Prediction of Live Birth Rate After ICSI/IVF Cycles in Patients with Polycystic Ovary Syndrome Using a Clinical Prediction Model and Nomogram

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Research

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**Abstract**

**Background:** Achievement of a live birth is the marker of success in *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatments. For patients with polycystic ovary syndrome (PCOS) who are undergoing these treatments, some predictive models and nomograms have been published. However, further development of these models is required for their useful application in clinical settings.

**Method:** To establish and validate a clinical prediction model and nomogram to predict a live birth rate in women with PCOS undergoing IVF/ICSI. Records on 1193 patients underwent their first IVF/ICSI cycles for PCOS infertility from January 2014 to December 2019. The nomogram was built by a training cohort of 835 patients and tested on a validation cohort of 358 patients.

**Results:** Female age, duration of infertility, total gonadotropin dose, the day of embryo transfer, no. of transferred embryos and the serum testosterone (T) level in PCOS groups were significantly associated with live birth rate. The predictive model was built by female age, duration of infertility, total gonadotropin dose, the day of embryo transfer, no. of transferred embryos, no. of retrieved oocytes, the serum T level, the serum progesterone (P) level, type of fecundation and endometrial thickness on embryo transfer day. The area under the curve (AUC) of the PCOS-specific predictive model in the training cohort was 0.72 (95% CI, 0.68-0.76) and the AUC for the validation cohort was 0.63 (95% CI, 0.56-0.69).

**Conclusions:** Our clinical prediction model and nomogram graphically demonstrated the risk factors that were associated with IVF/ICSI live birth rates in patients with PCOS. These findings offer improved clinical guidance for clinicians and patients.

**Introduction**

Over the last two decades, infertility has become more common worldwide and polycystic ovary syndrome (PCOS) is one of the common causes. The prevalence of the disease is 25–40% [1] in infertile women and accounts for about 10% of indications for *in vitro* fertilization (IVF). PCOS is a highly heterogeneous cystic ovarian syndrome, and the leading causes of anovulation are dyslipidemia, hyperandrogenemia, hyperinsulinemia, oxidative stress, and infertility [2, 3].

IVF has become a viable option for women with PCOS who have failed ovulation induction therapy, or who have blocked fallopian tubes, or if male infertility is a factor [4]. The live birth rate is an important indicator of IVF outcome and previous studies failed to have the same conclusion. Some studies have found similar results for PCOS patients and non-PCOS patients and other studies showed a lower live birth rate[5, 6]. In addition, some studies have shown that PCOS patients have a higher live birth rate[7, 8].

Several studies report prediction models regarding live birth rate and IVF outcome among women with PCOS and offer a number of indicators used to predict live birth rate. And a prognostic model was established for IVF/ICSI live births in patients with PCOS[9]. However, there is no consensus on the relationship between live birth rate and PCOS in women undergoing IVF treatment. The aim of this study
was to establish a nomogram to predict the likelihood of a live birth after assisted reproductive techniques (ART) in patients with PCOS.

**Materials And Methods**

**Patients**

A cohort was created of 1139 women with PCOS who had undergone ICSI/IVF treatment at the First Affiliated Hospital of Zhengzhou University from January 2014 to December 2019. The sample size of this study was determined to include all eligible patients who had received their first fresh IVF/ICSI cycles with autologous oocytes from 2014 to 2019. PCOS patients were diagnosed according to the Rotterdam criteria[10]. None of the patients who participated in the study had other endocrine diseases, such as Cushing’s disease, congenital adrenal hyperplasia, etc. Patients with infertility due to female subjects with a medical history of endometriosis, reproductive malformation, or uterine fibroids were also excluded. In addition, patients who used donor oocytes or spermatozoa or had undergone preimplantation genetic diagnosis (PGD) or preimplantation genetic screening (PGS) were also excluded.

The study received approval from the Ethics in Research Committee of The First Affiliated Hospital of Zhengzhou University. The ethical approval number of the study is 2020-KY-419. Because it is difficult to trace patients for their informed consent in a retrospective analysis, this study was exempted following approval of the Ethics Committee.

**Procedure**

All individuals included in the study underwent controlled ovarian hyperstimulation according to a currently established gonadotropin-releasing hormone (GnRH) agonist protocol. Long-acting gonadotropin-releasing hormone agonist (3.75 mg) was administered on the 2nd to 3rd day of menstruation. After 30–42 days, the down-regulation criteria were reached, and gonadotropin was then administered for controlled ovarian hyperstimulation (COH). Gonadotropin dose was determined according to body mass index (BMI), anti-Müllerian hormone (AMH) and primary follicular condition. Gonadotropin dose was adjusted according to follicle size and hormone level, and human menopausal gonadotrophic hormone was added. When at least one follicle with a mean diameter more than 18 mm, human chorionic gonadotropin (hCG) was given, and 37 h after hCG injection, oocyte retrieval was performed under the guidance of vaginal ultrasound. After co-culture of spermatozoa and oocytes for 5 h, the cumulus cells surrounding the oocytes were removed to observe and record the appearance of the second polar body. Morula formation on Day 3 (D3) and blastocyst formation on Day 5 (D5) and Day 6 (D6) were observed and recorded. After embryo transfer, routine vaginal administration of progesterone gel was performed for luteal support. Fresh embryo transfers were performed on Day 3 or Day 5. 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.

**Blood test and outcome**
Hormone and metabolite level analysis, including serum follicle-stimulating hormone (FSH) luteinizing hormone (LH), estradiol (E2), testosterone (T), progesterone (P), and Prolactin (PRL) were evaluated on days 2 to 4 of menstruation using a radioimmunoassay method. This study used ultrasonography to detect the number of antral follicles on day 2. Since P data and T data displays a skewed distribution, the logarithm was converted to normally distributed data named P_log and T_log.

The primary endpoint was the live birth rate. Blood samples were taken at 14 days and 18 days after embryo transfer to determine serum β-hCG. Clinical pregnancy was achieved when the intrauterine gestational sac was recognized by ultrasonography after embryo transfer and a positive serum β-hCG >50 IU/L concentration was found. Live birth was defined as any birth event in which at least one baby is born alive.

**Development of the model**

The endpoint was the live birth rate. All included patients were randomly divided into training cohort and validation cohort in a ratio of 7 to 3 and patients with missing values for predictors were excluded. On the basis of Univariate and Multivariable Logistic Regression (MLR) analysis, a column with important risk factors was established to forecast the probability of a live birth in patients with PCOS using R software. The P-values were based on the Wald test. A P-value <0.05 was considered significant.

The nomogram was developed by MLR using a training group of 835 patients diagnosed with PCOS. Backward variable selection was performed to determine independent covariates. The minimum Akaike information criterion (AIC) model is the optimal model; AIC is a measure of statistical model “goodness of fit.” Increasing the number of free parameters improves the optimization of fit. AIC encourages the optimization of data fit but tries to avoid overfitting. Therefore, a preferred model would be one with the lowest AIC value. Assuming that a choice is made among $n$ models, the AIC value of $n$ models can be calculated, and the model corresponding to the minimum AIC value can be selected.

**Validation of the model**

The model was validated using data from 358 patients diagnosed with PCOS.

The correction of the model was assessed by discrimination and calibration. Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve and the area under the curve (AUC) to reflect the ability of the test to differentiate between results at all possible positive levels. In addition, the 95% confidence interval (95% CI) was calculated for each AUC.

The calibration curves were graphically assessed by plotting the frequency of observed outcomes against the average predicted outcome problem or risk to increase the estimated probability. The relative corrected C-index was calculated by bootstrapping verification (1000 bootstrap resampling) for internal validation.
IBM SPSS Statistics Premium V22.0 (SPSS Inc., Chicago, IL, USA) and RStudio (Version 1.3.1073) were used for statistical analysis. Differences between groups were compared using Student’s *t*-test or Chi-squared test. The difference of proportions between groups was compared using false discovery rate. A *P*-value <0.05 was considered significant. To develop and validate the clinical model and nomogram, we used “regplot,” “pROC,” “ggplot2,” “glmnet,” “riskRegression,” “plotROC,” “ggridges,” “survminer,” “survival,” “ipred,” “MASS,” “VGAM,” “rms,” and some other packages in R-Studio.

Results

After excluding all patients with missing data, there were 1193 patients with PCOS who were eventually included in the analysis. The training cohort included 835 patients with PCOS whose data were used to build the clinical model. To validate the model, 358 patients with PCOS who underwent IVF/ICSI were included in the validation cohort. Epidemiological, clinical, biological demographics, and therapeutic strategies of the training and validation cohorts are summarized in Table 1. The variables showed no statistically significant difference between the groups. 614 patients (73.5%) achieve live birth in the training cohort 262 patients (73.2%) achieve live birth in the validation cohort.

Figure 1 summarizes univariate and multivariate analysis. Female age (OR 0.8344; 95% CI 0.7931–0.8762; *p* < 0.0001), duration of infertility (OR 1.0680; 95% CI 1.0047 1.1389; *p* = 0.04), total gonadotropin dose (OR 0.9997; 95% CI 0.9995 0.9999; *p* = 0.001), the day of embryo transfer (OR 4.7595; 95% CI 1.7564 13.5624; *p* = 0.002) and the serum T level (OR 0.8006; 95% CI 0.6502 0.9871; *p* = 0.03) in the PCOS training cohort were significantly correlated with live birth by multivariate analysis (Fig. 2).

The nomogram built by the multivariate logistic regression model is shown in Fig. 2. Risk factors were selected by backward variable selection and AIC of the model. Variables entered into the PCOS-specific predictive model were: female age, duration of infertility, total gonadotropin dose, the day of embryo transfer, no. of transferred embryos, no. of retrieved oocytes, the serum T level, the serum P level, type of fecundation and endometrial thickness on embryo transfer day. The specific method for reading a nomogram is to identify the corresponding point of each variable on the corresponding axis of the graph, and then the corresponding point represented by the horizontal axis of the corresponding point of each variable is the corresponding score. The intersection of the lines on the fractional line is the score of the variable, and the total score is the sum of the scores of each variable. In the same way, the total score is read on the risk axis to obtain the predicted occurrence probability of PCOS.

The equation describing the probability of live birth in the PCOS-specific predictive model was \[ P = \frac{1}{1 + \exp(2X)} \], where \[ X = 2.7140231174 - 0.1810326257 \cdot V_1 + 0.0658167090 \cdot V_2 - 0.0002789732 \cdot V_3 + 1.5601364863 \cdot V_4 + 1.5500843894 \cdot V_5 - 0.0332133613 \cdot V_6 - 0.2223722800 \cdot V_7 - 0.1448945104 \cdot V_8 + 0.3391718194 \cdot V_9 + 0.0706527423 \cdot V_{10} \], where V1 female age, V2 duration of infertility, V3 total gonadotropin dose, V4 the day of embryo transfer (D5 ET), V5 no. of transferred embryos, V6 no. of retrieved oocytes, V7 T _log, V8 P _log, V9 type of fecundation (IVF) and V10 endometrial thickness on embryo transfer day.
The AUC of the PCOS-specific predictive model was 0.72 (95% CI, 0.68–0.76) for the training cohort (Fig. 3). There was no significant difference between the predicted probabilities corrected by bootstrap (B = 1000). The calibration was acceptable with mean absolute errors of 0.019. The AUC of the ROC curve in the validation cohort was 0.63 (95% CI, 0.56–0.69).

Discussion

In this study, the relevant risk factors obtained from previous studies were combined to establish and validate a clinical prediction model and nomogram applicable to PCOS. At present, nomograms are widely used as prognostic tools in oncology and medicine. Nomograms rely on a user-friendly digital interface that improves accuracy and makes the prognosis easier to understand, so assisting clinical decision-making [11]. As a statistical tool, a nomogram prediction model can provide a most accurate prediction through simple graphical representation. It has been proven to have a prognostic capability similar to that of the TNM staging system of the American Joint Committee on Cancer (AJCC), thus becoming an alternative or even a new standard [12, 13].

The PCOS-specific clinical model included ten risk factors. Female age is a well-known predictive factor in IVF/ICSI, increasing female age is associated with a lower chance of pregnancy [14]. Similar to some other previous studies [14, 15] our study shows that age was negatively correlated with live birth rate in PCOS clinical models by multivariable analysis. Some reports indicate that the live birth rate of the blastocyst transfer is higher than that of the early cleavage stage embryo transfers in the fresh cycle embryo transfer [16, 17]. Consistent with our results, patients who underwent the embryo transfer on Day 5 had a higher live birth rate than Day 3. Our study also found a positive correlation between the number of embryo transfer and the live birth rate, which is consistent with previous studies [18, 19]. BMI was not included in this study by the Backward variable selection. Although BMI was associated with live birth rate in univariate regression analysis, multivariate regression analysis yielded different results.

The current prediction model was based on the most basic clinical data of patients, without considering the complete dynamic process. Although the data was convenient and easy to obtain, bias could have easily been introduced due to the lack of other possible confounding factors. It is true that our research model does not produce a particularly ideal AUC. However this can happen for a variety of reasons. We used R to build a prediction model, and the basis for incorporating model indicators using stepwise regression is AIC. Therefore, although the AUC model is not particularly ideal, the prediction model established by AIC also has certain application value. In addition, it may be related to the size of sample size. When the sample size is large, the AUC may not be ideal, but the reliability of the model may be better than that of the model with small sample size with a good AUC.

The largest limitation of this study was that it was a retrospective analysis with data collected only from our single center; there was no validation data collected from other hospitals. Needless to say, live birth is associated with multiple factors through multiple links. Despite some limitations, our study screened several risk factors associated with live birth rate and successfully established and validated nomogram
prediction models for PCOS and endometriosis. Use of the nomogram will assist with efficient communication between clinicians and patients and provide a basis for the scientific formulation of individual plans for ovulation induction therapy for infertile couples.

**Conclusions**

In conclusion, this study established and validated an objective and accurate clinical prediction model for the live birth rate of infertility patients with PCOS by incorporating clinical data. Our nomogram is a simple and intuitive visualization tool which can accurately predict the live birth rate of PCOS patients. Therefore, our prediction model can help clinicians and patients to improve relevant indicators before receiving IVF treatment to achieve better live birth rate and reduce costs.

**List Of Abbreviations**

IVF In vitro fertilization

ICSI Intracytoplasmic sperm injection

PCOS Polycystic Ovary Syndrome

T Testosterone

P progesterone

LH Luteinizing hormone

FSH Follicle-stimulating hormone

GnRH Gonadotrophin-releasing hormone

PRL Prolactin

E2 Estrogen

ET Embryo transfer

MLR Multivariable logistic regression

AUC Area under the curve

ART Assisted reproduction technology

BMI Body mass index

hCG Human chorionic gonadotropin
AMH Anti-Mullerian hormone

COH Controlled ovarian hyperstimulation

AIC Akaike information criterion

CI Confidence interval

OR Odds ratio

PGS preimplantation genetic screening

PGD preimplantation genetic diagnosis

**Declarations**

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Haixia Jin and Yuanyuan Liu contributed equally to the article. All authors participated in article drafting and revision. All authors read and approved the manuscript.

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**Competing interests:**

The authors declare that they have no competing interests.

**Ethics approval and consent to participate:**

Ethics in Research Committee of The First Affiliated Hospital of Zhengzhou University (2020-KY-419).

**Consent for publication:**

Not applicable.

**Availability of data and materials:**

All data generated or analyzed during the current study are available from the corresponding author on reasonable request.
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Table
Table 1
Baseline characteristics of infertile women in the training cohort and validation cohort of the live birth prediction model

| Patients with PCOS \((n = 1495)\) | Training cohort | Validation cohort | \(p\) |
|----------------------------------|-----------------|------------------|------|
| live birth                       | 835             | 358              |      |
| Female age (years)               | 28.98 (3.61)    | 28.76 (3.69)     | NS   |
| Male age (years)                 | 30.01 (4.30)    | 29.90 (4.32)     | NS   |
| ICSI (%)                         | 123 (14.7)      | 46 (12.8)        | NS   |
| IVF (%)                          | 712 (85.3)      | 312 (87.2)       | NS   |
| No. of retrieved oocytes         | 14.82 (5.84)    | 15.31 (6.08)     | NS   |
| No. of transferred embryos       | 1.69 (0.46)     | 1.69 (0.46)      | NS   |
| BMI (kg/m\(^2\))                | 24.35 (3.48)    | 24.15 (3.30)     | NS   |
| Duration of infertility (years)  | 4.10 (2.71)     | 3.83 (2.51)      | NS   |
| FSH (IU/L)                       | 5.86 (1.57)     | 5.84 (1.41)      | NS   |
| E2 (pg/mL)                       | 56.75 (117.75)  | 46.22 (38.07)    | NS   |
| T (ng/mL)                        | 1.02 (5.92)     | 1.02 (6.08)      | NS   |
| P (ng/mL)                        | 0.78 (1.68)     | 0.69 (1.22)      | NS   |
| PRL (ng/mL)                      | 20.84 (41.04)   | 18.15 (25.50)    | NS   |
| LH (mIU/ml)                      | 9.38 (6.97)     | 9.29 (6.03)      | NS   |
| Days of gonadotropin use (d)     | 14.17 (2.98)    | 14.44 (3.14)     | NS   |
| Total Gonadotropin dose (IU)     | 2163.91 (952.49)| 2190.85 (996.08)| NS   |
| Endometrial thickness on embryo transfer day (mm) | 11.90 (2.33) | 12.05 (2.47) | NS |
| Primary infertility (%)          | 781 ± 64.5      | 165 (57.9)       | NS   |
| Secondary infertility (%)        | 429 ± 35.5      | 120 (42.1)       | NS   |
| D3 ET (%)                        | 595 (71.3)      | 247 (69.3)       | NS   |
| D5 ET (%)                        | 240 (28.7)      | 110 (30.7)       |      |

BMI body mass index, FSH follicular stimulation hormone, E2 estrogen, T testosterone, P progesterone, PRL Prolactin, LH luteinizing hormone, D3 ET embryo transfer on day3, D5 ET embryo transfer on
Continuous variables were described as Mean ± SD, categorical variables were described as frequency (percentage).