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Original Research

Association of the Number of Embryos Transferred with Ectopic Pregnancy after Embryo Transfer in Patients with Salpingectomy or Proximal Tubal Occlusion

Caihe Wen[1,2,†], Yuan Zhang[1,†], Xinru Xia[1], Xiang Ma[1], Yundong Mao[1], Dao Wu Wang[1,*], Jiayin Liu[1,*]

[1]State Key Laboratory of Reproductive Medicine, the Center for Clinical Reproductive Medicine, The First Affiliated Hospital of Nanjing Medical University, 210029 Nanjing, Jiangsu, China
[2]The Department of Obstetrics and Gynecology, Hangzhou Women's Hospital, 310008 Hangzhou, Zhejiang, China
*Correspondence: david37212@hotmail.com (Daowu Wang); jyliu_nj@126.com (Jiayin Liu)
[†]These authors contributed equally.
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Abstract

Background: With the prevalence of assisted reproductive technology (ART), the incidence of ectopic pregnancy (EP) is increasing, especially in patients with salpingectomy or proximal tubal occlusion. **Methods**: A total of 11,609 women who were undergoing ART and had undergone salpingectomy or proximal tubal occlusion, and 5388 women who achieved a clinical pregnancy were included in the study. Statistical analysis was used to determine whether the number of embryos transferred was associated with EP. **Results**: Both the number of embryos transferred and the day of embryo transfer differed significantly between those with and without EP ($p < 0.05$), while the number of embryos transferred was associated with interstitial pregnancy (IP) ($p < 0.05$) in those undergoing frozen-thawed embryo transfer (ET) cycles. Following multivariate modeling, the odds of having an EP in women undergoing frozen-thawed ET cycles increased with the number of embryos transferred (odds ratio [OR] 2.003, 95% confidence interval [95% CI] 1.036–3.876). **Conclusions**: The embryo transfer number was considered a risk factor for EP in patients undergoing frozen-thawed ET who had undergone salpingectomy or proximal tubal occlusion.

Keywords: interstitial pregnancy; ectopic pregnancy; IVF-ET; numbers of embryos transferred; days of embryo transfer

1. Introduction

As a complication of assisted reproductive technology (ART), ectopic pregnancy (EP) is a serious consequence on women's health. In the United States [1], from 2001 to 2011, the incidence of EP after ART ranged from 2.0% to 1.6%. It has also been reported that the incidence of EP after *in vitro* fertilization-embryo transfer (IVF-ET) is between 2.1 and 8.6% [2]. The widely accepted risk factors for EP include tubal factor infertility, the number of embryos transferred, embryo transfer in a fresh cycle, and day 3 embryo transfer [3–5]. Tubal factor infertility significantly increases the risk of EP by 25% [1].

In addition, the incidence of some rare EPs, such as interstitial pregnancies (IPs) and heterotopic pregnancies (HPs) (both an ectopic and intrauterine pregnancy at the same time [6]), is also increasing. These conditions are difficult to diagnose and treat after ART. IP refers to an EP in which implantation occurs in the interstitial duct, which is the fallopian tubal segment that traverses through the myometrium. Some IPs may last up to 7–16 weeks of gestation, at which time rupture can result in massive bleeding and high mortality [7]. Some recent studies have indicated that the incidence of IP is 0.8% per pregnancy and 35.5% in all EP cases after ART [8]. The mortality rate of IP is 2.5%, which is seven times greater than that of EP [9–11].

The incidence of EP from IVF-ET is increased 2.5- to 5.0-fold compared with that of ectopic spontaneous pregnancy [3]. Similarly, the incidence of IP is lower in natural pregnancy but more common after ART [8]. The reasons for this are unclear. In our original research, we analyzed the clinical data of 21 patients with IP after ART. The results showed that 90.48% of the IP patients had a history of tubal-related surgery, among whom 78.95% had unilateral or bilateral tubal resection or proximal tubal occlusion. Approximately 85.71% of the IP patients had undergone double embryo transfer. Therefore, we hypothesized that there was an increased incidence of EP and IP after ART in patients with a history of tubal surgery, especially in those who had undergone salpingectomy or proximal tubal occlusion. The number of embryos transferred may be a related risk factor.

The purpose of our study was to investigate the effect of different numbers of transferred embryos on the EP outcome after ET in patients who had undergone salpingectomy or proximal tubal occlusion, especially regarding the related factors of IP.

2. Materials and Methods

The clinical outcomes of 11,609 patients undergoing IVF-ET in the Centre for Clinical Reproductive Medicine, The First Affiliated Hospital of Nanjing Medical University, from January 2005 to November 2017 were retrospectively analyzed. Among them, 5388 women who achieved a clinical pregnancy were included in the study. The inclusion criteria were as follows: Patients who had a history of at least one unilateral/bilateral salpingectomy or proximal tubal occlusion and patients with a clinical pregnancy that was obtained after ART. The exclusion criterion was as follows: Patients who had not undergone salpingectomy or proximal tubal occlusion.

Once IVF treatment was initiated in our clinical center, the patients' baseline characteristics, medical history, IVF process data, and follow-up pregnancy outcomes were routinely captured in the reproductive medicine clinical center database. Trained nurses continued to collect information about the patient's treatment during the entire course of treatment until the end of each treatment with a clinical outcome.

The selection process of the patients is shown in Fig. 1. A clinical pregnancy was defined as the ultrasound observation of one or more pregnancy sacs after ET, including intrauterine and extrauterine pregnancies. A clinical intrauterine pregnancy was diagnosed as one or more pregnancy sacs in the uterus. EP was defined as one or more pregnancy sacs outside the uterus, including a clinical HP. Ipsilateral EP on a tubal remnant, contralateral EP and bilateral IP can occur after salpingectomy.

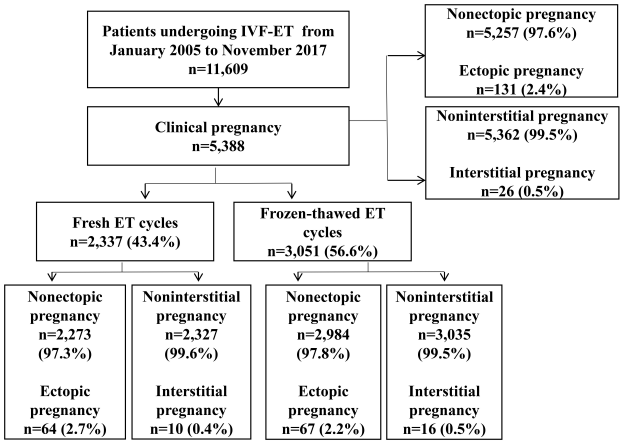

Fig. 1. Patient selection flowchart.

The diagnosis criteria of IP under ultrasound were as follows: no pregnancy sac in the uterus, a gestational sac located laterally in the interstitial (intramural) part of the tube and surrounded by thin (<5 mm) myometrial tissue, and the presence of the "interstitial line sign" [12,13]. EP and IP were diagnosed by laparoscopic surgery or ultrasound.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2018-SR-063). This study was retrospective, so informed consent was not needed.

3. Statistical Analysis

Descriptive statistics (frequencies and means) were initially performed. Before analysis, continuous variables (maternal age, infertility duration, body mass index (BMI), antral follicle count, follicle-stimulating hormone (FSH) level) were examined to determine compliance with normal distribution. Since these variables were not normally distributed, we used the Mann–Whitney U test to examine the association between these variables in participants. Categorical variables were analyzed with chi-square tests. If the expected frequencies were less than 5, Fisher's exact test was used for the analysis. Variables with a $p < 0.05$ were included in multivariate logistic regression analysis. Statistical Package for Social Science (SPSS) 25.0 (IBM, Armonk, New York, USA) was used for statistical analysis. A value of $p < 0.05$ was considered statistically significant.

4. Results

Among the 11,609 patients undergoing IVF-ET, 5388 women achieved clinical pregnancy in our study. The overall clinical pregnancy rate was 46.4%. Among these 5388 women, 131 women (2.4%) had an EP, and 26 women (0.5%) had an IP. The characteristics of the patients are shown in Table 1.

To explore the potential risk factors for EP and IP, the baseline and clinical characteristics were analyzed. The results are shown in Tables 2,3. Maternal age, infertility duration, BMI, antral follicle count, FSH level, type of infertility and type of embryo transfer cycle were not significantly different between the two groups ($p > 0.05$). The day of embryo transfer and number of embryos transferred were significantly different between the nonectopic pregnancy and ectopic pregnancy groups ($p < 0.05$). However, only the number of embryos transferred was significantly different between the noninterstitial and interstitial pregnancy groups ($p < 0.05$).

4.1 Fresh ET Cycles

A total of 2337 women conceived after undergoing fresh ET cycles. The EP rate and IP rate were 2.7% and 0.4%, respectively, for women undergoing fresh ET cycles. The baseline and clinical characteristics after fresh ET cycles are displayed in Tables 4,5. Maternal age, infertility duration, BMI, antral follicle count, FSH level, the type of infertility, the day of embryo transfer and the number of embryos transferred were not significantly different between the nonectopic pregnancy and ectopic pregnancy groups or the noninterstitial and interstitial pregnancy groups ($p > 0.05$).

Table 1. Overall descriptive statistics for patients.

	No.	M (P25, P75)/% (95% CI)
Maternal age (yrs.)	5388	31.0 (28.0, 34.0)
Infertility duration (yrs.)	4885	3.0 (2.0, 5.0)
BMI, kg/m^2	5309	21.9 (20.2, 23.9)
Antral follicle count, n (%)	5011	12.0 (9.0, 17.0)
FSH level, IU/L	5251	7.2 (6.1, 8.7)
Type of infertility, n (%)		
Primary infertility	1682	31.2 (30.0–32.5)
Secondary infertility	3706	68.8 (67.5–70.0)
Type of embryo transfer cycle, n (%)		
Fresh embryo transfer cycles	2337	43.4 (42.0–44.7)
Frozen-thawed embryo transfer cycles	3051	56.6 (55.3–58.0)
Number of embryos transferred n (%)		
1	1919	35.6 (34.3–36.9)
2	3469	64.4 (63.1–65.7)
Day of embryo transfer, n (%)		
2–4	4542	87.1 (86.2–88.0)
5–6	671	12.9 (12.0–13.8)
EP, n (%)		
No	5257	97.6 (97.1–98.0)
Yes	131	2.4 (2.0–2.9)
IP, n (%)		
No	5362	99.5 (99.3–99.7)
Yes	26	0.5 (0.3–0.7)

yrs., years; M, median; 95% CI, 95% confidence interval.

Table 2. Comparison between participants with and without ectopic pregnancy.

	Nonectopic pregnancy	Ectopic pregnancy	Z/χ^2 score	p
Maternal age (yrs.)	31.1 (28.0, 34.0)	31.0 (28.0, 34.0)	0.163	0.871
Infertility duration (yrs.)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	0.696	0.486
BMI, kg/m^2	22.0 (20.3, 24.0)	21.8 (20.0, 23.4)	1.617	0.106
Antral follicle count, n (%)	12.0 (9.0, 17.0)	14.0 (9.0, 18.0)	0.835	0.404
FSH level, IU/L	7.3 (6.1, 8.7)	6.9 (5.7, 9.4)	0.857	0.391
Type of infertility, n (%)				
Primary infertility	1642 (31.2)	40 (30.5)	0.029	0.864
Secondary infertility	3615 (68.8)	91 (69.5)		
Type of embryo transfer cycle, n (%)				
Fresh embryo transfer cycles	2273 (43.2)	64 (48.9)	1.642	0.200
Frozen-thawed embryo transfer cycles	2984 (56.8)	67 (51.1)		
Day of embryo transfer, n (%)				
2–4	4419 (87.0)	123 (93.9)	5.483	0.019
5–6	663 (13.0)	8 (6.1)		
Number of embryos transferred, n (%)				
1	1887 (35.9)	32 (24.4)	7.33	0.007
2	3370 (64.1)	99 (75.6)		

yrs., years.

4.2 Frozen-Thawed ET Cycles

A total of 3051 women conceived after undergoing frozen-thawed ET cycles. The EP rate and IP rate were 2.2% and 0.5%, respectively, in women undergoing frozen-thawed ET cycles.

Table 6 shows that the maternal age, infertility duration, BMI, antral follicle count, FSH level and type of infertility were not significantly different between the nonectopic pregnancy and ectopic pregnancy groups in frozen-thawed ET cycles ($p > 0.05$). The day of embryo transfer and number of embryos transferred were significantly different between the nonectopic pregnancy and ectopic pregnancy groups in women undergoing frozen-thawed ET cycles ($p < 0.05$).

Table 3. Comparison between participants with and without interstitial pregnancy.

	Noninterstitial pregnancy	Interstitial pregnancy	Z/χ^2 score	p
Maternal age (yrs.)	31.1 (28.0, 34.0)	30.5 (27.8, 33.5)	0.128	0.898
Infertility duration (yrs.)	3.0 (2.0, 5.0)	2.0 (2.0, 5.5)	0.745	0.456
BMI, kg/m^2	21.9 (20.2, 23.9)	20.7 (19.5, 23.0)	1.704	0.088
Antral follicle count, n (%)	12.0 (9.0, 17.0)	11.0 (8.0, 17.0)	0.389	0.698
FSH level, IU/L	7.2 (6.1, 8.7)	7.3 (5.9, 10.1)	0.510	0.610
Type of infertility, n (%)				
Primary infertility	1674 (31.2)	8 (30.8)	0.002	0.961
Secondary infertility	3688 (68.8)	18 (69.2)		
Type of embryo transfer cycle, n (%)				
Fresh embryo transfer cycles	2327 (43.4)	10 (38.5)	0.257	0.612
Frozen-thawed embryo transfer cycles	3035 (56.6)	16 (61.5)		
Day of embryo transfer, n (%)				
2–4	4517 (87.1)	25 (96.2)	1.898	0.168
5–6	670 (12.9)	1 (3.8)		
Number of embryos transferred, n (%)				
1	1915 (35.7)	4 (15.4)	4.663	0.031
2	3447 (64.3)	22 (84.6)		

yrs., years.

Table 4. Comparison between participants with and without ectopic pregnancy in women undergoing fresh ET cycles.

	Nonectopic pregnancy	Ectopic pregnancy	Z/χ^2 score	p
Maternal age (yrs.)	30.0 (28.0, 33.0)	31.0 (28.3, 33.0)	0.990	0.322
Infertility duration (yrs.)	3.0 (2.0, 5.0)	3.0 (1.0, 5.0)	0.491	0.623
BMI, kg/m^2	21.9 (20.2, 23.8)	21.8 (19.6, 23.4)	0.801	0.423
Antral follicle count, n (%)	12.0 (9.0, 16.0)	12.0 (8.0, 15.3)	0.872	0.383
FSH level, IU/L	7.3 (6.1, 8.7)	6.9 (5.6, 8.7)	1.301	0.193
Type of infertility, n (%)				
Primary infertility	684 (30.1)	19 (29.7)	0.005	0.944
Secondary infertility	1859 (69.9)	45 (70.3)		
Day of embryo transfer, n (%)				
2–4	2112 (98.4)	63 (98.4)	0.000	1.000
5–6	34 (1.6)	1 (1.6)		
Number of embryos transferred, n (%)				
1	583 (25.6)	15 (23.4)	0.16	0.689
2	1690 (74.4)	49 (76.6)		

yrs., Years.

Table 7 shows that the maternal age, infertility duration, BMI, antral follicle count, FSH level, type of infertility and day of embryo transfer were not significantly different between the noninterstitial and interstitial pregnancy groups in women undergoing frozen-thawed ET cycles ($p > 0.05$). The number of embryos transferred was significantly different between the noninterstitial and interstitial pregnancy groups in women undergoing frozen-thawed ET cycles ($p < 0.05$).

As shown in Table 8, to evaluate the impact of these risk factors on the occurrence of EP, the day of embryo transfer and number of embryos transferred were included in the multivariate logistic regression analysis. The day of embryo transfer ($p > 0.05$) had no correlation with the occurrence of EP in the women undergoing frozen-thawed ET cycles. The risk of EP in women undergoing frozen-thawed ET cycles with single embryo transfer was lower than that of those with double embryo transfer (OR = 2.003, 95% CI = 1.036–3.876).

5. Discussion

During ART treatment, fallopian tube factors remain a major risk factor for EP, especially in women with a prior history of fallopian tube surgery [14]. Patients who undergo a conservative operation or tubal microsurgery have a higher incidence of EP after assisted pregnancy [15]. Some researchers also supposed that salpingectomy and tubal infertility were the most important variables affecting the risk of IP [13]. Therefore, it is of great significance to find effective intervention measures to reduce the risk of EP for

Table 5. Comparison between participants with and without interstitial pregnancy in women undergoing fresh ET cycles.

	Noninterstitial pregnancy	Interstitial pregnancy	Z/χ^2 score	*p*
Maternal age (yrs.)	30.0 (28.0, 33.0)	29.5 (27.0, 32.0)	0.398	0.691
Infertility duration (yrs.)	3.0 (2.0, 5.0)	2.0 (1.0, 7.5)	0.654	0.513
BMI, kg/m^2	21.9 (20.2, 23.9)	21.9 (18.6, 25.5)	0.462	0.644
Antral follicle count, n (%)	12.0 (9.0, 16.0)	11.0 (7.5, 13.5)	1.147	0.251
FSH level, IU/L	7.3 (6.1, 8.7)	6.8 (5.4, 10.9)	0.135	0.893
Type of infertility, n (%)				
Primary infertility	700 (30.1)	3 (30.0)	0.000	1.000
Secondary infertility	1627 (69.9)	7 (70.0)		
Day of embryo transfer, n (%)				
2–4	2165 (98.4)	10 (100.0)	-	1.000*
5–6	35 (1.6)	0 (0.0)		
Number of embryos transferred, n (%)				
1	596 (25.6)	2 (20.0)	0.002	0.966
2	1731 (74.4)	8 (80.0)		

yrs., Years; *Fisher's exact test.

Table 6. Comparison between participants with and without ectopic pregnancy in women undergoing frozen-thawed ET cycles.

	Nonectopic pregnancy	Ectopic pregnancy	Z/χ^2 score	*p*
Maternal age (yrs.)	31.0 (28.0, 34.0)	31.0 (28.0, 33.0)	0.563	0.573
Infertility duration (yrs.)	3.0 (2.0, 6.0)	3.0 (2.0, 5.0)	0.477	0.633
BMI, kg/m^2	21.9 (20.3, 23.9)	21.6 (20.0, 22.9)	1.471	0.141
Antral follicle count, n (%)	13.0 (9.0, 18.0)	15.0 (10.0, 19.3)	1.938	0.053
FSH level, IU/L	7.2 (6.0, 8.7)	7.1 (5.9, 9.4)	0.001	0.999
Type of infertility, n (%)				
Primary infertility	958 (32.1)	21 (31.3)	0.017	0.895
Secondary infertility	2026 (67.9)	46 (68.7)		
Day of embryo transfer, n (%)				
2–4	2307 (78.6)	60 (89.6)	4.727	0.030
5–6	629 (21.4)	7 (10.4)		
Number of embryos transferred, n (%)				
1	1304 (43.7)	17 (25.4)	8.965	0.003
2	1680 (56.3)	50 (74.6)		

yrs., Years.

Table 7. Comparison between participants with and without interstitial pregnancy in women undergoing frozen-thawed ET cycles.

	Noninterstitial pregnancy	Interstitial pregnancy	Z/χ^2 score	*p*
Maternal age (yrs.)	31.0 (28.0, 34.0)	31.5 (28.3, 35.0)	0.443	0.658
Infertility duration (yrs.)	3.0 (2.0, 6.0)	2.0 (2.0, 5.0)	0.441	0.659
BMI, kg/m^2	21.9 (20.3, 23.9)	20.7 (20.0, 21.8)	1.815	0.069
Antral follicle count, n (%)	13.0 (9.0, 18.0)	12.5 (8.0, 20.0)	0.387	0.699
FSH level, IU/L	7.2 (6.0, 8.7)	7.7 (6.1, 9.8)	0.766	0.444
Type of infertility, n (%)				
Primary infertility	974 (32.1)	5 (31.3)	0.005	0.943
Secondary infertility	2601 (67.9)	11 (68.8)		
Day of embryo transfer, n (%)				
2–4	2352 (78.7)	15 (93.8)	1.343	0.247
5–6	635 (21.3)	1 (6.2)		
Number of embryos transferred, n (%)				
1	1319 (43.5)	2 (12.5)	6.214	0.013
2	1716 (56.5)	14 (87.5)		

yrs., Years.

Table 8. Variables associated with EP following multivariate analysis in women undergoing frozen-thawed ET cycles.

	b-value	*p*	OR (95% CI)
Day of embryo transfer, n (%)			
2–4*	–0.344	0.472	0.709 (0.278–1.810)
5–6			
Number of embryos transferred, n (%)			
1*	0.695	0.039	2.003 (1.036–3.876)
2			

*control group.

this population experiencing infertility. In our original research, a history of salpingectomy or proximal tubal occlusion and the number of embryos transferred were suggested to be risk factors for IP. Therefore, we specifically analyzed the clinical outcome during IVF treatment for patients who had undergone salpingectomy or proximal tubal occlusion. We found that the incidence of EP was 2.4% (131/5388) in the patients who obtained a clinical pregnancy in our study, which is higher than the average incidence of EP after ART (range between 1.38 and 2.10% of clinical pregnancies) [3].IP is a rare condition, accounting for 2–4% of all tubal pregnancies after ART [11]. However, IPs accounted for 19.85% of the EPs in our study. The reason may be that the electrocoagulation-damaged fallopian tube stump produces chemokines that may lead to embryonic migration to and implantation in the uterine horn [16].

We found that the incidence of EP and IP in patients with single embryo transfer was significantly lower than that in patients with double embryo transfer during all ET cycles, especially frozen-thaw ET cycles. Perhaps we can select single embryo transfer for IVF-ET treatment in frozen-thawed ET cycles in patients who have undergone salpingectomy or proximal tubal occlusion to reduce the risk of EP, especially that of IP. In recent years, elective single embryo transfer (eSET) has been supported. Some researchers have suggested that eSET is associated with a better perinatal outcome [17]. eSET has been shown to reduce the number of pregnancy complications and neonatal morbidity and mortality with no impact on cumulative live-birth rates [18].

Because different IVF treatments would bias the results, we assessed fresh and frozen-thaw ET cycles respectively. In our study, the incidence of EP per clinical pregnancy following frozen-thaw ET cycles (2.2%) appeared to be slightly lower than that following fresh ET cycles (2.7%). The EP rate in our study was similar to the rate reported previously, which ranged from 1.28% to 2.22% for frozen–thawed ET cycles and from 1.92% to 4.62% for fresh ET cycles [5,19,20]. We hypothesized that the reason for the low EP rate of frozen–thawed ET cycles compared to fresh ET cycles was that frozen-thaw ET cycles have better endometrial receptivity and synchronization than stimulated fresh ET cycles, and the uterine environment is better for frozen-thaw embryo implantation. Unexpectedly, the incidence of IP per clinical pregnancy following frozen-thaw ET cycles (0.5%) appeared to be slightly higher than that following fresh ET cycles (0.4%). This observation is in contrast with the report that frozen-thaw ET cycles have a lower incidence of EP but is similar to the findings of Wang *et al*. [8]. The exact reason is unclear, and further studies are required to determine the reason.

Our study also found that the day of embryo transfer were associated with the incidence of EP in women undergoing frozen-thaw ET cycles. Transplanting blastocysts (day 5–6 embryos) in patients undergoing frozen-thaw ET cycles significantly reduces the risk of EP. However, multivariate analysis showed that the incidence of EP was only related to the number of embryos transferred. This may be related to the small number of EP patients. Cong Fang *et al*. [21] showed that fresh transfers and frozen-thawed day 3 transfers were associated with a higher EP rate than frozen-thawed day 5 blastocyst transfers in patients undergoing ART. Bingqian Zhang *et al*. [22] indicated that day 5 blastocyst transfer reduces the risk for EP in cycles compared with day 3 blastocyst transfer. It was also reported that [23] the EP rate was 3.4% in day 3 embryo transfer cycles and 2.1% in day 5 blastocyst transfer cycles. The reason may be that higher levels of progesterone and 17 β-estradiol can allow transferred day 3 embryos to readily enter the fallopian tube and have a negative effect on intrauterine embryo implantation. Single blastocyst transplantation is recommended to increase the implantation rate and reduce the EP rate and IP rate. We hope to expand the sample size in subsequent studies to determine the relationship between the day of embryo transfer and EP.

We recognize that this study has some limitations. First, although our study enrolled 11,609 subjects, it was limited by the retrospective nature of the analysis. It is possible that not all confounders were accounted for, and a prospective cohort study is needed. More confounders, such as controlled ovarian hyperstimulation protocols and doses, need to be included. Second, the number of women with ectopic pregnancy and interstitial pregnancy whose data were analyzed was relatively small. The limited sample size precluded us from drawing solid conclusions. Finally, the perinatal outcome results were lacking, which biased our conclusions.

6. Conclusions

In summary, the findings of our study showed that the embryo transfer number is a risk factor for EP, especially IP, in patients undergoing in frozen-thaw ET cycles who have undergone salpingectomy or proximal tubal occlusion. Therefore, it is recommended to select single embryo transfer for IVF-ET treatment in patients undergoing frozen-thawed ET who have undergone salpingectomy or proximal tubal occlusion to reduce the risk of EP, especially IP. Furthermore, we considered how to manage the interstitial part of the fallopian tube in salpingectomy or proximal tubal occlusion operations to reduce the risk of IP. Can we perform blastocyst transplantation to reduce the incidence of ectopic pregnancy in women with tubal infertility?

Author Contributions

Conception and design of the study, acquisition of data, or analysis and interpretation of data—CW, YZ, XX, XM, YM. Drafting the article or revising it critically for important intellectual content—CW, YZ, DWW. Final approval of the version to be submitted—DWW and JL. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The Ethics Committee of the First Affiliated Hospital of Nanjing Medical University approved the study (2018-SR-063). This study was retrospective, so informed consent was not needed. This manuscript conforms to the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network guidelines.

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Conflict of Interest

The authors declare no conflict of interest.

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