Original Article

Predicting the probability of a live birth after a freeze-all based in vitro fertilization-embryo transfer (IVF-ET) treatment strategy

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Background: The predictors for live birth rate (LBR) following one episode of in vitro fertilization (IVF) cycle for patients using a "freeze-all" strategy are not entirely clear.

Methods: A retrospective cohort study utilizing a prediction model was developed to assess the relationship to the LBR. Women undergoing IVF with a freeze-all strategy were screened. Univariate models were first fitted for female age at oocytes retrieval/frozen-thawed embryo transfer (FET), body mass index (BMI), duration and etiology of infertility, previous IVF failures, total dose and duration of gonadotrophin, ovarian sensitivity index (OSI), number of oocytes collected, method of fertilization, number of embryos created, number and stage of embryos frozen, type and number of FET cycles, endometrial thickness (EMT)/pattern, hormone level on transplantation day, storage duration, number of embryos thawed and damaged thawed embryos, number and stage of embryos transferred and number of different quality embryos transferred. Variables with $P<0.05$ in the univariate model were selected for further analysis of the final multivariate discrete-time logistic regression model.

Results: A total of 7,602 women undergoing one ovarian stimulation resulted in 9,964 FETs, of whom 3,066 (40.33%) had a live-birth after their first FET and 3,929 (51.68%) after total FETs. The EMT and woman's age at oocyte retrieval were the most important predictors. In the first FET, the LBR of women with an EMT ≤8 mm [27.40%; 95% confidence interval (CI): (21.60–33.81%)] was significantly lower than that of women with EMT between 9 and 11 mm [36.51%; 95% CI: (34.25–38.81%)] and thicker than 12 mm [44.23%; 95% CI: (42.22–46.25%)] ($P<0.05$). The optimistic and conservative cumulative LBRs of women younger than 31 years [87.5%; 95% CI: (86.32–88.61%) and 63.04%; 95% CI: (61.36–64.69%)] were significantly decreased in women aged 31–35, 36–40 and >40 ($P<0.001$).

Conclusions: Our study provides an effective prediction model for a woman's chance of having a baby after a "freeze-all" policy. The use of EMT and female age as tools to identify LBR are shown to be justified, and repeated FETs cannot reverse the age-dependent decline in fertility.

Keywords: In vitro fertilization (IVF); live birth rates (LBRs); freeze-all strategy; frozen-thawed embryo transfer (FET); prediction model

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Introduction

The first live birth following embryo cryopreservation was reported by a Dutch team in 1984. Since then, this technique has become widespread throughout the world and led to rapid development of in vitro fertilization-embryo transfer (IVF-ET)/intracytoplasmic sperm injection (ICSI) protocols (1). Currently, the quality of frozen embryos and their potential for implantation are similar to or even exceed those of fresh embryos (2,3). This favors the so-called 'freeze-all' strategy performed with the elective cryopreservation of all viable embryos in a fresh IVF/ICSI cycle with the frozen-thawed embryos transferred in the following cycles (4). In order to place the embryos in a more favorable intrauterine environment (and thereby optimize IVF/ICSI outcome), without facing the possible negative effect of ovarian hyperstimulation on the endometrium, the metric for success of IVF/ICSI has changed from live-birth rate in a single fresh cycle (5) to cumulative live birth rates (CLBRs). In practice, the freeze-all strategy can reduce the risk of ovarian hyperstimulation syndrome (OHSS) in the ovarian stimulation cycle by avoiding a pregnancy (6) and obtain better results. Previous studies have shown improved live birth rate (LBR) and a significant decrease in the risk of OHSS and adverse perinatal outcomes in pregnancies after the transfer of frozen embryos (3,7,8). Chen *et al.* (9) report the results of a multicenter, randomized clinical trial among infertile women with polycystic ovary syndrome (PCOS). As expected, the rate of live birth was significantly higher (49.3% *vs.* 42.0%) and the rate of the OHSS significantly lower in the frozen-embryo group than in the fresh embryo group (1.3% *vs.* 7.1%). Though other studies, including two randomized trials showed a similar LBR comparing freeze-all strategy with fresh embryo transfer in general infertile patients, a lower risk of OHSS in the frozen-thawed embryo transfer (FET) group was found (10,11). Thus, among generally infertile patients, including the subgroups of patients who are at high risk for OHSS or those with improper endometrial status, a freeze-all strategy may be beneficial.

The CLBR estimates the outcome of the entire course of treatment to provide an all-inclusive success rate (12,13). However, CLBRs are often reported either as one overall rate which include fresh and FET cycles per initiated ovarian stimulation (14) or the likelihood of a live birth during repeat IVF/ICSI cycles which include frozen embryo replacements as well as subsequent treatment episodes (15,16). However, these studies were performed in patients with fresh IVF/ICSI treatments. As previous studies support the adoption of an individualized "freeze-all" strategy instead of fresh ET to get better IVF outcomes (17,18), the shift from fresh ET to FET may become a trend in many programs. Therefore patients and physicians are keen to know the chance of a live birth for the individual couple over an entire IVF/ICSI program combined with a "freeze-all" strategy. A retrospective observational study found variables of freeze-all-IVF cycles with single blastocyst FET selected by multiple logistic regression to predict LB significantly were female age, infertility duration, FET number and blastocyst quality (19). They also found ovarian reserve variables were not significantly selected by the regression model in predicting LBR. However, in this study only the first oocyte retrieval attempt performed for each patient-couple were retained and all IVF treatments were performed using single blastocyst FET. Its design may limit the generalizability of evidence.

The objectives in the present study are to explore the predictors of CLBRs following one complete IVF cycle for unselected patients using a "freeze-all" strategy, and then to develop and validate a prediction model based on patient demographic and cycle characteristics. The model is designed to estimate the individualized CLBR after all FET cycles from one stimulated cycle. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-589/rc).

Methods

Patients

We performed a retrospective study with linkage of cycles to individual patients and data on birth outcomes at the Department of Assisted Reproduction of Shanghai First Maternity and Infant Hospital of Tongji University School of Medicine. In this population-based cohort study, records of all complete IVF/ICSI cycles were defined as all attempts at FET resulting from one episode of ovarian stimulation. Our cohort was limited to ovarian stimulation cycles initiated between January 1, 2015 and December 30, 2020, with live-birth outcome data collected up to December 2021. Patients were followed by face to face and/or telephone conversations during treatment at our department for at least 1 year until either termination of treatment or delivery of a first live birth. All women undergoing IVF/ICSI treatment with the freeze-all strategy

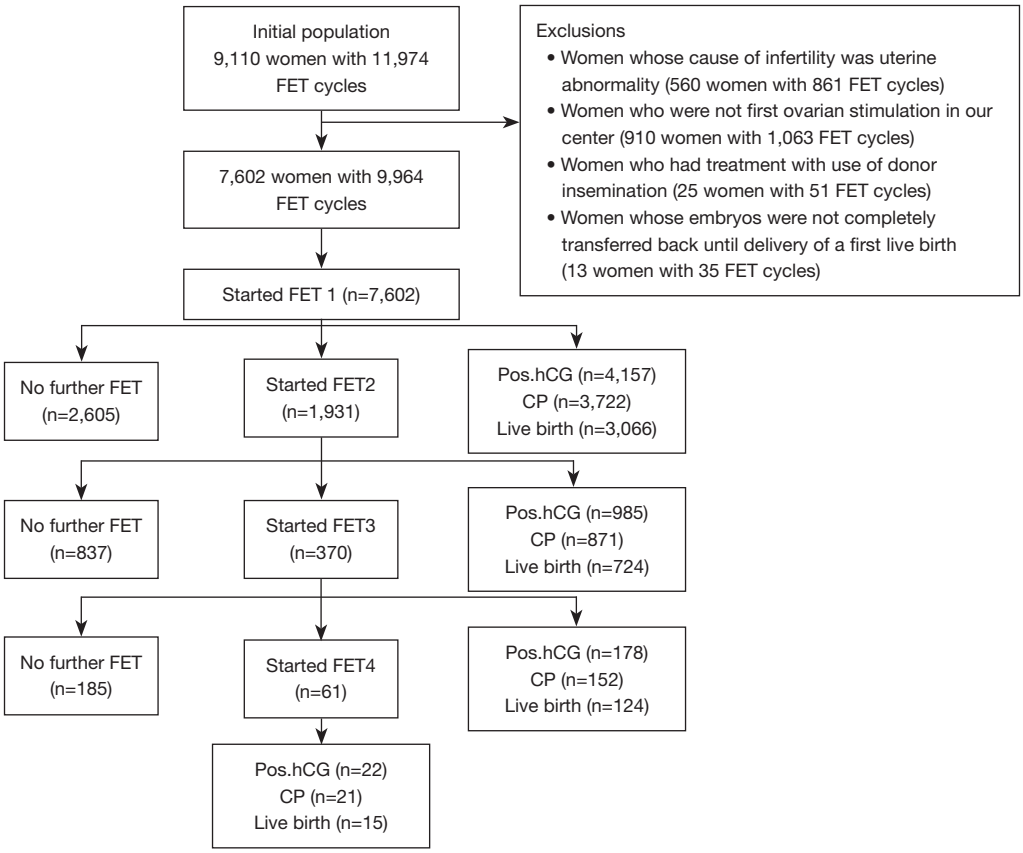

Figure 1 Trial flow chart. An overview of all started FET cycles and the overall reproductive outcomes. FET, frozen-thawed embryo transfer; Pos.hCG, positive human chorionic gonadotropin; CP, clinical pregnancy.

were screened. Exclusion criteria were uterine abnormality, donor insemination, "Re-entries" of couples after a live birth in a preceding cycle, and those patients who were not undergoing the first ovarian stimulation in our center. After exclusions were mode, our population of 7,602 women undergoing 9,964 FET cycles were analyzed (*Figure 1*).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Shanghai First Maternity and Infant Hospital of Tongji University School of Medicine (No. KS21282) and individual informed consent for this retrospective study was waived.

FET

Patients underwent regimens for ovarian stimulation, monitoring, and oocyte collection as previously described (20-22). In general, fertilization was carried out *in vitro*, by either conventional IVF or ICSI, depending on semen parameters. Embryos were cultured and scored (23) as previously described. Embryos (non-top-quality) not suitable for cryopreservation on day 3 were cultured to day 5 or 6 and vitrified if they reached the blastocysts stage. Then, good-morphology blastocysts were vitrified on day 5 or 6. The vitrification procedure was performed using the Cryotop carrier system (Kitazato Biopharma Co., Tokyo, Japan).

IVF/ICSI cycles with the use of cryopreserved embryos were performed either in natural cycles for women with regular menses, or in induced ovulation cycles for women with anovulatory infertility; or in case of thin endometria, in hormonal substitution cycles (22). Once pregnancy was achieved, exogenous progesterone (P) supplemention was continued until 10 weeks of gestation.

Reproductive outcomes

Live birth was defined as the complete expulsion or

extraction from its mother as product of fertilization, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life such as heart beat, umbilical cord pulsation, or definite movement of voluntary muscles, irrespective of whether the umbilical cord had been cut or the placenta was attached (24). CLBR was defined as the total chance of a live birth with all cycles up to and including that given cycle number. Thus, CLBR was calculated by including the first live birth generated during the complete IVF cycle as the numerator and censoring additional live births out. The denominator was defined as all women allocated to treatment (12). The conservative CLBRs were based on the assumption that none of the women who discontinued treatment would have had a live birth. These two curves show the best- and worst-case estimates of the CLBRs in the study group. The optimal CLBRs were based on the assumption that women who discontinued treatment would have had the same chance of a pregnancy resulting in a live birth as those who remained in treatment. These CLBRs reflect the worst- and best-case estimates, respectively.

Statistical analysis

Descriptive statistics were calculated for patients and treatment characteristics at the IVF/ICSI-FET treatment. Data were presented as mean ± standard deviation (SD) if they demonstrated normal distributions, or presented as median (interquartile range) for non-normal distributions, and qualitative data were presented as percentages. Normality was tested using the Kolmogorov-Smirnov test. The STROBE reporting checklist was completed.

Model development

A discrete time logistic regression model (25) was used to predict the chance of a live birth after a complete IVF/ICSI-FET cycle using the characteristics of patients and cycle characters. From this model, we treated the FET cycle number as a discrete time variable and calculated the cumulative probability of a live birth over sequential complete FET cycles up to cycle number 4.

First, univariate models were fitted with the LBR as the dependent variable for all individual predictors (adjusted for complete cycle number). The duration of infertility, number of previous IVF failures, number of frozen embryos in cleavage stage, number of frozen embryos in blastocyst stage and number of blastocyst transferred all had non-linear relations with the LBR so they were analyzed with restricted cubic splines. To prevent overfitting of the model, the data was randomly divided into two parts: 70% of all observations were used for the primary analyses (training set; n=7,007) and 30% of observations were used for internal model validation (validation set; n=2,957). Variables with $P<0.05$ in univariate models were selected for further analysis of the final multivariate discrete time logistic regression model by means of a manual backward selection process. For the final multivariate model, multicollinearity among all variables was examined. Effect estimates were presented with the odds ratio (OR), 95% confidence interval (CI), P value and adequacy for each predictor. All analyses were performed in statistical software R version 3.4.2 (R Core Team, Vienna, Austria). A two-sided P value <0.05 was considered to be statistically significant.

Missing data

This procedure assumes that the missing data are "missing at random". We compared the characteristics of the women with or without missing data. Single imputation was performed for the predictors with missing data.

Predictive ability

We used c-statistics and calibration to assess the ability of the multivariate models. The c-statistic is routinely used in the medical literature to quantify the capacity of the estimated risk score in discriminating subjects with different event times and is analogous to the area under the receiver-operating characteristic curve in assessing the model's discriminative capacity (26-28). Calibration, assessed by whether predicted probabilities are consistent with observed proportions, was quantified by means of the Hosmer-Lemeshow χ^2 statistic (26,27). Moreover, adequacy statistics were calculated to investigate the explanatory value of each predictor to the entire set (29).

Results

Characteristics of the patients

After exclusions (see methods), the eligible dataset included 7,602 women who underwent 9,964 FET cycles (see *Figure 1*).

Baseline characteristics of the cohort and clinical characteristics of their oocyte retrieval cycle resulting from one episode of ovarian stimulation are summarized

in *Table 1*. Among the 7,602 women, the average age at oocyte retrieval was 32.28±4.85 years, the average body mass index (BMI) was 21.71±3.03 kg/m^2 and the median duration of infertility was 3 years (interquartile range, 2–5); 5,409 of these women had regular menstruation (71.15%), 1,314 women had irregular periods (17.28%) and 879 were missing data (11.56%); 3,538 of these women had previous pregnancies (46.54%) resulting in 730 deliveries (9.60%), while 4,064 of these women never had a pregnancy before (53.46%). Indicators for IVF/ICSI treatments were tubal factor (49.75%), anovulation (3.59%), endometriosis (2.37%), male factor (11.81%), unexplained (1.71%), other (3.79%) and mixed factor (26.98%). The mean time of previous IVF failures was 0 (0–1). For the ovarian stimulation cycle, the median of total dose and duration of gonadotrophin was 1,800 IU (interquartile range, 1,500–2,025) and 9 days (interquartile range, 8–10), respectively. The median number of oocytes collected was 9 (interquartile range, 5–15), and median ovarian sensitivity index (OSI) was 1.65 (interquartile range, 1.20–2.08). For the method of fertilization, 5,249 of all included patients performed IVF (69.05%) and 2,353 of those performed ICSI (30.95%). This created a median number of 6 embryos (interquartile range, 4–10) and a median number of 4 frozen embryos (interquartile range, 2–6). Of those frozen embryos, the median number of cleavage stage and blastocyst stage embryos was 3 (interquartile range, 2–5) and 0 (interquartile range, 0–1), respectively.

Characteristics of FET cycles

Cycle characteristics of FET were summarized in *Table 2*. The patients underwent a maximum of 4 FET cycles. Among the 9,964 FETs, endometrial preparation with induced cycle was used in more FET cycles (3,905 cycles, 39.19%). The remaining FETs prepared the endometrium with a natural cycle (2,766 cycles, 27.76%) or a hormonal substitution cycle (3,293 cycles, 33.05%). These endometrial preparations resulted in a median EMT of 10.80 (interquartile range, 9.40–12.40) mm. The heterogeneous, homogeneous and trilinear endometrial patterns were determined, respectively, as 40.90% (4,075/9,964), 51.12% (5,094/9,964) and 5.9% (588/9,964). In addition, 2.08% (207/9,964) of all cases lacked the data for endometrial pattern. The mean serum estradiol (E_2) and P concentration on the day of transplantation were 174 (interquartile range, 105–258) pg/mL and 16.6 (interquartile range, 11.3–22.5) ng/mL, respectively. E_2/P ratio on transplantation day was calculated from these data giving a median value of 10.86 (interquartile range, 5.73–20.27). The median value of storage duration, number of thawed and damaged thawed embryos, number of embryos transferred and number of top quality embryos transferred were 124 (interquartile range, 76–182) days, 2 (interquartile range, 2–2), 0 (interquartile range, 0–0), 2 (interquartile range, 2–2) and 0 (interquartile range, 0–1). In the majority of FET cycles, cleavage stage embryos were transferred. The median number of cleavage stage embryos transferred in all FET cycles was 2 (interquartile range, 2–2), while the median number of blastocyst stage embryos transferred was 0 (interquartile range, 0–1).

Treatment outcomes

Of all FET cycles, the chance of having a child was 39.43% (3,929/9,964). The optimal and conservative estimates of CLBRs were 81.30% (95% CI: 80.41–82.17%) and 51.68% (95% CI: 50.55–52.81%), respectively. The LBR for the first FET cycle was 40.33% (95% CI: 39.23–41.44%), the subsequent FET cycles were correlated with lower LBRs [37.49% (95% CI: 35.33–39.70%), 33.51% (95% CI: 28.72–38.58%) and 24.59% (95% CI: 14.46–37.29%), for FET cycle 2 to 4, respectively (see *Table 3*)]. Of the remaining cycles, the differences of conservative CLBRs were small. The specific values were 49.86% (95% CI: 48.72–50.99%), 51.49% (95% CI: 50.36–52.62%) and 51.68% (95% CI: 50.55–52.81%), respectively in cycle 2–4. However, the optimal CLBRs were continued to increase from cycle 2 to 4 [62.70% (95% CI: 61.60–63.79%), 75.20% (95% CI: 74.22–76.17%) and 81.30% (95% CI: 80.41–82.17%), respectively (see *Table 4*)].

LBRs and CLBRs varied when female age at oocyte retrieval, number of oocytes collected and endometrial thickness (EMT) on the day of embryos transferred were different (Table S1).

Predictors of the CLBRs

Among the categories collected before and during treatment, all characteristics had statistically significant univariate associations with LBRs, except for the method of fertilization, P level and E_2/P ratio on transplantation day, embryos transferred and number of top-quality embryos (Table S2).

Table 5 presents the best prediction model which contained

Table 1 Baseline characteristics of patients and their treatment cycles of IVF/ICSI

Characteristics	Data
No. of IVF/ICSI cycles	7,602
No. of female	7,602
Patient characteristics	
Age at oocyte retrieval (year)★	32.28±4.85
BMI (kg/m^2)★	21.71±3.03
Duration of infertility (years)▲	3 [2–5]
No previous pregnancy in couple, n (%)	4,064 (53.46)
Previous pregnancy in couple, n (%)	3,538 (46.54)
Previous delivery, n (%)	730 (9.60)
Infertility etiology, n (%)	
Tubal	3,782 (49.75)
Anovulatory	273 (3.59)
Endometriosis	180 (2.37)
Male factor	898 (11.81)
Unexplained	130 (1.71)
Other causes	288 (3.79)
>1 type	2,051 (26.98)
No. of previous IVF failures	0 [0–1]
Year of oocytes retrieval, n (%)	
2015	108 (1.42)
2016	420 (5.52)
2017	868 (11.42)
2018	1,662 (21.86)
2019	2,109 (27.74)
2020	2,435 (32.03)
Treatment characteristics of ovarian stimulation cycle	
Total dose of gonadotrophin (IU)▲	1,800 (1,500–2,025)
Total duration of stimulation (days)▲	9 [8–10]
OSI▲	1.65 (1.20–2.08)
No. of oocytes collected▲	9 [5–15]
Method of fertilization, n (%)	
IVF	5,249 (69.05)
ICSI	2,353 (30.95)
No. of embryos created▲	6 [4–10]
No. of embryos frozen▲	4 [2–6]
Cleavage stage	3 [2–5]
Blastocyst stage	0 [0–1]

★, values are presented as mean ± SD; ▲, values are presented as median (interquartile range). OSI = log (number of oocytes collected ×1,000/total dose of gonadotropin). OSI is a composite variable to measure ovarian response. IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; BMI, body mass index; OSI, ovarian sensitivity index; SD, standard deviation.

eight predictors using the multivariate analysis. The factors that predicted the cumulative rates of having a live birth over a complete "freeze-all" policy were the woman's age at oocyte retrieval, EMT, number of oocytes, previous IVF failures, number of embryos frozen, duration of infertility and number of blastocysts transferred. The odds of a live birth decreased with every increasing number of FET cycle which derived from one episode of ovarian stimulation.

Figure 2 shows CLBRs stratified according to categorical variables of positive significance in the multivariate model. *Figure 2A*,*2B* show the respective conservative and optimistic CLBRs stratified according to EMT. *Figure 2C*,*2D* show the conservative and optimistic CLBRs stratified according to female age at oocyte retrieval, respectively. *Figure 2E*,*2F* show the conservative and optimistic CLBRs stratified according to the number of oocytes collected, respectively.

Figure 3 shows the adjusted (multivariate model) relation between the predicted likelihood of live birth with the "freeze-all" policy and the number of previous IVF failures, duration of infertility, number of cleavage- and blastocyst-stage embryos frozen, and number of blastocysts transferred by using restricted cubic splines analysis. The probability of a live birth decreased linearly with increasing number of previous IVF failures and duration of infertility. Increasing numbers of blastocysts transferred, cleavage- and blastocyst-stage embryos frozen improved the chance of live birth.

Assessing the ability of the prediction model

The c-statistic for the model in the training set was 0.67

Table 2 Cycle characteristics of FET

Characteristics	Data
No. of FET cycles	9,964
No. of frozen treatments	
1	7,602 (68.94)
2	1,931 (19.38)
3	370 (3.71)
4	61 (0.61)
Type of FET cycles, n (%)	
Natural cycle	2,766 (27.76)
Induced cycle	3,905 (39.19)
Hormonal substitution cycle	3,293 (33.05)
EMT (mm)★	10.80 (9.40–12.40)
Endometrial pattern, n (%)	
Heterogeneous pattern	4,075 (40.90)
Homogeneous pattern	5,094 (51.12)
Trilaminar pattern	588 (5.90)
Missing	207 (2.08)
E_2 level on transplantation day (pg/mL)▲	174 (105–258)
P level on transplantation day (ng/mL)★	16.6 (11.3–22.5)
E_2/P on transplantation day▲	10.86 (5.73–20.27)
Storage duration (days)★	124 (76–182)
Embryos thawed (n)▲	2 (2–2)
Damaged thawed embryos (n)▲	0 (0–0)
Embryos transferred (n)▲	2 (2–2)
Cleavage stage (n)▲	2 (2–2)
Blastocyst stage (n)▲	0 (0–1)
Top quality embryos transferred (n)▲	0 (0–1)

★, values are presented as mean ± SD; ▲, values are presented as median (interquartile range). FET, frozen-thawed embryo transfer; EMT, endometrial thickness; E_2, estradiol; P, progesterone; SD, standard deviation.

Table 3 Clinical outcomes following FET cycles

Characteristics	Data
FET 1, n (%)	
Positive β-hCG	4,157/7,602 (54.68)
Preclinical losses to follow-up	120/4,157 (2.89)
Biochemical pregnancies (preclinical losses)	203/7,602 (2.67)
Ectopic pregnancy	112/7,602 (1.47)
Clinical pregnancies	3,722/7,602 (48.96)
Clinical losses to follow-up	55/3,722 (1.48)
Abortion <12 weeks of gestation	442/3,722 (11.88)
Abortion >12 weeks of gestation	151/3,722 (4.06)
Live births	3,066/7,602 (40.33)
Still births	8/7,602 (0.11)
Deliveries	
Singleton	2,211/3,074 (71.93)
Twin	854/3,074 (27.78)
Triplet	9/3,074 (0.29)
FET 2, n (%)	
Positive β-hCG	985/1,931 (51.00)
Preclinical losses to follow-up	21/985 (2.13)
Biochemical pregnancies (preclinical losses)	61/1,931 (3.16)
Ectopic pregnancy	32/1,931 (1.66)
Clinical pregnancies	871/1,931 (45.11)
Clinical losses to follow-up	13/871 (1.49)
Abortion <12 weeks of gestation	101/871 (11.60)
Abortion >12 weeks of gestation	31/871 (3.56)
Live births	724/1,931 (37.49)
Still births	2/1,931 (0.10)
Deliveries	
Singleton	540/726 (74.38)
Twin	186/726 (25.62)
Triplet	0
FET 3, n (%)	
Positive β-hCG	178/370 (48.11)
Preclinical losses to follow-up	5/178 (2.81)

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Data
Biochemical pregnancies (preclinical losses)	13/370 (3.51)
Ectopic pregnancy	8/370 (2.16)
Clinical pregnancies	152/370 (41.08)
Clinical losses to follow-up	2/152 (1.32)
Abortion <12 weeks of gestation	23/152 (15.13)
Abortion >12 weeks of gestation	3/152 (1.97)
Live births	124/370 (33.51)
Still births	0
Deliveries	
Singleton	94/124 (75.81)
Twin	30/124 (24.19)
Triplet	0
FET 4, n (%)	
Positive β-hCG	22/61 (36.07)
Preclinical losses to follow-up	0
Biochemical pregnancies (preclinical losses)	1/61 (1.64)
Ectopic pregnancy	0
Clinical pregnancies	21/61 (34.43)
Clinical losses to follow-up	2/21 (9.52)
Abortion <12 weeks of gestation	4/20 (20.00)
Abortion >12 weeks of gestation	0
Live births	15/61 (24.59)
Still births	0
Deliveries	
Singleton	12/15 (80.00)
Twin	3/15 (20.00)
Triplet	0
Total FETs, n (%)	
Positive β-hCG	5,342/9,964 (53.61)
Preclinical losses to follow-up	146/5,342 (2.73)
Biochemical pregnancies (preclinical losses)	278/9,964 (2.79)
Ectopic pregnancy	152/9,964 (1.53)
Clinical pregnancies	4,766/9,964 (47.83)
Clinical losses to follow-up	72/4,766 (1.51)
Abortion <12 weeks of gestation	570/4,766 (11.96)
Abortion >12 weeks of gestation	185/4,766 (3.88)
Live births	3,929/9,964 (39.43)
Still births	10
Deliveries	
Singleton	2,857/3,939 (72.53)
Twin	1,073/3,939 (27.24)
Triplet	9/3,939 (0.23)

All pregnancies are counted, showing the total reproductive outcome. Twins are counted as one live birth. FET, frozen-thawed embryo transfer; hCG, human chorionic gonadotropin.

and was similar to the validation set (0.68). The calibration slope as assessed by the Hosmer-Lemeshow test, showed a P value of >0.05 in both sets (0.94 and 0.16, respectively) indicating no overfitting of predictor effects.

Discussion

As there are increasing concerns about the adverse effects of controlled ovarian stimulation (COS) (30) combined with fresh embryo transfer (ET) therapies, the "freeze-all" strategy (defined as the entire cohort of fresh embryos being cryopreserved in an IVF or ICSI cycle followed by the frozen-thawed embryos transfer in later cycles with improved embryo cryopreservation techniques), has gradually attracted the attention of many reproductive centers around the world. Although the freeze-all policy seems to be an ideal alternative to fresh ET as it has some potential advantages (3,31), it remains unclear what the long-term reproductive consequences will be with regards to LBR. Previous studies on the chance of a live birth after IVF or ICSI (16,32,33), have either made predictions for a complete package of IVF cycle including all fresh and FETs, or made predictions for live birth after IVF/ICSI treatment but with single-embryo transfer (SET) after 2 days of embryo culture (33). A recent study by Chang *et al*. (34) reported the comparison of CLBRs between the "freeze-all" population (study group) and "fresh ET" population (control

Table 4 LBR within each FET cycle and CLBRs across all FET cycles for 7,602 patients undergoing 9,964 FET cycles

Cycle No.	No. of cycles	No. of live births	LBR within each cycle, % (95% CI)	CLBRs across all FET cycles, % (95% CI)	
				Optimal estimate[a]	Conservative estimate[b]
1	7,602	3,066	40.33 (39.23, 41.44)	40.33 (39.23, 41.44)	40.33 (39.23, 41.44)
2	1,931	724	37.49 (35.33, 39.70)	62.70 (61.60, 63.79)	49.86 (48.72, 50.99)
3	370	124	33.51 (28.72, 38.58)	75.20 (74.22, 76.17)	51.49 (50.36, 52.62)
4	61	15	24.59 (14.46, 37.29)	81.30 (80.41, 82.17)	51.68 (50.55, 52.81)

[a], it was based on the assumption that women who discontinued treatment would have had the same chance of a pregnancy resulting in a live birth as those who remained in treatment; [b], it was based on the assumption that none of the women who discontinued treatment would have had a live birth. LBR, live-birth rate; FET, frozen-thawed embryo transfer; CLBRs, cumulative live birth rates; CI, confidence interval.

Table 5 The effect and importance of predictors on live birth associated with freeze-all policy, with their categories, ORs with CIs, P values and adequacies

Parameter	Value	OR (95% CI)	P value	Adequacy
FET cycle number	1 (reference)	1		NA
	2	0.891 (0.741, 1.071)	0.218	
	3	0.609 (0.402, 0.923)	0.019	
	4	0.235 (0.061, 0.913)	0.036	
EMT	≤8 mm (reference)	1		0.938
	>8 mm, ≤12 mm	1.423 (1.006, 2.013)	0.046	
	>12 mm	1.777 (1.261, 2.505)	<0.001	
Age at oocyte retrieval	<31 years (reference)	1		0.082
	31–35 years	0.779 (0.672, 0.903)	<0.001	
	36–40 years	0.516 (0.411, 0.648)	<0.001	
	>40 years	0.125 (0.074, 0.210)	<0.001	
No. of oocytes collected	0–5 (reference)	1		0.027
	6–10	0.900 (0.734, 1.105)	0.314	
	11–15	0.968 (0.768, 1.220)	0.780	
	16–20	0.742 (0.564, 0.975)	0.032	
	>20	0.895 (0.651, 1.230)	0.493	
No. of previous IVF failures		0.921 (0.876, 0.967)	<0.001	0.025
No. of embryos frozen	Blastocyst stage	1.078 (1.020, 1.140)	0.008	0.022
	Cleavage stage	1.062 (1.020, 1.104)	0.003	0.017
Duration of infertility		0.968 (0.944, 0.994)	0.015	0.014
No. of blastocyst transferred		1.446 (1.229, 1.701)	<0.001	0.006

ORs, odds ratios; CIs, confidence intervals; FET, frozen-thawed embryo transfer; EMT, endometrial thickness; IVF, in vitro fertilization.

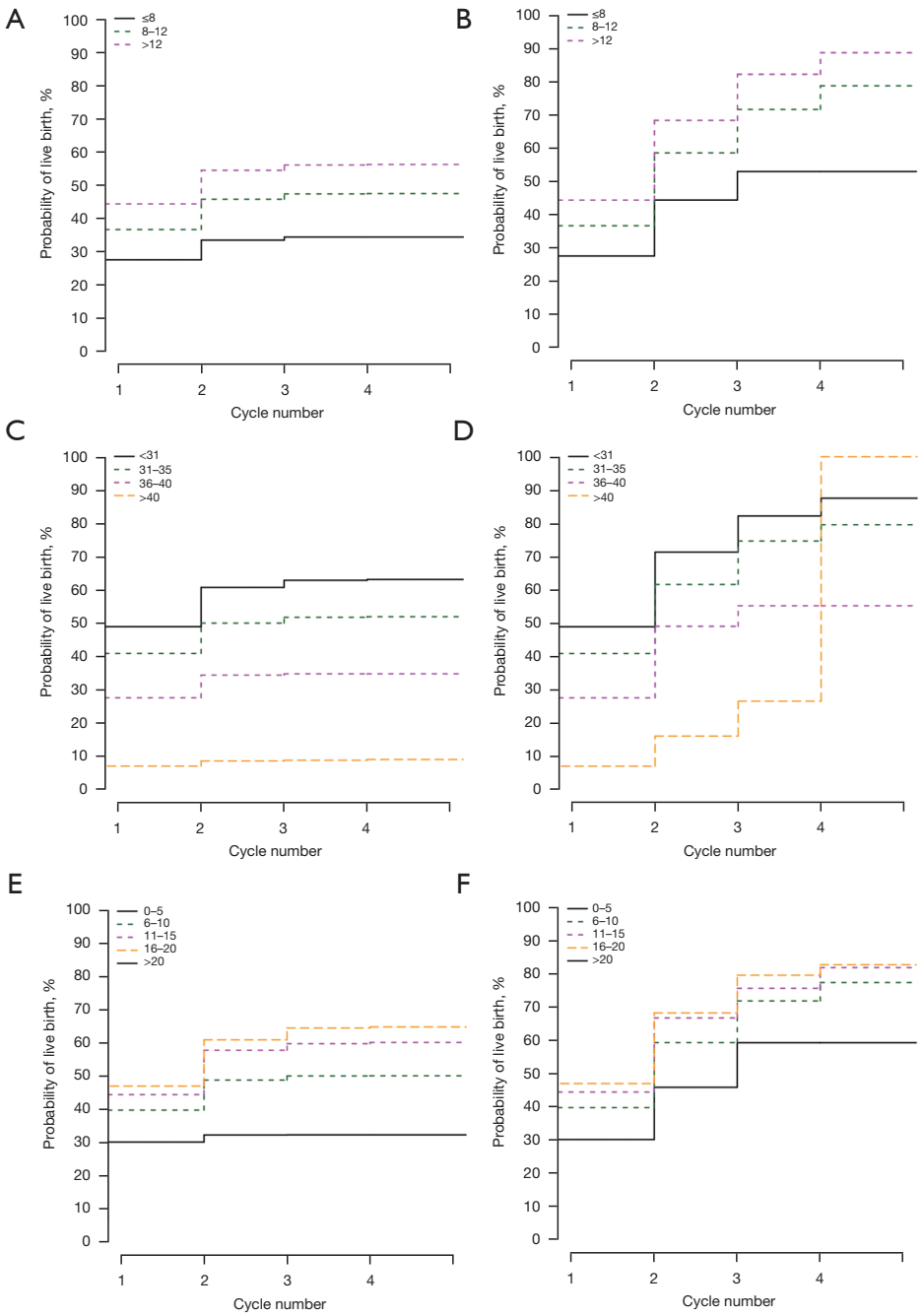

Figure 2 CLBRs stratified according to the categorical variables of positive significance in multivariate model. (A,B) Show the conservative and optimistic CLBRs stratified according to EMT, respectively. (C,D) Show the conservative and optimistic CLBRs stratified according to female age at oocyte retrieval, respectively. (E,F) Show the conservative and optimistic CLBRs stratified according to the number of oocytes collected, respectively. The conservative CLBRs were based on the assumption that none of the women who discontinued treatment would have had a live birth. These two curves show the best- and worst-case estimates of the CLBRs in the study group. The optimal CLBRs were based on the assumption that women who discontinued treatment would have had the same chance of a pregnancy resulting in a live birth as those who remained in treatment. These CLBRs reflect the worst- and best-case estimates, respectively. CLBRs, cumulative live birth rates; EMT, endometrial thickness.

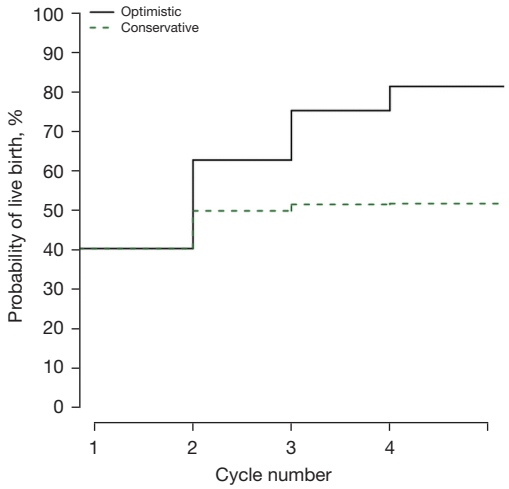

Figure 3 Kaplan-Meier curves for CLBRs among all women in the study. The optimal CLBRs were based on the assumption that women who discontinued treatment would have had the same chance of a pregnancy resulting in a live birth as those who remained in treatment. The conservative CLBRs were based on the assumption that none of the women who discontinued treatment would have had a live birth. These two curves show the best- and worst-case estimates of the CLBRs in the study group. CLBRs, cumulative live birth rates.

group) during the period from January 2012 to June 2014. The authors found that the CLBRs in two groups were significantly different (64.3% in study group *vs.* 45.8% in control group). Furthermore, the CLBRs in the study group were significantly higher (58.3% *vs.* 40.9%) when the number of eggs is between 4 and 15. Unsurprisingly, they came to the conclusion that the "freeze-all policy" improved the assisted reproductive technology (ART) outcome for normal responders. Our clinic found that the chance of having a child after the first complete IVF cycle was 50.74% with the freeze-all strategy (33). However, Chang *et al.* (34) neither constructed a predictive model to evaluate the risk factors which may affect the LBR with the "freeze-all" policy or explained the optimistic and pessimistic CLBRs, between which the realistic cumulative rates may exist.

The goal of this study was to elucidate the predictors of LBR with "freeze-all" policy over an entire IVF/ICSI treatment course and calculate meaningful CLBRs to answer a couple's most concerned question—what is the chance that the "freeze-all" policy will result in a baby? As demonstrated in previous studies where the CLBR does not vary substantively with the indication for ART treatment (35,36), we did not exclude women on the basis of age, BMI, ovarian-reserve function, or other prognostic factors except uterine abnormality. Thus, the inclusion of all subjects who presented for their first ovarian stimulation treatment and underwent "freeze-all" policy in our center increases the generalizability of our model outcomes. In total, 9,964 IVF/ICSI-FET cycles were performed in 7,602 couples and resulted in 3,929 live births. The CLBR in the study population varied from 51.68% (95% CI: 50.55–52.81%) to 81.30% (95% CI: 80.41–82.17%) after four consecutive cycles of FET, and those values corresponded to the optimistic and conservative estimate, respectively. As expected, among the couples embarking on IVF or ICSI we found that the EMT on the day of embryo transferred was far the best predictor of live birth when the treatment procedure was carried out to the frozen-thawed cycles. Additionally, female age at oocytes retrieval, number of eggs collected, previous IVF failures, duration of infertility and the cryopreservation of embryos were the next best predictors.

A number of current reviews and meta-analyses have summarized the available knowledge concerning the association of EMT with the chance of achieving a pregnancy or live birth after IVF, but with conflicting results. Most of the previous studies found an association between EMT and pregnancy or live birth (37-40). Especially for some retrospective studies, it was found that EMT significantly affected the LBRs either in fresh autologous IVF cycle or FET cycle (39,40). In addition, one study reporting on EMT in natural FET cycles showed that pregnancy rates were significantly lower in patients with suboptimal endometrial development, suggesting an independent predictive role of EMT (41). However, a significant correlation between EMT and the chance to conceive or have a live birth has failed to be established by other authors (42-44). They concluded that the EMT is a poor predictor of IVF success and has a limited capacity for the occurrence of pregnancy while acknowledging that below a cut-off of 7 millimeters (mm), a lower chance of pregnancy can be observed in univariate analyses. In our study, EMT was assigned to the following categories: < or =8, (8,12) and >12 mm. These intervals were chosen according to previous studies (45,46) to facilitate the application of the results towards everyday clinical practice. We found that EMT < or =8 mm was associated with an obvious decrease in outcomes and it was a significant predictor for LBRs, results that are more in line with the conclusion of at least one previous study with a higher incidence of pregnancy rates as EMT increased from

the category of <8 to 8–12 and >12 mm as well (46). In addition to EMT, we also analyzed the effects of different endometrial preparation and endometrial pattern on LBRs, but no significant correlation was found. This outcome is consistent with the results of other studies (45). On the basis of these results, one could conclude that pregnancy prospects may improve with a thicker EMT, yet it is unclear why thin EMT is associated with poorer IVF outcomes.

There is a natural trend of age-related decline in fecundability, not only in the population surveyed in previous studies (47,48), but also in our cohort. Not surprisingly, we found that maternal age which is the most established predictor included in every prediction model for the success of IVF/ICSI (49,50) was negatively correlated with live birth. Women who were 40 years of age or younger and treated with up to 4 cycles of FET could achieve CLBRs that were similar to or even higher than published cumulative pregnancy proportion achieved naturally at 6 menstrual cycles (49). However, there's hardly any difference in the LBR both in our subjects and the above population once women are over 40 years of age. This suggests that IVF/ICSI-FET overcomes infertility in younger women but cannot completely reverse the age-dependent decrease in fertility for women older than 40 years. Thus, it is advisable to consider female age in individualized counselling before initiating an IVF journey.

A longstanding concern involves the importance of the total number of oocytes retrieved in models that predict pregnancy or live birth (51,52). Similar to previous studies (53), we found that LBR increases with increasing egg number in IVF cycles. However, LBR was significantly improved only when 16–20 oocytes were retrieved. Moreover, when >15 oocytes were retrieved, LBR almost plateaus and this is in line with the results of other studies (54,55). Due to the "freeze-all" policy, there was no late-onset OHSS occurrence. And there were only seven early-onset moderate OHSS and no severe OHSS in this dataset. Given the apparent relationship between high retrieved oocyte number and plateaued increase in LBR, it seems reasonable that optimal number of oocytes should be the pursuit of less aggressive stimulation protocols.

As well-known predictors for live birth, the number of previous IVF failures and duration of infertility were examined in the present study. Our findings are consistent with previous work showing that women who have less experience of IVF failures (56) and shorter duration of infertility have a better chance of subsequent live birth (57). It is speculated that those couples with fewer unsuccessful IVF journeys and a shorter duration of infertility are likely affected by fewer or less severe fertility factors and therefore may be expected to have superior outcomes after IVF. There is no doubt that the more eggs are obtained, the greater the probability of getting the available embryos and the higher the CLBRs is. And this has been confirmed in the present study that LBR increases when more embryo cryopreservation is available. To a certain extent, our finding is similar to other research (58), in that the number of blastocysts transferred correlated positively with the odds of live birth. Despite the number of blastocyst transfers having lower impact in the variation of the whole regression, it remained significant. This could be due to the much larger sample size in our data set.

It is worth noting that no obvious relationship between embryo quality and LBR was found and this is not consistent with other studies (33,59). Part of this may be related to the embryo selection strategy used in our center. We routinely freeze top-quality embryos, and the remaining embryos are cultured for blastocysts. Therefore, patients who are able to enter the FET cycle almost always have good quality embryos for transplantation; only those who have great difficulties in getting embryos will freeze and transfer the inferior embryos. This weakens the role of embryo quality in predicting live birth to a certain extent. On the other hand, our study is not based on elective SET which may contribute a more accurate inference to the relationship between embryo quality and live birth. Other parameters such as woman's age at FET, duration and total dosage of Gn, OSI and cleavage number were all excluded from analysis due to their collinearity with observed variables—e.g., the woman's age at oocyte retrieval and number of eggs collected that were always included and could not be removed because these are known predictors of pregnancy outcomes after IVF.

An advantage of our study is that the number of patients is sufficient for model construction and that the model is developed from a large number of variables recorded before and during the IVF treatment within a single clinic. Previous prediction models for LBR after IVF treatment have presented C-index of 0.68–0.73 and P value in the Hosmer-Lemeshow test of 0.88–0.998 (16,33). Referring to these data, the discriminative capacity of the present model was modest, while the test for calibration was excellent in the training set but not in the validation set. This indicated that there is a good parallelism between the predicted chance of success and the observed success rate in subjects. Although the conventional relationship between EMT

and the chance of achieving a live birth after IVF is not consistent across studies, the role of EMT as an expected variable has been strengthened by our predictive model when the "freeze-all" policy is carried out. The results from our model are relevant both for individual couples and their clinicians. Couples who would ideally like to know their overall chance of having a baby over a complete IVF procedure when they are fit for the "freeze-all" policy might be separately counselled by using this model. As an example, the probability of a live birth in the first FET cycle for a woman older than 40 years is 6.83%, after two cycles of FET the conservative and optimal CLBRs increase to 8.59% and 26.4%, respectively. Irrespective of age, the probability of a live birth in the first FET cycle is 27.4% when one's EMT reached 8 mm, after a complete package of FET cycles the conservative and optimal CLBRs increase to 34.25% and 52.83%, respectively. Therefore, clinicians would use these predictions to support their clinical knowledge when communication with couples before the "freeze-all" policy is started.

Some limitations of this study need to be addressed. Although we successfully established a prediction model, all variables introduced in both univariate and multivariate analyses were retrospectively collected in study. Therefore, there probably is an inevitable risk of bias. It must also be mentioned that data collection in a single clinic while avoiding the heterogeneity of a cohort of managed patients on the one hand, can be a double-edged sword for the applicability to other IVF centers. Ideally, a prediction model for IVF should include potentially important predictors, such as: smoking, alcohol intake and complications like occurrence of COS, which were not available in our dataset and we were unable to adjust for. As a consequence, it may be inappropriate to make conclusions about the influence of potential confounders for the LBR. Moreover, stratification (such as female age and EMT individually stratified instead of multifactor stratification) in analyses was only performed for univariate analyses as the available data wasn't sufficient. It is worth looking forward to reveal the possible effects of the predictors on LBR under the interaction of predictors. These limitations of the present study must guide future studies.

Conclusions

In conclusion, this study has developed a novel model that can predict the cumulative chances of a live birth for an individual couple over an entire course of IVF cycle undergoing the "freeze-all" strategy. We confirmed female age at oocytes retrieval, previous IVF failures, duration of infertility, number of eggs collected, number of cleavage- and blastocyst-stage embryos frozen, EMT and number of blastocyst transferred as independent predictors. Not surprisingly, the chance of live birth increases with optimal endometrial development, increasing eggs, increasing cryopreserved embryos and increasing number of blastocyst transferred, whereas decreases with increasing age, increasing number of previous IVF failures and increasing duration of infertility. It is suggested that the present prediction model will help to facilitate couples' counselling before and during IVF with the "freeze-all" policy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-21-589/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-21-589/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-21-589/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of

Shanghai First Maternity and Infant Hospital of Tongji University School of Medicine (No. KS21282) and individual informed consent for this retrospective study was waived.

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Supplementary

Table S1 LBR within each FET cycle and CLBRs across all FET cycles, stratified by positive predictors in multivariable discrete time logistic regression model

Cycle no.	No. of cycles	No. of live births	LBR within each cycle, % (95% CI)	CLBRs across all FET cycles, % (95% CI)	
				Optimal estimate[a]	Conservative estimate[b]
EMT ≤8 mm					
1	219	60	27.40 (21.60, 33.81)	27.40 (21.6, 33.81)	27.4 (21.6, 33.81)
2	56	13	23.21 (12.98, 36.42)	44.25 (37.56, 51.1)	33.33 (27.13, 40)
3	13	2	15.38 (1.92, 45.45)	52.83 (45.99, 59.59)	34.25 (27.99, 40.94)
4	2	0	0 (0, 84.19)	52.83 (45.99, 59.59)	34.25 (27.99, 40.94)
EMT >8 mm, ≤12 mm					
1	1,753	640	36.51 (34.25, 38.81)	36.51 (34.25, 38.81)	36.51 (34.25, 38.81)
2	463	160	34.56 (30.23, 39.08)	58.45 (56.1, 60.77)	45.64 (43.28, 48)
3	89	28	31.46 (22.03, 42.17)	71.52 (69.35, 73.63)	47.23 (44.87, 49.6)
4	8	2	25 (3.19, 65.09)	78.64 (76.65, 80.54)	47.35 (44.99, 49.72)
EMT >12 mm					
1	2,383	1,054	44.23 (42.22, 46.25)	44.23 (42.22, 46.25)	44.23 (42.22, 46.25)
2	560	241	43.04 (38.89, 47.25)	68.23 (66.32, 70.1)	54.34 (52.32, 56.36)
3	87	38	43.68 (33.06, 54.74)	82.11 (80.51, 83.63)	55.94 (53.92, 57.94)
4	11	4	36.36 (10.93, 69.21)	88.61 (87.27, 89.86)	56.11 (54.09, 58.11)
Women aged ≤30 years					
1	3,287	1,604	48.8 (47.08, 50.52)	48.8 (47.08, 50.52)	48.8 (47.08, 50.52)
2	886	389	43.91 (40.61, 47.25)	71.28 (69.7, 72.82)	60.63 (58.94, 62.31)
3	185	70	37.84 (30.83, 45.25)	82.15 (80.79, 83.44)	62.76 (61.08, 64.42)
4	30	9	30 (14.73, 49.4)	87.5 (86.32, 88.61)	63.04 (61.36, 64.69)
Women aged 31–35 years					
1	2,795	1,139	40.75 (38.92, 42.6)	40.75 (38.92, 42.6)	40.75 (38.92, 42.6)
2	727	255	35.08 (31.6, 38.67)	61.53 (59.7, 63.34)	49.87 (48, 51.75)
3	144	49	34.03 (26.35, 42.38)	74.62 (72.97, 76.23)	51.63 (49.76, 53.5)
4	26	5	19.23 (6.55, 39.35)	79.5 (77.96, 80.99)	51.81 (49.94, 53.67)
Women aged 36–40 years					
1	1,066	292	27.39 (24.73, 30.18)	27.39 (24.73, 30.18)	27.39 (24.73, 30.18)
2	246	73	29.67 (24.04, 35.81)	48.94 (45.9, 51.99)	34.24 (31.39, 37.18)
3	33	4	12.12 (3.4, 28.2)	55.13 (52.08, 58.14)	34.62 (31.76, 37.56)
4	4	0	0 (0, 60.24)	55.13 (52.08, 58.14)	34.62 (31.76, 37.56)
Women aged >40 years					
1	454	31	6.83 (4.69, 9.55)	6.83 (4.69, 9.55)	6.83 (4.69, 9.55)
2	72	7	9.72 (4, 19.01)	15.89 (12.65, 19.58)	8.37 (5.99, 11.31)
3	8	1	12.5 (0.32, 52.65)	26.4 (22.4, 30.71)	8.59 (6.18, 11.56)
4	1	1	100 (2.5, 100)	100 (99.19, 100)	8.81 (6.37, 11.8)
No. of oocytes collected 0–5					
1	2,006	613	30.56 (28.55, 32.63)	30.56 (28.55, 32.63)	30.56 (28.55, 32.63)
2	190	43	22.63 (16.89, 29.25)	46.27 (44.07, 48.49)	32.7 (30.65, 34.8)
3	4	1	25 (0.63, 80.59)	59.71 (57.52, 61.86)	32.75 (30.7, 34.85)
4[f]	0	0	–	–	–
No. of oocytes collected 6–10					
1	2,320	932	40.17 (38.17, 42.2)	40.17 (38.17, 42.2)	40.17 (38.17, 42.2)
2	642	210	32.71 (29.09, 36.49)	59.74 (57.71, 61.75)	49.22 (47.17, 51.28)
3	93	29	31.18 (21.98, 41.63)	72.3 (70.43, 74.11)	50.47 (48.42, 52.53)
4	5	1	20 (0.51, 71.64)	77.84 (76.09, 79.51)	50.52 (48.46, 52.57)
No. of oocytes collected 11–15					
1	1,572	705	44.85 (42.37, 47.35)	44.85 (42.37, 47.35)	44.85 (42.37, 47.35)
2	519	210	40.46 (36.21, 44.83)	67.16 (64.78, 69.48)	58.21 (55.72, 60.66)
3	114	31	27.19 (19.28, 36.33)	76.09 (73.9, 78.18)	60.18 (57.71, 62.61)
4	23	6	26.09 (10.23, 48.41)	82.33 (80.35, 84.18)	60.56 (58.09, 62.99)

Table S1 (*continued*)

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Table S1 (*continued*)

Cycle no.	No. of cycles	No. of live births	LBR within each cycle, % (95% CI)	CLBRs across all FET cycles, % (95% CI)	
				Optimal estimate[a]	Conservative estimate[b]
No. of oocytes collected 16–20					
1	926	439	47.41 (44.15, 50.68)	47.41 (44.15, 50.68)	47.41 (44.15, 50.68)
2	319	129	40.44 (35.01, 46.05)	68.68 (65.58, 71.65)	61.34 (58.12, 64.49)
3	91	33	36.26 (26.44, 47.01)	80.04 (77.31, 82.56)	64.9 (61.73, 67.98)
4	19	3	15.79 (3.38, 39.58)	83.19 (80.62, 85.54)	65.23 (62.06, 68.3)
No. of oocytes collected >20					
1	778	377	48.46 (44.89, 52.03)	48.46 (44.89, 52.03)	48.46 (44.89, 52.03)
2	261	132	50.57 (44.34, 56.8)	74.53 (71.31, 77.55)	65.42 (61.96, 68.77)
3	68	30	44.12 (32.08, 56.68)	85.76 (83.11, 88.14)	69.28 (65.91, 72.51)
4	14	5	35.71 (12.76, 64.86)	90.85 (88.6, 92.78)	69.92 (66.56, 73.13)
No. of previous IVF failures 0–1					
1	5,118	2,363	46.17 (44.8, 47.55)	46.17 (44.8, 47.55)	46.17 (44.8, 47.55)
2	999	365	36.54 (33.54, 39.61)	65.84 (64.52, 67.14)	53.3 (51.92, 54.68)
3	166	60	36.14 (28.84, 43.95)	78.19 (77.03, 79.31)	54.47 (53.1, 55.85)
4	24	8	33.33 (15.63, 55.32)	85.46 (84.46, 86.41)	54.63 (53.25, 56)
No. of previous IVF failures >1					
1	2,484	703	28.3 (26.54, 30.12)	28.3 (26.54, 30.12)	28.3 (26.54, 30.12)
2	932	359	38.52 (35.38, 41.73)	55.92 (53.94, 57.88)	42.75 (40.8, 44.73)
3	204	64	31.37 (25.07, 38.22)	69.75 (67.9, 71.55)	45.33 (43.36, 47.31)
4	37	7	18.92 (7.96, 35.16)	75.47 (73.73, 77.15)	45.61 (43.64, 47.59)
No. of cleavage-stage embryos frozen <4					
1	4,112	1,464	35.6 (34.14, 37.09)	35.6 (34.14, 37.09)	35.6 (34.14, 37.09)
2	564	186	32.98 (29.11, 37.03)	56.84 (55.31, 58.36)	40.13 (38.62, 41.64)
3	28	10	35.71 (18.64, 55.93)	72.25 (70.86, 73.62)	40.37 (38.87, 41.89)
4	2	0	0 (0, 84.19)	72.25 (70.86, 73.62)	40.37 (38.87, 41.89)
No. of cleavage-stage embryos frozen ≥4					
1	3,490	1,602	45.9 (44.24, 47.57)	45.9 (44.24, 47.57)	45.9 (44.24, 47.57)
2	1,367	538	39.36 (36.76, 42)	67.19 (65.61, 68.75)	61.32 (59.68, 62.94)
3	342	114	33.33 (28.35, 38.6)	78.13 (76.72, 79.49)	64.58 (62.97, 66.17)
4	59	15	25.42 (14.98, 38.44)	83.69 (82.42, 84.9)	65.01 (63.41, 66.6)
No. of blastocyst-stage embryos frozen 0–1					
1	4,388	1,569	35.76 (34.34, 37.2)	35.76 (34.34, 37.2)	35.76 (34.34, 37.2)
2	867	283	32.64 (29.53, 35.88)	56.73 (55.25, 58.2)	42.21 (40.74, 43.68)
3	118	29	24.58 (17.12, 33.35)	67.36 (65.95, 68.75)	42.87 (41.4, 44.35)
4	19	5	26.32 (9.15, 51.2)	75.95 (74.66, 77.21)	42.98 (41.51, 44.46)
No. of blastocyst-stage embryos frozen >1					
1	3,214	1,497	46.58 (44.84, 48.32)	46.58 (44.84, 48.32)	46.58 (44.84, 48.32)
2	1,064	441	41.45 (38.47, 44.47)	68.72 (67.08, 70.32)	60.3 (58.58, 62)
3	252	95	37.7 (31.69, 44)	80.51 (79.1, 81.87)	63.25 (61.56, 64.92)
4	42	10	23.81 (12.05, 39.45)	85.15 (83.88, 86.36)	63.57 (61.87, 65.23)
Duration of infertility ≤4.5 years					
1	5,503	2,341	42.54 (41.23, 43.86)	42.54 (41.23, 43.86)	42.54 (41.23, 43.86)
2	1,444	569	39.4 (36.87, 41.98)	65.18 (63.91, 66.44)	52.88 (51.55, 54.21)
3	274	92	33.58 (28.01, 39.51)	76.87 (75.74, 77.98)	54.55 (53.23, 55.87)
4	44	12	27.27 (14.96, 42.79)	83.18 (82.17, 84.16)	54.77 (53.44, 56.09)
Duration of infertility >4.5 years					
1	2,099	725	34.54 (32.51, 36.62)	34.54 (32.51, 36.62)	34.54 (32.51, 36.62)
2	487	155	31.83 (27.71, 36.17)	55.37 (53.22, 57.52)	41.92 (39.8, 44.07)
3	96	32	33.33 (24.04, 43.69)	70.25 (68.24, 72.2)	43.45 (41.32, 45.6)
4	17	3	17.65 (3.8, 43.43)	75.5 (73.6, 77.33)	43.59 (41.46, 45.75)

Table S1 (*continued*)

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Table S1 (*continued*)

Cycle no.	No. of cycles	No. of live births	LBR within each cycle, % (95% CI)	CLBRs across all FET cycles, % (95% CI)	
				Optimal estimate[a]	Conservative estimate[b]
No. of blastocyst transferred 0–1					
1	7,133	2,941	41.23 (40.09, 42.38)	41.23 (40.09, 42.38)	41.23 (40.09, 42.38)
2	1,666	623	37.39 (35.07, 39.77)	63.21 (62.08, 64.33)	49.96 (48.8, 51.13)
3	276	81	29.35 (24.04, 35.1)	74.01 (72.97, 75.02)	51.1 (49.93, 52.27)
4	42	11	26.19 (13.86, 42.04)	80.81 (79.88, 81.72)	51.25 (50.09, 52.42)
No. of blastocyst transferred >1					
1	469	125	26.65 (22.7, 30.9)	26.65 (22.7, 30.9)	26.65 (22.7, 30.9)
2	265	101	38.11 (32.24, 44.26)	54.61 (49.98, 59.18)	48.19 (43.58, 52.82)
3	94	43	45.74 (35.42, 56.34)	75.37 (71.21, 79.21)	57.36 (52.74, 61.88)
4	19	4	21.05 (6.05, 45.57)	80.56 (76.68, 84.04)	58.21 (53.6, 62.72)

[a], it was based on the assumption that women who discontinued treatment would have had the same chance of a pregnancy resulting in a live birth as those who remained in treatment; [b], it was based on the assumption that none of the women who discontinued treatment would have had a live birth; [f], there were no subject and no live births for this cycle, hence CIs could not be calculated. LBR, live-birth rate; FET, frozen-thawed embryo transfer; CLBRs, cumulative live birth rates; CI, confidence interval; EMT, endometrial thickness; IVF, in vitro fertilization.

Table S2 The variables recorded before and during IVF/ICSI-FET cycle, with their categories, ORs with CIs and P values for their respective associations with LBR

Parameter	OR	95% CI	P value
Female age (at OPU)			
<31 years (reference)	–	–	–
31–35 years	0.733	(0.659, 0.814)	<0.001
36–40 years	0.427	(0.364, 0.501)	<0.001
>40 years	0.080	(0.054, 0.119)	<0.001
BMI	0.968	(0.952, 0.984)	<0.001
Duration of infertility	0.935	(0.919, 0.951)	<0.001
Infertility etiology			
Tubal	0.915	(0.856, 0.978)	0.009
Anovulatory	1.083	(0.886, 1.324)	0.435
Endometriosis	1.243	(0.978, 1.58)	0.076
Male factor	1.120	(1.013, 1.239)	0.027
Unexplained	0.845	(0.577, 1.239)	0.389
Other causes	0.879	(0.684, 1.13)	0.315
>1 type	1.008	(0.933, 1.089)	0.847
No. of previous IVF failures	0.841	(0.812, 0.87)	<0.001
Total dose of gonadotrophin (at OPU cycle)	1.000	(1.000, 1.000)	0.012
Total duration of stimulation (at OPU cycle)	1.027	(1.005, 1.050)	0.016
OSI (OSI at OPU cycle)	2.169	(1.868, 2.520)	<0.001
No. of oocytes collected			
0–5 (reference)	–	–	–
6–10	1.550	(1.348, 1.783)	<0.001
11–15	1.895	(1.631, 2.201)	<0.001
16–20	1.930	(1.627, 2.289)	<0.001
>20	2.359	(1.974, 2.820)	<0.001
Method of fertilization (IVF reference)	0.908	(0.817, 1.008)	0.071
No. of embryos created	1.050	(1.040, 1.060)	<0.001
No. of embryos frozen			
Cleavage stage	1.103	(1.079, 1.128)	<0.001
Blastocyst stage	1.187	(1.146, 1.229)	<0.001

Table S2 (*continued*)

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Table S2 (*continued*)

Parameter	OR	95% CI	P value
Type of FET cycles			
Natural cycle (reference)	–	–	–
Induced cycle	1.137	(1.010, 1.280)	0.033
Hormonal substitution cycle	0.858	(0.758, 0.972)	0.016
EMT			
≤8 mm (reference)	–	–	–
>8 mm, ≤12 mm	1.609	(1.152, 2.246)	0.005
>12 mm	2.145	(1.543, 2.983)	<0.001
Endometrial pattern			
Heterogeneous pattern (reference)	–	–	–
Homogeneous pattern	1.144	(1.034, 1.266)	0.009
Trilaminar pattern	1.640	(1.338, 2.010)	<0.001
E_2 level on transplantation day	1.000	(1.000, 1.000)	0.038
P level on transplantation day	0.999	(0.992, 1.007)	0.838
E_2/P on transplantation day	0.999	(0.997, 1.001)	0.145
Storage duration	0.998	(0.997, 0.999)	<0.001
Embryos thawed	1.526	(1.347, 1.729)	<0.001
Damaged thawed embryos	0.803	(0.581, 1.109)	0.183
Female age at ET	0.909	(0.900, 0.918)	<0.001
Embryos transferred			
Cleavage stage	1.019	(0.944, 1.099)	0.636
Blastocyst stage	1.306	(1.182, 1.443)	<0.001
Top quality embryos transferred	1.103	(0.980, 1.241)	0.104
good quality embryos transferred	1.030	(0.963, 1.101)	0.394
Moderate quality embryos transferred	1.207	(1.092, 1.334)	<0.001
Poor quality embryos transferred	0.889	(0.708, 1.115)	0.308

OSI = log (number of oocytes collected ×1,000/total dose of gonadotropin). OSI is a composite variable to measure ovarian response. IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; FET, frozen-thawed embryo transfer; ORs, odds ratios; CIs, confidence intervals; OPU, ovum pick-up; BMI, body mass index; OSI, ovarian sensitivity index; EMT, endometrial thickness; E_2, estradiol; P, progesterone; ET, embryo transfer.

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