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ORIGINAL ARTICLE

Overweight and high serum total cholesterol were risk factors for the outcome of IVF/ICSI cycles in PCOS patients and a PCOS-specific predictive model of live birth rate was established

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Abstract

Purpose The clinical outcome after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) is diverse in infertility patients with polycystic ovary syndrome (PCOS). The aim of this study was to develop a nomogram based on an association of patients' characteristics to predict the live birth rate in PCOS patients.

Methods All women in a public university hospital who attempted to conceive by IVF/ICSI for PCOS infertility from January 2014 to October 2018 were included. The nomogram was built from a training cohort of 178 consecutive patients and tested on an independent validation cohort of 81 patients. PCOS was confirmed in all participants.

Results Three variates significantly associated with live birth rate of PCOS patients were BMI, total serum cholesterol (TC) and basal FSH. This predictive model built on the basis of BMI, TC, basal FSH, type of embryo transferred and age showed good calibration and discriminatory abilities, with an area under the curve (AUC) of 0.708 (95% CI 0.632–0.785) for the training cohort. The nomogram showed satisfactory goodness-of-fit and discrimination abilities in the independent validation cohort, with an AUC of 0.686 (95% CI 0.556–0.815).

Conclusion Our simple evidence-based nomogram presents graphically risk factors and prognostic models for IVF/ICSI outcomes in patients with PCOS, which can offer useful guidance to clinicians and patients for individual adjuvant therapy.

Keywords Polycystic ovary syndrome · BMI · Serum total cholesterol · Infertility · Predictive model

Abbreviations

IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection
PCOS	Polycystic ovary syndrome
ART	Assisted reproduction technology
AUC	Area under the curve
CI	Confidence interval
OR	Odds ratio
TC	Total cholesterol
FSH	Follicle-stimulating hormone
BMI	Body mass index
ERB	Ethical Review Board
GnRH	Gonadotrophin-releasing hormone
LH	Luteinizing hormone
hCG	Human chorionic gonadotropin
OHSS	Ovarian hyperstimulation syndrome
MLR	Multivariable logistic regression
RMS	Regression Modeling Strategies
TG	Triglycerides
LDL-C	Low-density lipoprotein cholesterol
VLDL-C	Very low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
E_2	Estrogen
T	Testosterone
AMH	Anti-Mullerian hormone
HDL	High-density lipoprotein
COH	Controlled ovarian hyperstimulation

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Introduction

PCOS is the most common endocrine disorder in women of reproductive age, with a prevalence range of 5–15% [1]. It is a heterogeneous endocrine disorder and associated with both reproductive (hyperandrogenism, oligo/amenorrhea, infertility, increased pregnancy complications) and metabolic abnormalities (dyslipidemia, metabolic syndrome and coronary heart disease) [2].

Assisted reproduction technology (ART), including IVF and ICSI, is increasingly being used for managing PCOS-related infertility [3]. ART results, however, vary according to reports, with some showing identical outcome as in PCOS-free counterparts and others describing lower pregnancy rates [4, 5]. Several studies showed that obese patients with PCOS have more impaired ovulation and lower live birth rates than normal-weight patients with this syndrome [6, 7]. In addition, results from a retrospective trial on PCOS have provided evidence that dyslipidemia has a negative impact on IVF/ICSI clinical outcomes [8]. Prediction of live birth based on a woman's individual characteristics not only provides an accurate picture of the risks to inform decision-making, but also promotes effective communication between clinicians and patients. Furthermore, awareness of one's risk status may lower any anxiety arising from the unpredictable pregnancy outcome, and promote adherence to medication through risk-informed counseling.

Research in this field has focused on the prediction of clinical outcome in ART. Several prognostic models using patient and/or treatment characteristics have been proposed for the prediction of the probability of an ongoing pregnancy or a live birth after IVF/ICSI cycles [9–12]; few of them are applicable for patients with PCOS and cannot evaluate the chances of live birth for individual patients as well. The goal of this study was, therefore, to identify prognostic factors for PCOS patients and develop a nomogram to predict the live birth rate of PCOS before IVF/ICSI procedure.

Materials and methods

Characteristics of study patients

From January 2014 to December 2018, 259 women diagnosed with PCOS by the Rotterdam criteria [13, 14] who had undergone IVF/ICSI treatment at the Reproductive Medicine Center of The Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China, were retrospectively identified. All of them had been infertile for at least 1 year. Secondary factors of ovulation dysfunction and hyperandrogenism were ruled out prior to the diagnosis of PCOS, such as adrenal 21 hydroxylase deficiency, congenital adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, adrenal tumor or ovarian interstitial tumor. Patients were included if they had received their first fresh or frozen IVF/ICSI cycles with autologous oocytes. ICSI was performed only if indicated by semen parameters. All of the patients had received lipid profile examination and basal sex hormone test. The treatment cycles were excluded if donor oocytes or in vitro maturation was utilized. Female subjects with medical conditions of type 1 or type 2 diabetes mellitus, endometriosis, uterine fibroids and reproductive malformation were excluded. Couples who received a preimplantation genetic screening or underwent preimplantation genetic diagnosis were excluded. To develop the prognostic nomogram and validate it, the PCOS patients who received IVF/ICSI treatment from January 2014 to December 2017 were included in a derivation set ($n = 178$) and from January 2018 to December 2018 were absorbed into a validation ($n = 81$) set. Patients with missing values on any of the analyzed predictors were excluded. Different descriptions are used in Table 1 based on the types of statistics. Specifically, statistics such as age, BMI, and AMH which had a Gaussian distribution were presented as mean ± SD, while data like type of embryo transferred and live birth, which were categorical variables, were described as absolute frequencies. This study was approved by the Ethical Review Board (ERB) of Sixth Affiliated Hospital of Sun Yat-sen University. The requirement of informed consent was waived by the ERB based on the retrospective nature.

IVF/ICSI treatment procedure

Patients were stimulated using a long GnRH agonist protocol, antagonist protocol or short agonist protocol. We regularly monitored follicle growth by transvaginal ultrasound and the serum estradiol (E_2), progesterone and LH levels during the cycle. When at least one follicle had a mean diameter of more than 18 mm, human chorionic gonadotropin (hCG) was administrated, and oocyte aspiration was performed 36 h later. Fresh embryo transfers were performed on Day 3 or Day 5, and subsequent frozen–thawed transfer was performed through a natural cycle with or without hCG or through an artificial cycle using estradiol. The number of embryos transferred varied from one to two based on the recommendation of the Health Ministry of China and the requests of patients.

Indications for the freeze-all policy included moderate–severe ovarian hyperstimulation syndrome (OHSS), a high risk of developing moderate–severe OHSS, inadequate endometrial thickness and individual preference. Risk factors

Table 1 Details of women's characteristics in the training cohort ($N=178$) and validation cohort ($N=81$) of the live birth prediction model

Characteristics[a]	Derivation set ($n=178$)	Validation set ($n=81$)	P value
Live birth	79 (44.1)	42 (51.9)	
Age, years	29.93 ± 3.55	30.43 ± 3.55	0.295
BMI, kg/m^2	24.05 ± 3.88	24.54 ± 3.93	0.354
Duration of infertility, months	56.43 ± 34.03	57.96 ± 31.27	0.730
FSH, IU/L	5.97 ± 1.20	5.90 ± 1.34	0.699
E_2, pg/mL	41.26 ± 21.41	42.33 ± 23.53	0.727
T, ng/mL	0.40 ± 0.17	0.38 ± 0.24	0.573
AMH, ng/mL	9.66 ± 5.08	8.98 ± 3.93	0.292
TC, mmol/L	5.30 ± 0.87	5.30 ± 1.04	0.965
TG, mmol/L	1.42 ± 0.96	1.50 ± 1.26	0.621
HDL, mmol/L	1.51 ± 0.33	1.43 ± 0.33	0.060
Antral follicle counts, n	29.63 ± 6.58	28.52 ± 8.74	0.259
No. of retrieved oocytes	15.10 ± 8.26	16.35 ± 8.78	0.269
No. of embryo transferred	1.52 ± 0.50	1.57 ± 0.50	0.447
COH protocols			
Long agonist protocol	21 (11.73)	11 (13.6)	0.835
Antagonist protocol	143 (79.89)	65 (80.2)	
Other protocols	14 (7.82)	5 (6.2)	
Type of embryo transferred			
Fresh embryo	50 (28.09)	29 (35.8)	0.211
Frozen-thawed embryo	128 (71.9)	52 (64.2)	

BMI body mass index, *FSH* follicular stimulation hormone, E_2 estrogen, *T* testosterone, *AMH* anti-Mullerian hormone, *TC* total cholesterol, *TG* triglycerides, *HDL* high-density lipoprotein, *COH* controlled ovarian hyperstimulation

[a]Continuous variables are expressed as mean ± standard deviation, SD, categorical variables as absolute frequencies, *n* (%)

of developing moderate–severe OHSS included diagnosis of mild OHSS, low body mass, young women with good ovarian reserve, an estradiol level > 3500 pg/ml, and more than 15 oocytes retrieved. The decision regarding the freeze-all policy was made by experienced clinicians depending on clinical symptoms, laboratory parameters and the risk factors listed above. The luteal phase was supported by vaginal administration of micronized progesterone (400 mg/day) from the day of ovarian puncture to the day of the pregnancy test. Pregnancies were diagnosed by an increasing concentration of serum β-hCG, which was tested 14 days after embryo transfer. Clinical pregnancies were confirmed by the presence of a gestational sac on vaginal ultrasound examination during the fifth week. A live birth is defined as any birth event in which at least one baby is born alive.

Statistics software and data analysis

Development of the model

The nomogram was developed using the training cohort of 178 patients diagnosed from January 2014 to December 2017. The primary endpoint of the study was the likelihood of live birth after an IVF/ICSI cycle. To predict the probability of live birth, a multivariable logistic regression (MLR) analysis was performed including correlate predictive factors ($p<0.1$) at the univariable analysis and clinically relevant variables (Table S1). MLR was used to generate coefficients for each variable and the constant in the equation. A nomogram was constructed to be a graphic representation of the prediction model with the R software.

Backward stepwise selection was performed to determine independent covariates. Variables entered into the model were type of embryo transferred, TC and basal FSH levels, patient BMI and patient age. Variables were eliminated from the model if their removal actually improved the overall quality of the model (as measured by the Akaike information criterion). The p values in the multivariable analysis were based on Wald test. A p value of 0.05 was considered significant. Values for each of the model covariates were mapped to points on a scale ranging from 0 to 100. The total points obtained for each model corresponded to the probability of a live birth.

Validation of the model

The nomogram was confirmed using the validation cohort of 81 patients diagnosed from January 2018 to December

2018. A bootstrap re-sampling method to obtain relatively unbiased estimates (1000 repetitions) was used for external validation. For each group of 1000 bootstrap samples, the model was refitted and tested against the observed sample to estimate the predictive accuracy and bias. The predictive accuracy of the models was measured using the average optimism of the area under the curve (AUC), quantifying the level of agreement between the predicted probabilities and the actual possibility of having the event of interest.

Statistical analysis was carried out with SPSS 22.0 for Windows (IBM) and Regression Modeling Strategies (RMS, R version 3.34). For the nomogram establishment and the AUC measurements, we used the "regplot", "pROC" and "rms" in R software. Differences between groups were compared using Student's *t* test or Chi-squared test as appropriate.

Results

Characteristics and clinical outcomes of patients

After applying the inclusion and exclusion criteria of the current study, a total of 259 IVF/ICSI procedures in PCOS patients were gathered and analyzed. The model was built from a training cohort of 178 consecutive IVF/ICSI patients from January 2014 to December 2017. It was tested on an independent validation cohort of 81 consecutive patients from January 2018 to October 2018. Epidemiological, clinical, biological demographics and therapeutic strategies of the training and validation cohorts are summarized in Table 1. No significant difference was observed in the patients' characteristics between the two cohorts. 79 patients (44.69%) achieve live birth in the training cohort.

Logistic regression analysis revealed overweight, high TC and basal FSH were risk factors of IVF/ICSI outcome

Table S1 summarizes univariate and multivariate analyses. According to univariable logistic regression analysis, live birth was significantly correlated with TC ($p=0.005$), BMI ($p=0.010$) and basal FSH ($p=0.080$). In multivariable analysis of the training cohort, live birth was significantly correlated with TC (odds ratio [OR] 0.209; 95% CI 0.069–0.548; $p=0.003$), BMI (OR 0.478; 95% CI 0.250–0.900; $p=0.023$) and basal FSH (OR 1.291; 95% CI 0.990–1.705; $p=0.064$) (Fig. 1). TC > 6.11 ng/ml, increased BMI and higher FSH was associated with a decreased live birth rate.

Development of the models from the derivation cohort

On the basis of the univariate and multivariate logistic regression analyses we showed above, a nomogram incorporating the significant risk factors was established to predict the involvement probability of live birth (Fig. 2a). Age and type of embryo transferred were not statistically significantly related to the live birth rate but were included in the predictive model due to their clinical relevance and

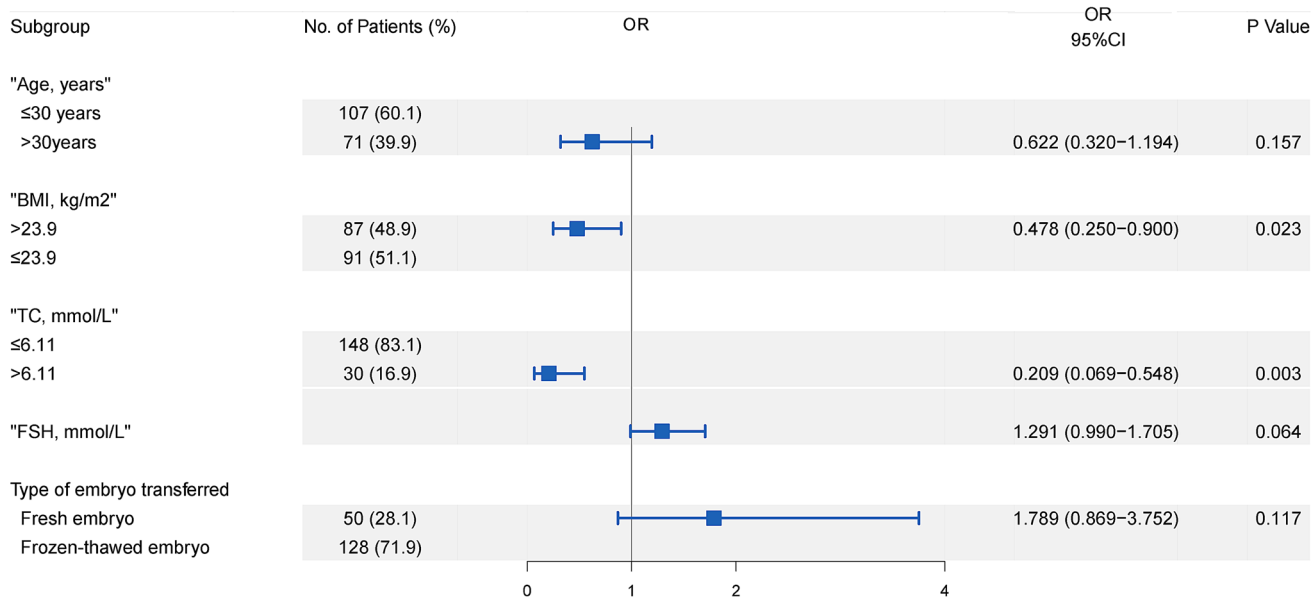

Fig. 1 Multivariate regression analysis in predictive factors of live birth regarding prognostic value in the training cohort. OR and 95% CI are presented to show the risk of predictive factors

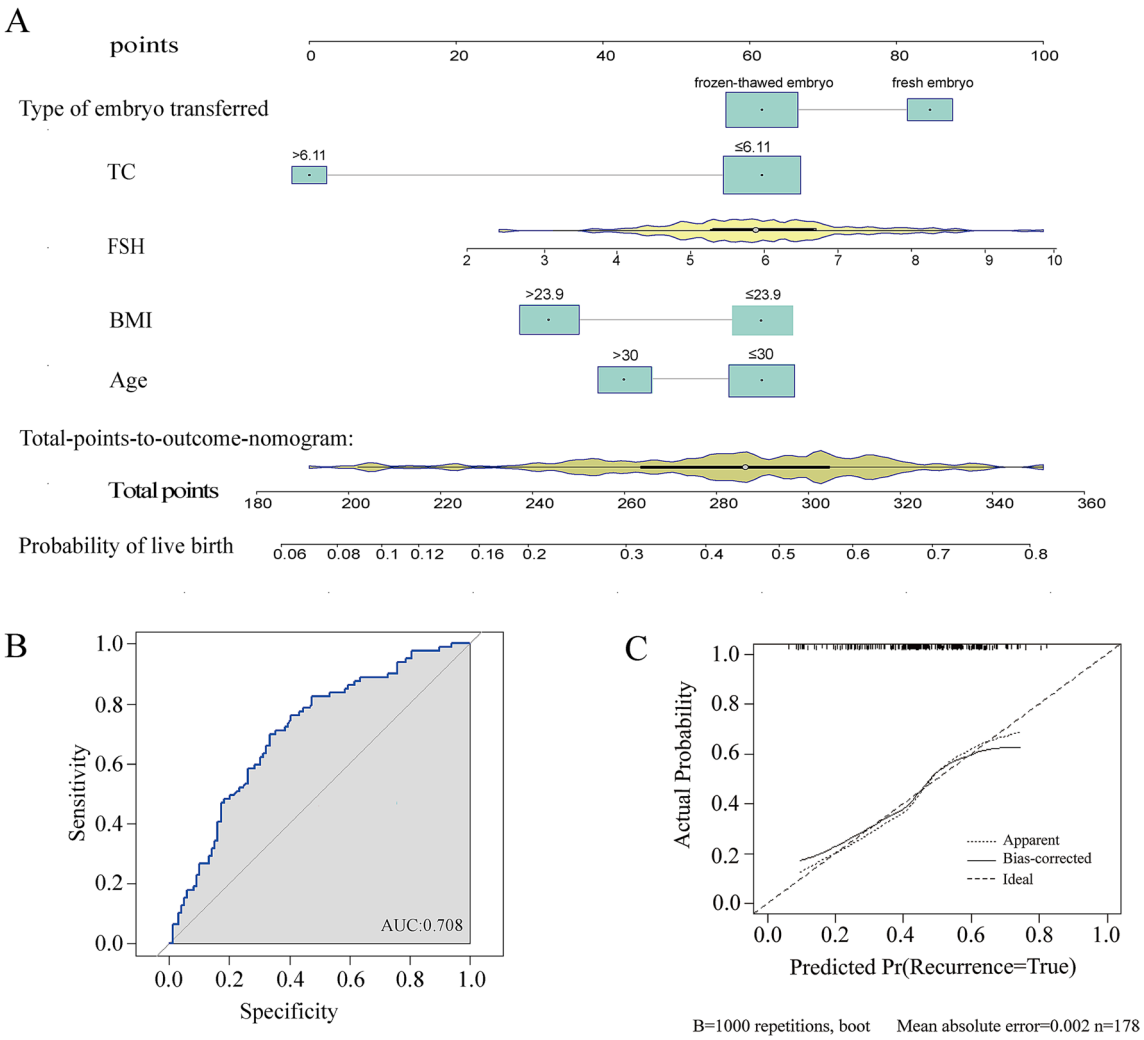

Fig. 2 Nomogram to predict the probability of live birth in PCOS-related infertility patients. **a** The probability of a live birth is calculated by drawing a line to the point on the axis for each of the following variables: type of embryo transferred, TC, basal FSH, BMI and age. The points for each variable are summed and located on the total points line. Next, a vertical line is projected from the total points line to the predicted probability bottom scale to obtain the individual probability of a live birth. **b** Discrimination for the training cohort. ROC curve of the model with an AUC of 0.708 (95% CI: 0.632-0.7847). **c** Calibration for the training cohort

their inclusion improved the overall quality of the model as well (as measured by the Akaike information criterion). A total score was calculated using the type of embryo transferred, TC, basal FSH, BMI and age. The equation describing the probability of live birth was $P = 1/(1 + \exp(2X))$, where $X = 0.50654 - 0.57801 \times V1 - 0.20514 \times V2 - 0.08219 \times V3 + 0.43403 \times V4 + 0.90164 \times V5$, where $V1$ was the type of embryo transferred (0 if frozen embryo and 1 if fresh embryo), $V2$ TC (0 if > 6.11 mmol/L and 1 if ≤ 6.11 mmol/L), $V3$ basal FSH serum level, $V4$ BMI (0 if > 23.9 kg/m^2 and 1 if ≤ 23.9 kg/m^2) and $V5$ age (0 if > 30 years and 1 if ≤ 30 years).

Validation of predictive accuracy

The calibration curves for live birth rate showed good calibration. The model showed an AUC of 0.708 (95% CI 0.632–0.785) in the training cohort (Fig. 2b, c), which denotes a good performance. The AUC of the ROC curve in the validation set was 0.686 (95% CI 0.556–0.815) indicating a fair performance.

Discussion

The predictive model we developed here is the first to predict the individual probability of a live birth for women with PCOS-related infertility. Our analysis of 259 infertile patients with PCOS suggests that individual likelihood of live birth can be predicted using a nomogram based on clinically significant data. The nomogram was developed in a training cohort including 178 patients and tested on an external independent validation cohort including 81 patients. Performance was evaluated using both calibration and discrimination, and our nomogram is a user-friendly graphical representation of the model (Fig. 2a). Its value lies in the combination of readily available clinical and biological characteristics, namely type of embryo transferred, TC, basal FSH, BMI and patient age. Another advantage of the nomogram lies in its dynamic nature: the model takes into account TC which influences the live birth rate during a patient's ART course. We hypothesize that the nomogram can be used in routine practice to facilitate patient counseling, especially for women with poor prognosis who need to improve underlying metabolic abnormalities.

Patient age has been considered to be a vital prognostic factor in reproductive medicine and frequently involved in assessing the probability of a live birth or pregnancy [11, 15]. Using a multivariable analysis, the probability of a live birth is lower for women over 30 years. These results are in keeping with those of previous studies showing a decrease in fertility results according to age [16–18]. Many papers have also shown the detrimental effects of obesity in PCOS patients who accepted assisted reproduction treatment, including impaired ovarian folliculogenesis, oocyte quality, embryonic development, uterine environment and thus adverse pregnancy outcomes [19–21]. A retrospective study shows that obese PCOS patients will experience worse clinical assisted reproductive technology outcomes, findings of a lower likelihood of achieving live birth with higher BMI [22]. BMI was a strong determinant factor of the live birth rate in our model. For patients with a higher BMI (> 23.9 kg/m^2), improvements can be achieved in fertility after weight loss among PCOS women before undergoing IVF/ICSI.

Another factor influencing live birth probability is lipid metabolism. As previously reported in a clinical trial, the most common lipid abnormalities among women with PCOS are elevated levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C) and low high-density lipoprotein cholesterol (HDL-C) levels [8, 23]. A large prospective cohort study indicates that both early and late spontaneous abortion were closely associated with hypercholesterolemia [24]. Although several studies have reported dyslipidemia is a key factor that affect fertility outcomes after IVF/ICSI in patients with PCOS, to date no predictive model is available considered the impact of dyslipidemia as a separate entity to evaluate the chance of achieving live birth for individual patients. Furthermore, while there are several scoring systems to evaluate the live birth rate in IVF/ICSI, none of them evaluated the chance of becoming delivery for individual patients with PCOS. Therefore, our nomogram provides realistic and precise information regarding IVF/ICSI success and can be used to guide couples and practitioners using clinical and biological criteria before transferring embryos.

The main limitation of our study is its retrospective nature which cannot exclude all potential biases. Furthermore, the data collection is based on a single center and there were not independent external validation cohorts from other hospitals in our study. The model was established based on very limited predictors obtained before an IVF/ICSI treatment. Pregnancy is a dynamic and ongoing process. Given the complexity of a delivery, we appreciate successful live birth depends on more than the factors in this model alone. There are many other confounders that have an impact at different time points. For example, factors such as number of oocytes retrieved, quality of embryos transferred or endometrial thickness on embryo transferred day which are crucial factors during an IVF/ICSI treatment, were not taken into account in this study. Therefore, prospective, large-scale and multicenter clinical trials should be carried out in future.

Despite these limitations, our results suggest that our nomogram predicting the live birth rate could be a useful tool in helping physicians and women with PCOS decide on a treatment option and pre-processing before IVF/ICSI. We highlight that the live birth rate could be relatively low without BMI control or normal lipid metabolism.

Conclusion

In conclusion, an objective and accurate prediction nomogram model for live birth rate was drawn up and validated in infertility patients with PCOS. Our new established nomogram model has proved to be a novel tool and easy to use to predict the live birth in PCOS patients. Furthermore, it was able to select patients with poor prognosis of live birth to plan appropriate treatment strategies, with the omission of IVF/ICSI cycles for low-live birth-rate patients. This type of nomograms will become increasingly important and will further advance the live birth rate of PCOS-related infertility patients. Last but not least, large-scale and multicenter clinical trials will provide more robust evidence to our observations.

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Author contributions Linzhi Gao, Manchao Li and Xing Yang designed the research. Yun Xie, Guihua Liu, Zhi Zeng, Yanfang Wang, and Bolun Zhang collected data. Jingjie Li and Xiaoyan Liang performed the analysis. Linzhi Gao, Manchao Li and Lina Wei wrote the manuscript. Linzhi Gao and Manchao Li contributed equally to this work.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethical Review Board (ERB) of Sixth Affiliated Hospital of Sun Yat-sen University.

Informed consent For this type of study formal consent is not required.

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