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RESEARCH

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Early pregnancy loss rate in first-time fresh cycles of low prognosis patients according to the POSEIDON criteria: a single-center data analysis

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Abstract

Backgrounds The study was designed to analyze early pregnancy loss rates in first-time fresh embryo transfer cycles in low prognosis patients according to the POSEIDON criteria.

Methods This was a retrospective cohort study, including patients with positive human chorionic gonadotropin after first fresh cycles in the Reproductive Center of Henan Province People's Hospital from June 2018 to February 2023. A total of 2392 cycles were included in this study, which were divided into 4 groups according to the POSEIDON criteria. The general condition, laboratory indexes, and early pregnancy loss rates of patients were compared in each group and the prediction model was constructed in POSEIDON group 4.

Results The early pregnancy loss rate ranked from high to low in order of Group D (32.82%), Group B (23.31%), Group C (15.34%), and Group A (13.68%). After adjusting confounding factors, multivariate logistic regression analysis revealed that the early pregnancy loss rate was significantly higher in groups B and D than in groups A and C (all $P<0.05$). The comparison between Group A and Group C, as well as between Group B and Group D, showed no statistical differences (both $P>0.05$). Group D was randomly divided into training and validation cohorts according to 7:3. The prediction model was constructed based on risk factors. The AUC of the training cohort was 0.761(95% CI: 0.680–0.841), and the AUC of the validation cohort was 0.604(95% CI: 0.440–0.767).

Conclusions Patients in POSEIDON group 4 have the highest early pregnancy loss rate, followed by group 2, while patients in groups 3 and 1 have the lowest rate in first-time fresh cycles. The prediction model was successfully established which can predict the occurrence of early pregnancy loss in first-time fresh cycles in POSEIDON group 4.

Keywords POSEIDON criteria, Poor ovarian response, Early pregnancy loss, In vitro fertilization, Low prognosis patient

Introduction

Controlled ovarian stimulation (COS) is a critical step in in vitro fertilization-embryo transfer (IVF-ET) for infertility treatment. Accurate assessment of ovarian response prior to IVF-ET is essential for developing personalized treatment strategies and improving pregnancy outcomes [1]. Poor ovarian response (POR) refers to a reduced ovarian sensitivity to gonadotropins, which mainly results in higher gonadotropin dosage, increased cycle

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cancellation rate, fewer oocytes retrieved, lower cumulative live birth rate [2, 3].

The Bologna criteria for defining POR was first proposed by the ESHRE groups in 2011 [4]. However, POR patients were highly heterogeneous according to the criteria which could only provide limited guidance to clinicians. To address these shortcomings, the POSEIDON criteria were introduced in 2016. These criteria classify POR patients into four subgroups based on age, antral follicle count (AFC), anti-Müllerian hormone (AMH) levels, and the number of oocytes retrieved, reframing the concept of POR to focus on "low prognosis patients" [5].

Miscarriage is a frequent complication in human pregnancies. The early pregnancy loss rates in IVF-ET ranging from 10 to 15% in Beijing from 2013 to 2015, which continues to be a challenging issue for reproductive physicians [6, 7]. Despite its importance, few clinical studies have examined early pregnancy loss among low prognosis patients according to the POSEIDON criteria after IVF-ET.

To explore the differences in early pregnancy loss across POSEIDON subgroups, we conducted a retrospective analysis of clinical data from human chorionic gonadotropin (hCG)-positive patients after IVF-ET. Additionally, we developed a prediction model for the POSEIDON group 4 in an effort to provide some suggestions in tailoring individualized treatment strategies.

Materials and methods

Study population

This study was a single-center retrospective study of women with positive hCG after IVF-ET at the Reproductive Medicine Center of Henan Provincial People's Hospital from June 2018 to February 2023. The inclusion criteria were as follows: 1) first fresh embryo-transfer cycles; 2) cycles with the gonadotropin-releasing hormone (GnRH) agonist protocol or the GnRH antagonist protocol; 3) diagnosed as low prognosis patients according to the POSEIDON criteria. The exclusion criteria were as follows:1) cycles with missingness or outliers; 2) endocrine disorders such as abnormal thyroid function, diabetes, and hyperprolactinemia; 3) preimplantation genetic testing and couples with chromosomal abnormalities; 4) uterine abnormalities including abnormal uterine morphology, endometrial abnormalities, fibroids, and uterine adhesions; 5) endometriosis and adenomyosis; 6) ectopic pregnancy after transplantation. The study was approved by the Ethics Committee of Reproductive Medicine of Henan Provincial People's Hospital with the number SYSZ-LL-2021091501. The study adhered to the fundamental tenets of the Helsinki Declaration.

Grouping

Patients were divided into four groups with reference to the POSEIDON criteria: Group A (POSEIDON group 1): age < 35 years, AMH ≥ 1.2 ng/mL, the number of oocytes retrieved ≤ 9. Group B (POSEIDON group 2): age ≥ 35 years, AMH ≥ 1.2 ng/mL, the number of oocytes retrieved ≤ 9. Group C (POSEIDON group 3): age < 35 years, AMH < 1.2 ng/mL. Group D (POSEIDON group 4): age ≥ 35 years, AMH < 1.2 ng/mL [8].

Ovarian stimulation

GnRH agonist protocol

The long-acting GnRH agonist was injected once at a total of 3.75 mg on the day 2 or 3 of the menstruation. Serum hormone levels and the ultrasound were monitored on the 28th to the 35th day after GnRH agonist administration. On top of that, the same examinations could be accomplished after a short-acting GnRH agonist 0.1 mg/day was injected for 14–18 days starting from the middle luteal phase of the previous menstrual cycle. When the requirements for downregulation were met, a dose of 100–300 IU Gn was administered based on age, ovarian reserve, and body mass index (BMI). During the stimulation process, the gonadotropin dose was adjusted according to follicular development, as determined by ultrasound and serum hormone levels.

GnRH antagonist protocol

Ovarian stimulation was initiated from day 2 or 3 of menstruation with the appropriate amount of gonadotropin at a dose of 100–300 IU/day until the hCG trigger day. The gonadotropin dose was adjusted during the stimulation process in the same way. A daily dose of 0.25 mg GnRH antagonist was initiated when a dominant follicle reached a mean diameter of 12–14 mm or when the blood luteinizing hormone levels exhibited a significant upward trend until the day of hCG injection.

If there were three follicles of ≥ 16 mm diameter, two follicles of ≥ 17 mm diameter, or one follicle of ≥ 18 mm diameter, 5,000–10,000 IU of hCG was injected. Approximately 36–38 h after the trigger, oocytes were retrieved transvaginally.

Fresh embryo transfer and luteal support

IVF / intracytoplasmic sperm injection (ICSI) fertilization was performed depending on male semen parameters. After 3–6 days after oocyte retrieval, the best 1 or 2 cleavage embryos or blastocysts were selected according to the routine protocol of our center and then transferred into the uterus under ultrasound guidance. Fresh cycle transplant patients started receiving luteal support on ovulation day with dydrogesterone 10 mg orally bid and

progesterone vaginal gel 90 mg qd. After confirming early pregnancy loss, all luteal support medications were discontinued. For ongoing pregnant patients, luteal support medications maintained until 8–10 weeks of gestation.

Outcomes

The primary outcome of this study was the early pregnancy loss rate. Peripheral blood hCG > 50 mIU/mL at 14 days after embryo transferred was considered as pregnancy, and clinical pregnancy was confirmed by the presence of at least one intrauterine gestational sac 4–5 weeks after transfer (ectopic pregnancy was not included in this study). Biochemical pregnancy referred to a positive hCG but no gestational sac seen in the uterus. Early miscarriage was defined as a miscarriage occurring within the first 12 weeks of pregnancy. Early pregnancy loss included biochemical pregnancy and early miscarriage. Early pregnancy loss rate = (biochemical pregnancy cycles + early miscarriage cycles)/ positive hCG cycles × 100%.

Statistical analysis

The measurement data conforming to normal distribution were expressed as mean ± SD, and one-way ANOVA was used for comparison among groups. All counting data were expressed by percentage (%), and the chi-square test was used to compare the count data between groups. The Bonferroni method was used to compare multiple groups by pairwise comparison.

Cycles in group D were divided into training and validation cohorts using the random sampling method by 7:3. Univariate logistic regression analysis was performed in the training cohort. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate analysis and the nomogram was successfully established. The predictive performance was verified through receiver operating characteristic (ROC) curves. Calibration curves were used to assess the performance of the prediction model. Decision curve analysis was also performed to assess the clinical applicability of the model. Statistical analysis was performed using SPSS 25.0 and software packages R (http://www.R-project.org, The R Foundation). A two-tailed P value < 0.05 was considered statistically significant.

Results

Patients and treatment characteristics

Based on the inclusion and exclusion criteria, a total of 2,392 cycles were included and classified into four groups according to the POSEIDON criteria: group A ($n = 1528$), group B ($n = 356$), group C ($n = 313$), group D ($n = 195$). (Fig. 1). Table 1 shows the demographic and clinical characteristics of the four groups. Significant differences were observed in female age, male age, body mass index (BMI), duration and type of infertility, basal follicle-stimulating hormone (FSH), AMH, AFC, COS protocols, starting dosage of gonadotropin (Gn), endometrial thickness (EMT) on trigger day, and the number of embryos transferred among the groups (Bonferroni correction, all $P < 0.05$). However, no statistically significant differences were found in insemination methods or development days of transfer embryos (Bonferroni correction, both $P > 0.05$).

Laboratory data and pregnancy outcomes

The number of oocytes retrieved, mature oocytes, two pronuclei (2PN) zygotes, and early pregnancy loss rates all differed among the four groups (Table 2).

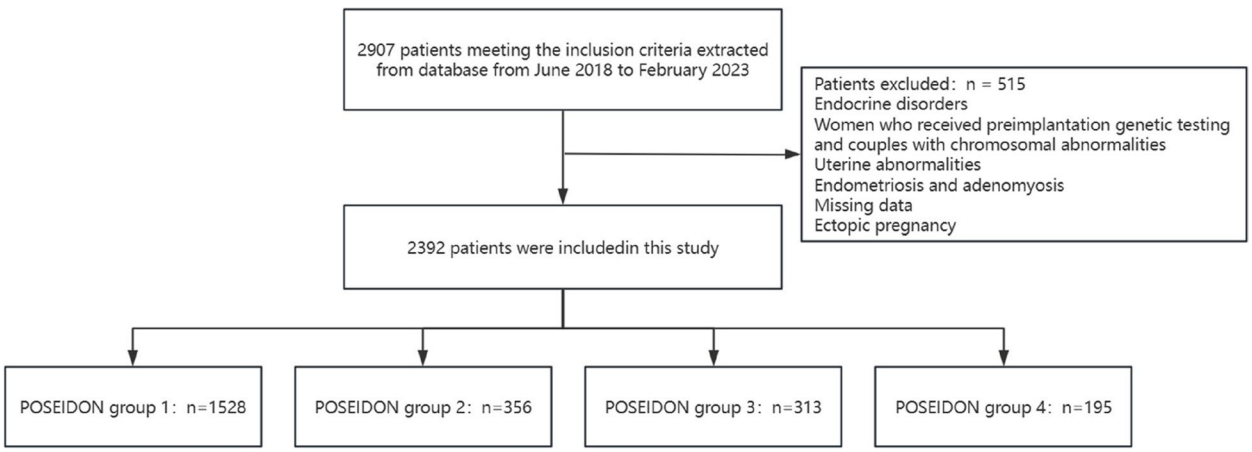

Fig. 1 A flow-chart of cycles' selection and exclusions

Table 1 The basic characteristics of patients among four groups

Item	Group A	Group B	Group C	Group D	χ^2/ F value	*P* value
No. of cases	1528	356	313	195		
Female age (year)	29.52 ± 3.06	37.17 ± 2.29[a]	30.11 ± 2.93[ab]	38.18 ± 2.55[abc]	F = 1057.61	< 0.001
Male age (year)	30.46 ± 3.80	37.48 ± 4.21[a]	31.04 ± 3.92[b]	38.34 ± 5.24[ac]	F = 461.58	< 0.001
Body mass index (kg/m^2)	23.67 ± 3.80	23.99 ± 3.49	23.07 ± 3.56[b]	23.60 ± 3.38	F = 3.59	0.013
Duration of infertility (year)	3.26 ± 2.25	4.23 ± 3.39[a]	3.21 ± 2.38[b]	4.51 ± 3.86[ac]	F = 24.35	< 0.001
Type of infertility (%)					χ^2 = 164.75	< 0.001
Primary	56.35 (861/1528)	25.00 (89/356)[a]	47.28 (148/313)[ab]	23.59 (46/195)[ac]		
Secondary	43.65 (667/1528)	75.00 (267/356)	52.72 (165/313)	76.41 (149/195)		
Basal FSH (IU/L)	6.79 ± 1.96	7.05 ± 2.09	8.24 ± 3.81[ab]	8.24 ± 2.89[ab]	F = 44.79	< 0.001
AMH (ng/ml)	3.79 ± 2.66	2.91 ± 1.91[a]	0.84 ± 0.26[ab]	0.77 ± 0.29[ab]	F = 222.44	< 0.001
AFC	14.30 ± 5.67	11.18 ± 4.84[a]	8.07 ± 3.68[ab]	6.26 ± 2.99[abc]	F = 242.83	< 0.001
Controlled ovarian stimulation protocol (%)					χ^2 = 253.89	< 0.001
GnRH-a protocol	82.53 (1261/1528)	75.56 (269/356)[a]	58.79 (184/313)[ab]	34.87 (68/195)[abc]		
GnRH-A protocol	17.47 (267/1528)	24.44 (87/356)	41.21 (129/313)	65.13 (127/195)		
Starting dosage of Gn (IU)	152.70 ± 45.84	198.77 ± 61.65[a]	220.47 ± 63.79[ab]	257.05 ± 53.20[abc]	F = 363.55	< 0.001
Insemination method (%)					χ^2 = 3.90	0.272
IVF	81.74 (1249/1528)	85.67 (305/356)	83.71 (262/313)	84.62 (165/195)		
ICSI	18.26 (279/1528)	14.33 (51/356)	16.29 (51/313)	15.38 (30/195)		
Endometrial thickness on trigger day (mm)	11.39 ± 2.77	11.11 ± 2.67	11.14 ± 2.79	10.27 ± 2.62[abc]	F = 9.86	< 0.001
Development days of transfer embryos (%)					χ^2 = 5.83	0.120
Cleavage embryo	87.83 (1342/1528)	88.48 (315/356)	84.03 (263/313)	90.77 (177/195)		
Blastocyst	12.17 (186/1528)	11.52 (41/356)	15.97 (50/313)	9.23 (18/195)		
No. of embryos transferred (%)					χ^2 = 24.81	< 0.001
1	44.57 (681/1528)	31.46 (112/356)[a]	45.37 (142/313)[b]	35.90 (70/195)		
2	55.43 (847/1528)	68.54 (244/356)	54.63 (171/313)	64.10 (125/195)		

[a] represents $P < 0.05$, compared with group A

[b] represents $P < 0.05$, compared with group B

[c] represents $P < 0.05$, compared with group C; positive number/total number in brackets

Table 2 Comparison of laboratory indexes and early pregnancy loss rate among the four groups

Item	Group A	Group B	Group C	Group D	*χ2*/ F value	*P* value
No. of cases	1528	356	313	195		
No. of oocytes retrieved	6.63 ± 1.85	6.36 ± 1.99	6.67 ± 3.52	5.12 ± 2.97[abc]	F = 27.01	< 0.001
No. of mature oocytes	5.70 ± 1.90	5.65 ± 1.89	5.81 ± 3.11	4.41 ± 2.58[abc]	F = 22.02	< 0.001
No. of 2PN zygotes	4.21 ± 1.78	4.21 ± 1.76	4.47 ± 2.59	3.38 ± 2.15[abc]	F = 13.71	< 0.001
Early pregnancy loss rate (%)	13.68 (209/1528)	23.31 (83/356)[a]	15.34 (48/313)	32.82 (64/195)[ac]	χ^2 = 57.49	< 0.001

[a] represents $P < 0.05$, compared with group A

[b] represents $P < 0.05$, compared with group B

[c] represents $P < 0.05$, compared with group C; positive number/total number in brackets

Logistic regression analysis based on early pregnancy loss rates

Various confounding factors, including the female age, COS protocols, duration of infertility, type of infertility, basal FSH, AMH, AFC, BMI, starting dosage of Gn, number of oocytes retrieved, number of MII oocytes, number of 2PN oocytes, EMT on the trigger day, development days of transfer embryos, and number of embryos transferred, were adjusted in logistic regression analysis.

Multifactorial logistic regression analysis (Table 3) showed that, compared to group A, groups B and D had a significantly higher early pregnancy loss rate (OR = 1.82, 95% CI: 1.29, 2.55, $P < 0.001$; OR = 2.36, 95% CI: 1.51, 3.68, $P < 0.001$), while group A and C had similar rates.

Table 3 Logistic regression analysis of early pregnancy loss in four groups

Item	Early pregnancy loss group (*n* = 404)	Non-early pregnancy loss group (*n* = 1988)	Adjusted OR (95%CI)	*P* value
Group				
Group A	13.68 (209/1528)	86.32 (1319/1528)	Reference	
Group B[a]	23.31 (83/356)	76.69 (273/356)	1.82 (1.29, 2.55)	< 0.001
Group C[b]	15.34 (48/313)	84.66 (265/313)	1.09 (0.72, 1.64)	0.683
Group D[c]	32.82 (64/195)	67.18 (131/195)	2.36 (1.51, 3.68)	< 0.001
Group				
Group B	Reference			
Group C[c]			0.46 (0.28, 0.75)	0.002
Group D[b]			0.91 (0.56, 1.50)	0.722
Group				
Group C	Reference			
Group D[a]			2.04 (1.22, 3.41)	0.007

[a] Adjusted confounding factors include: COS protocols, duration of infertility, type of infertility, basal FSH, AMH, AFC, BMI, starting dosage of Gn, No. of oocytes retrieved, No. of MII, No. of 2PN, endometrial thickness on trigger day, development days of transfer embryos, No. of transferred embryos

[b] Adjusted confounding factors include: female age, COS protocols, duration of infertility, type of infertility, basal FSH, AFC, BMI, starting dosage of Gn, No. of oocytes retrieved, No. of MII, No. of 2PN, endometrial thickness on trigger day, development days of transfer embryos, No. of transferred embryos

[c] Adjusted confounding factors include: COS protocols, duration of infertility, type of infertility, basal FSH, AFC, BMI, starting dosage of Gn, No. of oocytes retrieved, No. of MII, No. of 2PN, endometrial thickness on trigger day, development days of transfer embryos, No. of transferred embryos; positive number/total number in brackets

Compared to group B, group C had a lower early pregnancy loss rate (OR = 0.46, 95% CI: 0.28, 0.75, $P = 0.002$). Compared to group C, groups D had a higher early pregnancy loss rate (OR = 2.04, 95% CI: 1.22, 3.41, $P = 0.007$).

Construction of the model in the POSEIDON advanced age group

Group D was randomly divided into training and validation cohorts in a 7:3 ratio using the simple random sampling method. No statistically significant differences were observed in baseline data between the two cohorts (all $P > 0.05$) (Table 4). Univariate logistic regression analysis revealed female age, male age, AFC, starting dosage of Gn, and EMT on the trigger day associated with the early pregnancy loss rate in the training cohort (both $P < 0.05$). These factors were included in the multivariate logistic regression analysis (Table 5) and used to develop the nomogram model (Fig. 2). Multivariate logistic regression analysis revealed that, except for Gn starting dosage and male age, all other factors were independent risk factors for early pregnancy loss.

Validation of the model

The accuracy of the prediction model was assessed by calculating the area under ROC curves (AUC), which was 0.761(95% CI: 0.680, 0.841) in the training cohort and 0.604(95% CI: 0.440, 0.767) in the validation cohort, showing that the model is effective (Fig. 3). The calibration plot revealed good predictive accuracy between actual and predicted probability in Fig. 4A. Furthermore, the decision curve analysis in Fig. 4B demonstrated that the prediction model was the higher line on the decision curve, indicating that the prediction model leads to a higher net benefit and greater clinical utility.

Discussion

The primary purpose of assisted reproductive technology (ART) is to help infertile couples in giving live birth. The most prevalent type of ART-associated pregnancy loss is early pregnancy loss, which puts patients under both the emotional and physical strain [9]. Age, embryo chromosomal abnormalities, immune dysfunction, and the history of previous miscarriages are the key factors affecting early pregnancy loss, with most studies emphasizing age as the predominant factor [10, 11]. The POSEIDON patients are distinguished by older age, lower ovarian reserve indicators, higher use of gonadotropins, and fewer retrieved embryos, all of which contribute to higher early pregnancy loss rates than the non-POSEIDON patients. However, no studies have specifically compared early pregnancy loss rates across the four POSEIDON groups. Our study looked into differences of early pregnancy rates among four groups. Significant differences were observed in clinical characteristics and laboratory data among the groups, with early pregnancy loss rates as follows: Group 4 (32.82%), Group 2 (23.31%), Group 3 (15.34%), and Group 1 (13.68%).

Table 4 Baseline characteristics of patients in POSEIDON group 4 in the validation and training cohorts

Item	validation cohort	training cohort	*χ2/Z* value	*P* value
No. of cases	59	136		
Female age (year)	38.02 ± 2.53	38.25 ± 2.57	t = −0.58	0.560
Male age (year)	37.49 ± 3.77	38.71 ± 5.73	t = −1.76	0.081
Type of infertility (%)			$\chi^2 = 0.16$	0.691
Primary	25.42 (15/59)	22.79 (31/136)		
Secondary	74.58 (44/59)	77.21 (105/136)		
Duration of infertility (year)	4.74 ± 4.05	4.41 ± 3.79	t = 0.55	0.582
Body mass index (kg/m^2)	23.63 ± 3.25	23.59 ± 3.45	t = 0.08	0.937
FSH	7.95 ± 3.30	8.37 ± 2.69	t = −0.93	0.353
AMH (ng/ml)	0.74 ± 0.31	0.78 ± 0.27	t = −1.08	0.281
Antral follicle count	5.98 ± 3.07	6.38 ± 2.96	t = −0.84	0.402
Controlled ovarian stimulation protocol (%)			$\chi^2 = 1.37$	0.242
GnRH-a protocol	28.81 (17/59)	37.50 (51/136)		
GnRH-A protocol	71.19 (42/59)	62.50 (85/136)		
Starting dosage of Gn (IU)	253.60 ± 56.24	258.55 ± 51.97	t = −0.60	0.552
Endometrial thickness on trigger day (mm)	10.54 ± 2.86	10.16 ± 2.51	t = 0.93	0.356
No. of oocytes retrieved	5.34 ± 3.14	5.02 ± 2.90	t = 0.68	0.495
No. of mature oocytes	4.58 ± 2.58	4.34 ± 2.59	t = 0.59	0.555
No. of 2PN oocytes	3.42 ± 2.34	3.36 ± 2.07	t = 0.19	0.850
Early pregnancy loss (%)			$\chi^2 = 0.62$	0.433
No	71.19 (42/59)	65.44 (89/136)		
Yes	28.81 (17/59)	34.56 (47/136)		
No. of embryos transferred (%)			$\chi^2 = 0.35$	0.554
1	38.98 (23/59)	34.56 (47/136)		
2	61.02 (36/59)	65.44 (89/136)		
Development days of transfer embryos (%)			$\chi^2 = 0.61$	0.436
Cleavage embryo	93.22 (55/59)	89.71 (122/136)		
Blastocyst	6.78 (4/59)	10.29 (14/136)		

Multivariate analysis was performed after adjusting confounding factors, and the results indicated that the early pregnancy loss rate was significantly higher in groups 2 and 4 than in groups 1 and 3. Patients over the age of 35 had a higher rate of early pregnancy loss than those under the age of 35, indicating that age plays a significant role. The number and quality of embryos and sperm decline with age [12, 13], implying that more attention should be paid in poor prognosis patients over the age of 35. Peuranpää et al. reported that AMH levels were not associated with early pregnancy loss in IVF/ICSI [14], whereas another study identified a correlation between low AMH levels and higher early pregnancy loss rates [15]. In our study, early pregnancy loss rates were comparable among young POSEIDON patients, regardless of ovarian reserve. A similar trend was observed in patients with advanced POSEIDON patients.

The risk factors for early pregnancy loss were investigated in the POSEIDON group 4, and the results revealed that the female age, AFC, and EMT on trigger day were important factors. The lack of differences in AMH levels could be attributed to the fact that age is a prominent factor among all factors. Women of advanced age face a higher risk of early pregnancy loss than younger women, which may be due to poor embryo maturity, chromosomal abnormalities in embryos, and poor embryo development potential, which may result in failed embryo implantation or development [16, 17]. In males, the forward motility of sperm and sperm DNA fragmentation worsened with age, resulting in a decline in sperm quality [18, 19]. Various studies have suggested that there is a relationship between ovarian reserve markers and chromosomal abnormalities in the products of conception [20, 21]. Bishop et al. reported that AFC was not significantly associated with pregnancy loss at any age [22]. However, our study demonstrated that lower AFC is associated with higher rates of early pregnancy loss in POSEIDON group 4, which may be related to chromosomal abnormalities.

Table 5 Logistic Regression analysis of early pregnancy loss in training cohort

Item	Early pregnancy loss rate			
	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Female age (year)	1.28 (1.10, 1.48)	0.001	1.25 (1.06, 1.48)	0.009
Male age (year)	1.07 (1.01, 1.14)	0.046	1.03 (0.96, 1.11)	0.416
Secondary infertility (%)	0.95 (0.41, 2.19)	0.902		
Duration of infertility (year)	0.97 (0.88, 1.07)	0.569		
Body mass index (kg/m^2)	1.02 (0.92, 1.13)	0.679		
AMH (ng/ml)	0.46 (0.12, 1.67)	0.235		
AFC	0.84 (0.74, 0.96)	0.013	0.86 (0.73, 0.99)	0.046
Controlled ovarian stimulation protocol (%)				
GnRH-a protocol	Reference			
GnRH-A protocol	1.68 (0.79, 3.56)	0.179		
Starting dosage of Gn (IU)	1.01 (1.01, 1.02)	0.027	1.01 (1.00, 1.02)	0.136
Endometrial thickness on trigger day (mm)	0.81 (0.69, 0.95)	0.009	0.80 (0.67, 0.96)	0.016
No. of oocytes retrieved	0.90 (0.79, 1.03)	0.122		
No. of mature oocytes	0.87 (0.75, 1.01)	0.074		
No. of 2PN	0.89 (0.74, 1.07)	0.228		
Blastocyst embryo transferred (%)	0.73 (0.22, 2.48)	0.620		
Two embryos transferred (%)	1.04 (0.49, 2.18)	0.927		

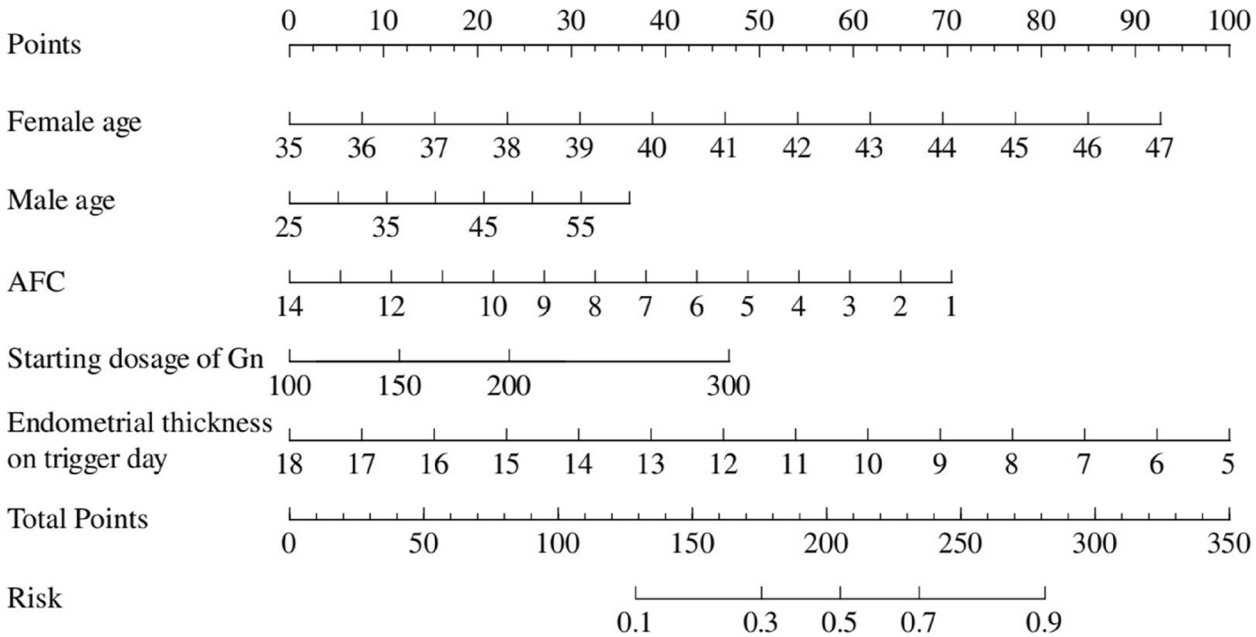

Fig. 2 A Nomogram to predict the risk of early pregnancy loss in POSEIDON group 4

Endometrial receptivity is assessed through diverse indicators, including morphological, molecular, and proteomic markers. Among these, endometrial thickness, a key morphological parameter, is the most widely used clinical metric due to its simplicity and ease of measurement [23]. Previous studies have demonstrated a correlation between endometrial thickness and reproductive outcomes, such as live birth and miscarriage rates [24, 25].Our study further reveals that in advanced-age patients with diminished ovarian reserve, increased endometrial thickness is significantly associated with reduced miscarriage rates, highlighting its importance as

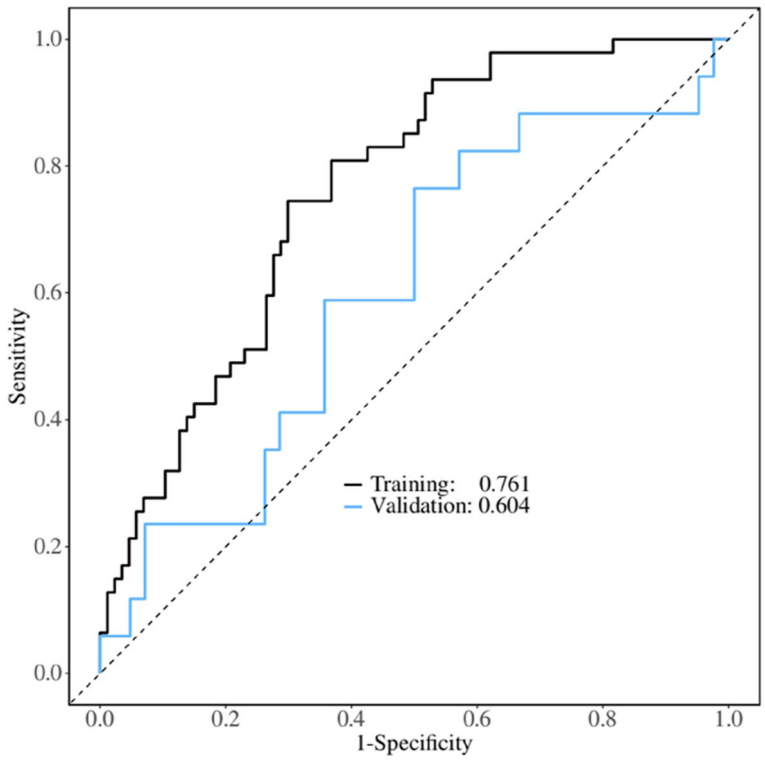

Fig. 3 The area under the receiver operating characteristic curve (AUC) of the training cohort was 0.761(95% CI: 0.680, 0.841). The AUC of the validation cohort was 0.604(95% CI: 0.440, 0.767)

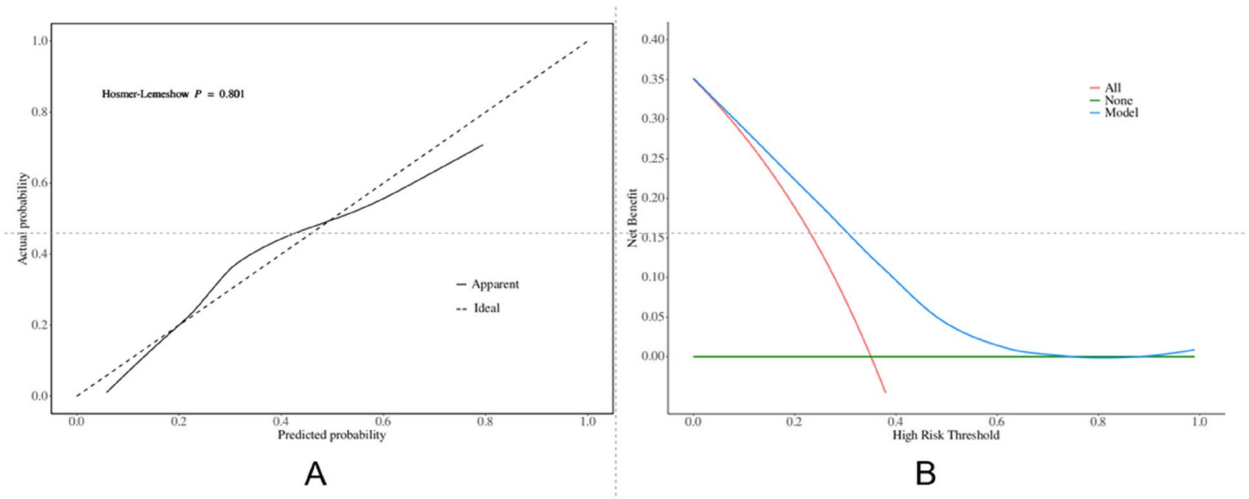

Fig. 4 **A** Calibration curve for the training cohort. Calibration curves were used to evaluate the calibration of the model. The horizontal axis is the predicted probability provided by this model, and the vertical axis is the observed incidence of pregnancy failure. The ideal line with a 45° slope represents a perfect prediction (the predicted probability equals the observed probability). **B** Decision curve analysis for the training cohort. Decision curve analysis of the model with the net benefit as the vertical axis and the threshold probability as the horizontal axis

a critical factor in optimizing reproductive outcomes for this population.

Our study successfully developed a model which can predict the risk of early pregnancy loss in POSEIDON group 4. Simultaneously, we plotted a nomogram to visualize our model. The AUC value of the combined prediction model reached 0.761, indicating the good discrimination of the model, and the validation confirmed the accuracy and feasibility of the model.

Compared with the Bologna criteria, the POSEIDON criteria provide more evidence for developing individualized reproductive strategies. In this study, we firstly explored the differences in early pregnancy loss after fresh cycles among the POSEIDON groups, and successfully constructed a prediction model in the POSEIDON group 4. However, there were still some limitations in this study: 1. It was a single-center retrospective study, so the patient source was fixed and the medication plan had bias; 2. Factors such as genetic factors, environmental interference, immunological factors, unhealthy lifestyles, and embryonic chromosomal abnormalities that also affect the probability of early pregnancy loss were not included in the study due to data source limitations; 3. The predictive discrimination of this model is acceptable, but stronger predictors must be identified in order to make it more precise.

In conclusion, the early pregnancy loss rate of first fresh cycles differs in patients divided by POSEIDON criteria. Patients in POSEIDON group 4 have the highest early pregnancy loss rate, followed by group 2, while patients in group 3 and 1 have the lowest rate first-time fresh cycles. We developed a prediction model that may predict whether early pregnancy loss occurs after first fresh cycles in POSEIDON group 4, which could be a useful guide for clinical decision-making.

Abbreviations

COS	Controlled ovarian stimulation
IVF-ET	In vitro fertilization-embryo transfer
ICSI	Intracytoplasmic sperm injection
POR	Poor ovarian response
AFC	Antral follicle count
AMH	Anti-Müllerian hormone
hCG	Human chorionic gonadotropin
GnRH	Gonadotropin-releasing hormone
ROC	Receiver operating characteristic
AUC	Area under receiver operating characteristic curve
BMI	Body mass index
FSH	Basal follicle-stimulating hormone
Gn	Gonadotropin
EMT	Endometrial thickness
2PN	Two pronuclei
ART	Assisted reproductive technology

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Authors' contributions
YJ conceived study design. CC and YL performed the data collection and statistical analysis. YJ edited the manuscript. CZ was responsible for providing data and guiding study. All authors contributed to the article and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The studies involving humans were approved by the Ethics Committee of Reproductive Medicine of Henan Provincial People's Hospital with the number SYSZ-LL-2021091501. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Consent for publication
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Competing interests
The authors declare no competing interests.

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