.675(1.084,6.512)	0.033	1.399(0.486,4.034)	0.534
Duration of oocyte frozen (month)	0.978(0.936,1.022)	0.323		
Oocyte retrieval time grouped by year				
2007-2011	1	0.190		
2012-2015	6.133(0.769,48.931)	0.087		
2016-2019	6.719(0.866,52.154)	0.068		
BMI:body mass index; AFC:antral follicle count; PCOS: polycystic ovary syndrome;				
POR-poor ovarian response diagnosis according to Bologna diagnosis criteria				
AID:artificial insemination by donor; TESA:testicular sperm aspiration;				
PESA:percutaneous epididymal sperm aspiration; MESA: microdissection testicular sperm extraction.				

Table 3. Potential predictors and multivariable logistic regression model for live birth rate				
Predictor	univariate analysis		multivariable analysis	
	OR[95%CI]	P	OR[95%CI]	P
Female age (years)	0.934[0.872,1.001]	0.055		
BMI(kg/m ²)	0.976(0.894,1.066)	0.593		
Duration of infertility (years)	0.928[0.817,1.055]	0.255		
Secondary infertility	1.991[0.859,4.615]	0.108		
Gravidity (times)	0.795(0.523,1.211)	0.286		
Delivery (times)	1.842(0.386,8.799)	0.444		
Endometriosis	4.345(0.939,20.099)	0.060	0.172(0.035,0.853)	0.031*
PCOS	0.622(0.233,1.662)	0.344		
POR	0.431(0.114,1.629)	0.215		
Tubal factor	1.174(0.462,2.978)	0.736		
IVF failure history	1.105(0.381,3.203)	0.854		
basal FSH (MIU/ml)	0.904[0.790,1.034]	0.141		
basal LH (MIU/ml)	0.865[0.731,1.025]	0.095		
basal E2 (mmol/L)	0.998(0.992,1.003)	0.393		
AFC	1.046[0.997,1.097]	0.066		
Duration of Gn applied (Days)	0.911[0.801,1.037]	0.158		
total Gn applied [units]	1.000[0.999,1.000]	0.034*		
LH on the day of hCG (MIU/ml)	1.036(0.898,1.194)	0.630		
E2 on the day of hCG (mmol/L)	1.000[1.000,1.000]	0.256		
P on the day of hCG (pmol/L)	0.861[0.699,1.061]	0.161		
The number of follicles with a diameter greater than 10 mm on the day of hCG(number)	1.071[1.019,1.125]	0.006*	1.088(1.030,1.149)	0.002*
Male age (years)	0.955[0.901,1.011]	0.113		
Semen quality				
Azoospermia	1	0.051		
Oligozoospermia	0.687(0.218,2.168)	0.522		

Normal semen	0.281(0.100,0.790)	0.016
Semen source		
AID	1	0.064
TESA/PESA	0.228(0.026,1.974)	0.179
MESA	1.977(0.767,5.097)	0.159
Masturbation	0.556(0.258,1.199)	0.134
Duration of oocyte frozen (month)	1.028(0.992,1.065)	0.130
Oocyte retrieval time grouped by year		
2007-2011	1	0.653
2012-2015	1.500(0.545,4.127)	0.432
2016-2019	1.146(0.438,2.996)	0.781
BMI:body mass index; AFC:antral follicle count; PCOS: polycystic ovary syndrome;		
POR-poor ovarian response diagnosis according to Bologna diagnosis criteria		
AID:artificial insemination by donor; TESA:testicular sperm aspiration;		
PESApercutaneous epididymal sperm aspiration; MESAmicrodissection testicular sperm extraction.		

Figures

Figure 1

Flowchart of the study

Figure 2

Discrimination and calibration of a model to predict no embryo to transfer of emergency oocyte frozen-thawed cycles (A-AUC, B- Calibration curve, C- nomogram). AUC, area under the ROC curve; FSH, follicle stimulating hormone; E2, estradiol; AID, artificial insemination by donor; TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration; MESA, microdissection testicular sperm extraction.

Figure 3

Discrimination and calibration of a model to predict cumulative live birth of emergency oocyte frozen-thawed cycles (A-AUC, B- Calibration curve, C- nomogram). AUC, area under the ROC curve; hCG, human chorionic gonadotropin.