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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Endometrial thickness as a predictor of ectopic pregnancy in 1125 in vitro fertilization-embryo transfer cycles: a matched case–control study

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Abstract

Purpose The ectopic pregnancy (EP) rate after in vitro fertilization-embryo transfer (IVF-ET) is higher than after spontaneous conception. The reason for the increased risk of EP is not clear. We aimed to determine the risk factors associated with EP in patients undergoing IVF-ET.

Methods This was a 1:4 matched case–control study that enrolled 225 EP patients and 900 matched intrauterine pregnancy patients from the ART center of Northwest Women's and Children's Hospital from January 2014 to April 2018. Conditional logistic regression was used to analyze the association between risk factors and EP, and a receiver-operating characteristic (ROC) curve was generated for the predictors of EP.

Results Our findings showed that tubal factor (OR 1.61; 95% CI 1.12–2.31) and pelvic surgery other than cesarean section (OR 2.04; 95% CI 1.26–3.29) were associated with a higher risk of EP ($p = 0.001$). An endometrial thickness > 12 mm prior to embryo transfer (OR 0.27; 95% CI 0.13–0.56) and the number of transferable embryos (OR 0.71; 95% CI 0.65–0.78) were protective factors against EP ($p < 0.001$). The other factors did not have a significant effect on the probability of developing ectopic pregnancy. The area under the curve of the endometrial thickness and the number of transferable embryos for EP prediction were higher than those for tubal factor and pelvic surgery other than cesarean section.

Conclusions An endometrial thickness > 12 mm is a strong protective factor against ectopic pregnancy. Attention should be paid to women with specific characteristics who have undergone IVF-ET.

Keywords Ectopic pregnancy · In vitro fertilization · Risk factors · Endometrial thickness

Introduction

Ectopic pregnancy (EP) was defined as the extrauterine implantation of embryos. EP is a serious complication during pregnancy and can be life threatening if it is not diagnosed or treated in time. It is estimated that 95% of EP occur in fallopian tubes, but it may also occur in other locations, such as an interstitial pregnancy, cornual pregnancy, cervical pregnancy and ovarian pregnancy. Heterotopic pregnancy is a very rare form of ectopic pregnancy. The incidence of EP in spontaneous pregnancies is 1–2%, while in IVF cycles, its incidence can reach 0.9–11% [1, 2]. As in vitro fertilization (IVF) has been used more worldwide, the incidence of EP has substantially increased. Some research has found that IVF has been consistently associated with increased EP rates [3].

The risk factors of EP include abnormal fallopian tubes, previous tubal surgery and pelvic inflammatory disease [4]. Unlike in spontaneous pregnancy, women who become pregnant after IVF treatment undergo routine follow-ups, such as human chorionic gonadotropin (hCG) tests and transvaginal ultrasound; therefore, the early diagnosis of EP becomes possible. However, the underlying etiology of increased EP

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rates has not been demonstrated. Different methods of IVF may have an impact on the prevalence of EP. The stimulation protocol, embryo transfer strategies, and laboratory techniques have been proposed as possible contributors to EP after IVF. Strategies to decrease the rates of EP are limited; thus, it is important to identify accurate risk factors for EP.

The aim of the present study was to compare the characteristics of EP with intrauterine pregnancy. We designed a matched case–control study to identify risk factors and protective factors contributing to EP. In this retrospective study, we determined the predictive value in regard to clinical outcome after 225 ectopic pregnancies and 900 matched intrauterine pregnancies. The primary outcome was endometrial thickness. The secondary outcome was population characteristics.

Materials and methods

Study design and patients

This was a 1:4 case–control study of all patients who received IVF treatment between January 2014 and April 2018 at the Center for Assisted Reproductive Technology of Northwest Women's and Children's Hospital, China. Data were extracted from clinical records. The selection process for IVF cycles is illustrated in Fig. 1. From the initial 47,126 patients, we selected 20,685 patients with a positive hCG value (14 days after embryo transfer). Patients were eligible if they met the following criteria: (1) good physical and mental health (not disabled and without psychological disorders and mental illness); (2) IVF/intracytoplasmic sperm injection (ICSI) cycle; and (3) positive hCG test 14 days after an embryo transfer. The exclusion criteria were as follows: (1) biochemical pregnancy; (2) first trimester abortion; (3) cesarean scar pregnancy; (4) preimplantation genetic testing; and (5) oocyte recipient cycle. We further selected patients who completed cycles that resulted in a clinical pregnancy of either EP or IUP. We used the female age, male age, and residential area (urban or rural residence) to match women with intrauterine pregnancy. We use residential area (urban or rural residence) as a matching factor because previous study have shown minority and low-income women are at increased risk for occurrence of ectopic pregnancy [5]. Our study reduced bias of population selection by adjustment of matching residential area. The sample sizes were 225 and 900 in the EP and IUP groups, with a ratio of 1:4. The power was calculated to be 99% with a 95% confidence interval, assuming a mean (SD) endometrial thickness of 11.61 (2.38) and 10.51 (1.97) in the EP and IUP groups, respectively.

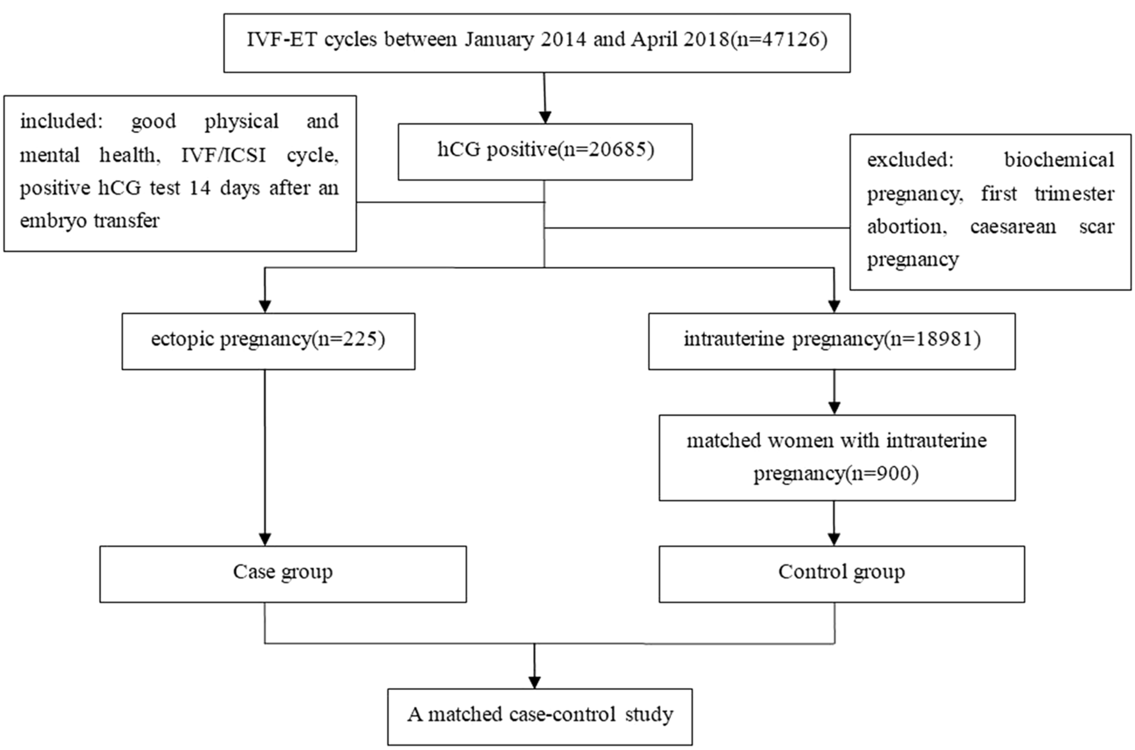

Fig. 1 Patient selection flowchart. *IVF-ET* in vitro fertilization-embryo transfer, *ICSI* intracytoplasmic sperm injection, *hCG* human chorionic gonadotropin

Definition of clinical outcomes

Biochemical pregnancy was defined as a pregnancy diagnosed only by the detection of beta hCG in the serum or urine. Intrauterine pregnancy was defined as a pregnancy with one or more gestational sacs in the uterus that are confirmed by ultrasound. Ectopic pregnancy was defined as a gestational sac outside the uterine cavity observed by ultrasound. Heterotopic pregnancy was defined as the coexistence of an intrauterine sac and ectopic pregnancy.

Risk factor selection

Based on previously published articles, the following risk factors were identified [6, 7]: body mass index (BMI); basal follicle-stimulating hormone (basal FSH); infertility type; gravidity; parity; previous EP; the type of infertility; previous pelvic surgery history; protocol; gonadotropin (Gn) dosage; the duration of Gn; endometrial thickness prior to embryo transfer; the number of oocytes; ICSI or IVF; the number of transferable embryos; the number of transferred embryos; the day of embryo transfer; fresh or frozen embryo transfer; and the hCG level after embryo transfer.

IVF treatment

For controlled ovarian hyperstimulation, the majority of patients underwent a gonadotropin-releasing hormone (GnRH) antagonist or GnRH agonist protocol. Ovarian stimulation started with daily injection of recombinant follicle-stimulating hormone (GONAL-f, Merck, Serono, Italy; Puregon, Organon, the Netherlands) and/or human menopausal gonadotropins (Menopur, Ferring, Germany). An hCG trigger was administered when at least three leading follicles had reached a diameter of 17 mm. Oocytes were retrieved 34–36 h later. Conventional IVF or ICSI was performed after oocyte retrieval. The presence of two pronuclei (2PN) was observed 16–18 h later, as the indicator of fertilization. Embryos were cultured in G5-medium (Vitrolife, Sweden). Three to five days after oocyte retrieval, only one or two high-quality embryos were transferred into the uterus.

All patients were followed up, and a pregnancy test with biochemical hCG was performed 14 days after ET. If serum hCG > 50 IU/L, luteal support was continued. Transvaginal ultrasound was performed 5 weeks after embryo transfer.

Ethical approval

The approval of the Institutional Review Board of Northwest Women's and Children's Hospital was obtained for this matched case–control study. All research was performed in accordance with relevant guidelines and regulations.

Statistical analysis

The descriptive data on participant characteristics were summarized using the mean and standard deviation for continuous variables. Counts and proportions were used for the categorical variables. Chi square tests were performed to compare the categorical variables. To compare the continuous variables among the groups, an analysis of covariance (normally distributed variables) or a Kruskal–Wallis test (abnormally distributed variables) were used. Univariate (Model 1) and multivariable (Model 2) conditional logistic regressions were used to analyze the relationship between the risk factors and ectopic pregnancy. A ROC curve was generated for the predictors of EP. The validity of the model was assessed by AUC. All of the analyses were performed with SPSS Version 13.0 (Statistical Package for Social Science, Inc., Chicago, IL, USA). The level of significance was set at $p<0.05$.

Results

A total of 225 ectopic pregnancies and 900 matched intrauterine pregnancies were included in this study. The baseline characteristics of the two groups are presented in Table 1. Due to the matching criteria employed in this study, there

Table 1 The baseline characteristics of the couples in the two groups

	EP ($n=225$)	IUP ($n=900$)	t	p value
Female age (years)	30.35 ± 4.15	30.26 ± 4.18	0.293	0.770
BMI (kg/m^2)	22.21 ± 2.96	22.27 ± 3.03	0.293	0.770
AFC	12.42 ± 6.02	10.38 ± 6.10	4.498	< 0.001
Basal FSH (IU/L)	6.97 ± 2.45	7.11 ± 3.31	0.555	0.579
Sperm concentration (*10^9/L)	58.74 ± 45.60	45.69 ± 37.32	4.454	0.057
Normal sperm morphology rate (%)	3.51	3.26	1.255	0.245
Infertility duration (years)	3.47 ± 2.42	3.62 ± 2.63	0.783	0.329

EP ectopic pregnancy, *IUP* intrauterine pregnancy, *BMI* body mass index, *AFC* antral follicle count, *basal FSH* basal follicle-stimulating hormone were no significant differences in the female and male ages. There were no differences in BMI, basal FSH, sperm concentration, normal sperm morphology rate or infertility duration between the two groups. Notably, the EP group had a higher antral follicle count (AFC) than that of the IUP group. The sites of ectopic pregnancy were as follows (Table 2): fallopian pregnancy (176, 78.22%), interstitial pregnancy (3, 1.33%), cornual pregnancy (16, 7.11%), cervical pregnancy (2, 0.89%), ovarian pregnancy (4, 1.78%) and heterotopic pregnancy (24, 10.67%).

To evaluate the effect of these risk factors on the incidence of ectopic pregnancy following IVF, we use univariate and multivariable logistic regression, restricting our analysis to the patients and clinical outcomes from these procedures. As listed in Table 3, no significant association between ectopic pregnancy and protocol, Gn dosage and duration, the number of oocytes retrieved, ICSI or IVF, the number of transferred embryos, the hCG level after embryo transfer, day 3/day 5 (D3/D5) embryo transfer and fresh/frozen embryo transfer could be found. BMI, basal FSH, infertility type, gravidity, parity and previous EP were not found to have a significant effect on the probability of developing ectopic pregnancy.

Pelvic surgery other than cesarean section (OR 2.07; 95% CI 1.34–3.19) and tubal factor (OR 1.61; 95% CI 1.12–2.31) were associated with a higher risk of EP ($p = 0.001$). The endometrial thickness > 12 mm (OR 0.27; 95% CI 0.13–0.56) prior to embryo transfer and the number of transferable embryos (OR 0.71; 95% CI 0.65–0.78) were protective factors against EP ($p < 0.001$). A summary of primary and secondary outcomes is shown in Table 4.

As listed in Table 5 and Fig. 2, we calculated the area under the curve (AUC) of the ROC, and found that the endometrial thickness and number of transferable embryos for EP prediction were higher than those for tubal factor and pelvic surgery other than cesarean section (the number of transferable embryos: AUC 0.68, 95% CI 0.64–0.72; endometrial thickness: AUC 0.60, 95% CI 0.56–0.64; pelvic surgery other than cesarean section: AUC 0.58, 95% CI 0.54–0.63; and tubal factor: AUC 0.55, 95% CI 0.51–0.59). The AUC of all four factors was 0.73 (95% CI 0.69–0.76).

Table 2 Distribution of the sites of EP

	Number	Percentage (%)
Fallopian pregnancy	176	78.22
Interstitial pregnancy	3	1.33
Cornual pregnancy	16	7.11
Cervical pregnancy	2	0.89
Ovarian pregnancy	4	1.78
Heterotopic pregnancy	24	10.67

EP ectopic pregnancy

Discussion

IVF has been widely used as a useful procedure for couples suffering from infertility. Although IVF allows embryos to be transferred into the uterine cavity, ectopic pregnancy is more common following IVF than in natural pregnancy and is a complication of IVF. The reason for the increased risk of EP following IVF remains inadequately understood, and measures that can be taken to decrease the incidence of EP are limited. We designed this matched case–control study, working backwards from the outcome to exposure, to identify risk factors related to EP in women undergoing IVF, with the hope that we could provide suggestions for EP prevention. To our knowledge, this is the largest single-center study of its kind.

This retrospective study found that tubal factor and pelvic surgery other than cesarean section were independent risk factors for developing EP following IVF. In contrast, endometrial thickness > 12 mm prior to embryo transfer and the number of transferable embryos were protective factors against EP. The other factors were not associated with an increased risk of EP in this study.

It can be speculated that the increased risk of ectopic pregnancy could be due to uterine peristalsis wave frequency, which may dislodge the uterus. This hypothesis is supported by one study [8], which indicated that the supraphysiologic hormone levels achieved with controlled ovarian hyperstimulation can increase the EP rate [9]. However, we failed to find correlations between fresh/frozen embryo transfer and EP. It could be speculated that the reason for this is that the best embryos are used for fresh embryo transfer, and the remaining embryos are frozen to be transferred later. It can be assumed that embryos of poorer quality have a lower chance of implanting in the uterine cavity and may have a higher chance of implanting outside the uterus. A greater number of transferable embryos are thought to be related to good ovarian reserve and with better embryo quality. Good embryo quality is associated with a lower ectopic pregnancy rate [10]. Thus, patients with more transferable embryos have a lower chance of EP.

Extended in vitro culture until D5 has been increasingly used to increase the pregnancy rate in IVF. Some articles have noted that D5 embryo transfer can reduce EP risk compared with that at D3 [11, 12]. However, our study observed no difference between D3 and D5 embryo transfer in regard to the EP rate, which is in accordance with a meta-analysis performed in 2009 [13]. Additionally, tubal factor infertility has been regarded as an important risk factor for EP [13, 14], which is in accordance with our study. Women with infertility who have undergone pelvic surgery other than cesarean section usually suffer

Table 3 Univariate analysis and multivariate analysis of the risk factors of ectopic pregnancy

	Model 1		Model 2	
	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Protocol, *n* (%)				
Agonist	1.00		1.00	
Antagonist	0.52 (0.29, 0.92)	0.024	0.60 (0.33, 1.06)	0.079
Others	0.45 (0.22, 0.93)	0.031	1.16 (0.59, 2.32)	0.663
Gn dosage (IU)	1.00 (1.00, 1.00)	0.496	1.00 (1.00, 1.00)	0.992
Duration of Gn (days)	0.98 (0.92, 1.04)	0.512	1.03 (0.93, 1.14)	0.595
Endometrial thickness prior to ET (mm)				
< 8	1.00		1.00	
8–12	0.70 (0.39, 1.24)	0.216	0.69 (0.35, 1.35)	0.280
> 12	0.28 (0.15, 0.28)	< 0.001	0.267 (0.13, 0.56)	< 0.001
No. of oocytes (*n*)	0.98 (0.96, 1.00)	0.063	1.03 (0.99, 1.06)	0.121
ICSI (*n*)				
No	1.00		1.00	
Yes	0.86 (0.61, 1.21)	0.391	0.94 (0.63, 1.412)	0.765
No. of transferable embryos (*n*)	0.77 (0.71, 0.83)	< 0.001	0.71 (0.65, 0.78)	< 0.001
No. of transferred embryos (*n*)	1.09 (0.78, 1.51)	0.621	1.10 (0.75, 1.61)	0.634
Day of embryo transfer				
Day 3	1.00		1.00	
Day 5	1.02 (0.76, 1.37)	0.892	1.45 (0.80, 1.64)	0.473
Fresh or frozen embryo transfer				
Fresh	1.00		1.00	
Frozen	1.03 (0.77, 1.38)	0.858	0.93 (0.66, 1.33)	0.705
hCG level after embryo transfer (IU/L)	1.00 (1.00, 1.00)	0.881	1.00 (1.00, 1.00)	0.510
BMI (kg/m^2)	0.99 (0.95, 1.04)	0.770	1.00 (0.95, 1.06)	0.974
Basal FSH (IU/L)	0.99 (0.94, 1.04)	0.579	0.95 (0.89, 1.02)	0.158
Infertility type				
Primary	1.00		1.00	
Secondary	1.25 (0.93, 1.68)	0.134	1.18 (0.45, 3.09)	0.734
Gravidity, *n* (%)				
0	1.00		1.00	
≥ 1	1.28 (0.96, 1.72)	0.097	0.85 (0.32, 2.25)	0.740
Parity, *n* (%)				
0	1.00		1.00	
≥ 1	1.08 (0.69, 1.67)	0.741	0.86 (0.46, 1.59)	0.623
Previous EP, *n* (%)				
No	1.00		1.00	
Yes	1.23 (0.81, 1.87)	0.331	0.77 (0.43, 1.37)	0.366
Type of infertility, *n* (%)				
Non tubal factor	1.00		1.00	
Tubal factor	1.52 (0.49, 0.89)	0.006	1.61 (1.12, 2.31)	0.010
Previous pelvic surgery history, *n* (%)				
No	1.00		1.00	
Cesarean section	1.58 (0.86, 2.90)	0.143	1.67 (0.74, 3.73)	0.214
Other pelvic surgery	2.20 (1.59, 3.06)	< 0.001	2.07 (1.34, 3.19)	0.001

Univariate (Model 1) and multivariable (Model 2) conditional logistic regressions were used to analyze the relationship between the risk factors and ectopic pregnancy. The BMI, basal FSH, infertility type, gravidity, parity, previous EP, the type of infertility, previous pelvic surgery history, protocol, Gn dosage, the duration of Gn, the endometrial thickness prior to embryo transfer, the number of oocytes, ICSI, the number of transferable embryos, the number of transferred embryos, the day of the embryo transfer, fresh/frozen embryo transfer and hCG level after embryo transfer were adjusted in Model 2

OR odds ratio, *CI* confidence interval, *ET* embryo transfer

Table 4 Summary of primary outcome and secondary outcome

	P value	Adjusted OR [95% CI]
Primary outcome		
Endometrial thickness > 12 mm prior to ET (vs < 8 mm)	< 0.001	0.267 (0.13, 0.56)
Number of transferable embryos	< 0.001	0.71 (0.65, 0.78)
Secondary outcome		
Tubal factor	0.010	1.61 (1.12, 2.31)
Pelvic surgery other than cesarean section (vs no pelvic surgery)	0.001	2.07 (1.34, 3.19)

ET embryo transfer

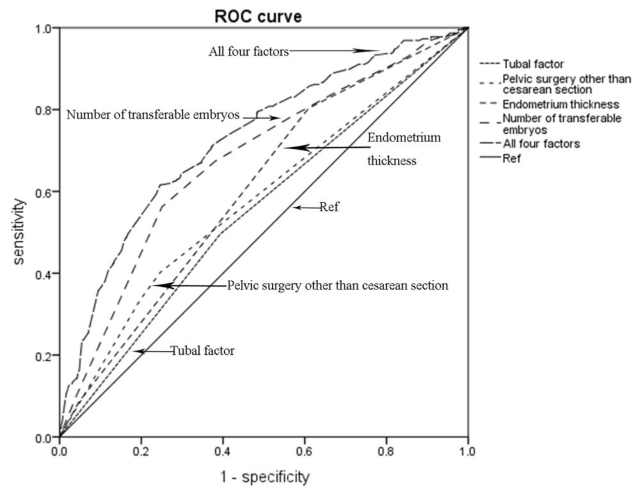

Fig. 2 ROC curve. *ROC* receiver-operating characteristic

from tubal obstruction, pelvic inflammation, tubal ligation and other conditions, all of which indicate tubal damage or malfunction and have a predominant role in the pathogenesis of the development of EP [15].

Endometrial receptivity plays an important role in embryo implantation. A thinner endometrium indicates poorer endometrial receptivity, with ectopic implantation occurring following the failure of the normal biological interactions with the endometrium [4]; however, some research contradicts this viewpoint [16]. Similarly, elevated hormone levels during IVF might affect endometrial receptivity, leading to an increased risk of EP. Our findings concur to some extent with a study that indicated that increased endometrial thickness predicts normal IUP in patients who present with vaginal bleeding and pregnancy of an unknown location [17] in the first trimester. Moreover, there is an association between a thin endometrium (< 8 mm) on the day of hCG administration and a reduced pregnancy rate [18]. It was hypothesized that because the endometrial decidual reaction relies on the gestational hormonal environment, a decreased endometrial thickness in early pregnancy may be predictive of an abnormal pregnancy and vice versa [19]. The timing of measuring the endometrial thickness varies from the day of hCG trigger to the time of a positive hCG test. Our study used an early time point, performing the assessment of the endometrial thickness on the day of the hCG trigger, and this had the advantage of providing an early predictive value of EP and confirmed that thin endometrial thickness was the cause not the effect of EP.

The cutoff point for endometrial thickness is still debated. One prospective study indicated that the best cutoff point as a predictor of IUP was 10 mm, with a sensitivity and specificity of 93.6% and 34.5%, respectively [20]. One retrospective study found that non-IUP pregnancy was associated with an endometrial thickness < 8 mm [17]. In another study, EP was associated with thin endometrial thickness compared with women with normal pregnancies (9.5 ± 5.7 mm vs 12.4 ± 5.9 mm) [21]. As in our study, compared with an endometrial thickness < 8 mm, an endometrial thickness between 8 and 12 mm did not increase the rate of IUP; however, an endometrial thickness > 12 mm was a strong protective factor against EP.

This study had some limitations. First, this was an observational study in which the causality of the endometrial thickness and EP could not be established. Additionally, although we used a matching technique and multivariable logistic regression to control for confounders between the two groups, the findings of our study might be potentially

Table 5 ROC curve results

Factors	Area under the curve (AUC)	95% CI	*P* value
Tubal factor	0.55	0.51–0.59	0.018
Pelvic surgery other than cesarean section	0.58	0.54–0.63	< 0.001
Endometrial thickness > 12 mm prior to ET	0.60	0.56–0.64	< 0.001
Number of transferable embryos	0.68	0.64–0.72	< 0.001
All four factors	0.73	0.69–0.76	< 0.001

All four factors included tubal factor, pelvic surgery other than cesarean section, endometrial thickness > 12 mm prior to ET, and number of transferable embryos

ROC receiver-operating characteristic

confounded by unmeasured or unidentified covariates. Finally, all data come from IVF treatment from a single center, and the results should be confirmed by a larger sample multicenter study.

In conclusion, the results of our study illustrated that tubal factor and pelvic surgery other than cesarean section were independent risk factors for developing EP following IVF. A decreased risk of EP was found in patients with an endometrial thickness > 12 mm prior to embryo transfer and with more transferable embryos.

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Author contributions XL: manuscript writing. PQ: data analysis. HB: protocol development. WS: protocol development. JS: protocol development.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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