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Research article

Effect of ART treatments on maternal and neonatal outcomes in singleton live births: A large-scale retrospective cohort study

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ABSTRACT

Background: The increased risk of pregnancy complications in the ART population has been reported, but the source of these risks remains controversial. The study aims to evaluate the association between ART treatments and patient characteristics with maternal and neonatal outcomes.

Methods: This was a retrospective analysis of 45,159 singleton pregnant women at a hospital between 2018 and 2021. The maternal and neonatal outcomes included pregnancy-induced hypertension (PIH), preeclampsia (PE), gestational diabetes mellitus (GDM), placental abruption (PA), placenta accreta spectrum (PAS), postpartum hemorrhage (PPH), cesarean section, iatrogenic and spontaneous preterm birth, small for gestational age (SGA), low birth weight (LBW), macrosomia, and birth defects. We assessed the outcomes among the fresh embryo transfer (ET), frozen embryo transfer (FET), and spontaneous conception (SC) groups. Potential risk factors were further analyzed in the ART population.

Results: FET was associated with higher risks for PIH (SC: AOR, 1.97(1.51–2.57); fresh ET: AOR, 1.68(1.03–2.72)), PE (SC: 2.28(1.86–2.80); fresh ET: AOR, 1.61(1.11–2.33)), PAS (SC: AOR, 3.89 (3.39–4.46); fresh ET: AOR, 2.23(1.70–2.92)), PPH (SC: AOR, 3.46(2.76–4.34)); fresh ET: 2.09 (1.39–3.14)), and macrosomia (SC: 1.53(1.25–1.86); fresh ET: AOR, 2.87(1.89–4.35). Fresh ET was associated with higher risks for PA (SC: AOR, 2.19(1.51–3.18); FET: AOR, 0.39(0.17–0.90)), SGA (SC: AOR, 1.56(1.06–2.31), FET: AOR, 0.42(0.19–0.91)), and LBW (SC: AOR, 2.24 (1.82–2.77), FET: AOR, 0.63 (0.44–0.89)), and fresh ET is an independent risk factor for PA and SGA. Furthermore, the risk of GDM was associated with the biological characteristic of low-fertility patients.

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Conclusions: Embryo status (fresh or frozen) is a key factor affecting the maternal and neonatal outcomes in ART treatments, while biological characteristics of infertile patients also play a certain role.

1. Introduction

As an effective means of treating infertility, the use of assisted reproductive technology (ART) has experienced remarkable progress in China. The number of licensed assisted reproductive centers has increased from 451 in 2016 to 559 in 2022, and ART cycles have reached 1.15 million in 2017 [1]. The prevalence of infertility in China increased from 11.9 % in 2007 to 15.5 % in 2010 [2]. Although ART provides infertile families with an opportunity to conceive a biological child, the use of fertility drug regimens to induce ovulation and to facilitate the early development of embryos through fertilization and culture in vitro may affect the health of ART mothers and newborns, and this has attracted increasing attention worldwide [3,4].

Some investigators reported a difference in the risk of obstetric complications between frozen embryo transfer (ET) group and fresh ET group [5,6]. The ART population also exhibits an increased risk of GDM, gestational hypertension, and preterm birth compared with spontaneous pregnancies, but these results are controversial [7–9]. In addition, it is currently unclear as to whether the higher risk of pregnancy complications in the ART population resulted from the ART treatments themselves or the biological characteristics of low-fertility couples. While Stern et al. speculated that ART treatments increased obstetric and neonatal risks more so than the underlying infertility diagnosis [9]; however, it is still unclear which factors in the ART treatment process have a great impact on

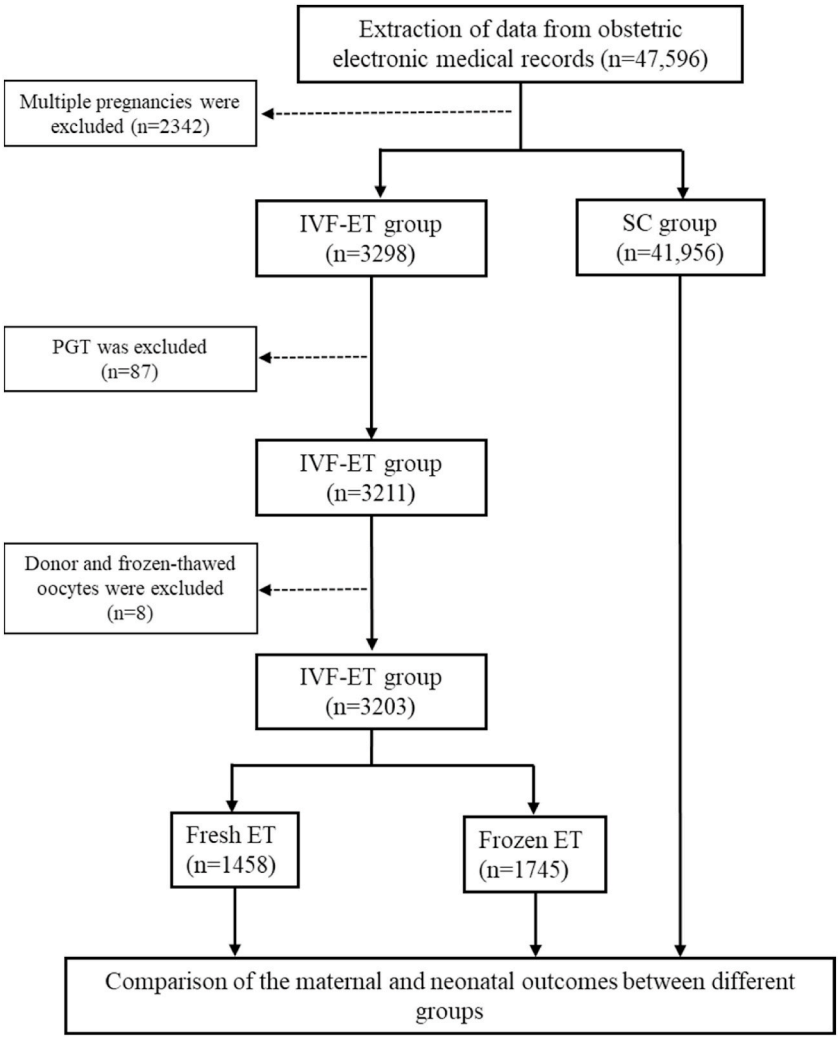

Fig. 1. The flow chart of the study.

maternal and neonatal outcomes. Lei et al. reported that an infertility diagnosis or other maternal or parental factors might contribute to adverse maternal and neonatal outcomes [7].

Most studies only reported a few maternal and neonatal outcomes, we comprehensively compared the risk of pregnancy complications and adverse neonatal outcomes between FET, fresh ET, and spontaneous-conception (SC) groups through a large-scale retrospective cohort study, and explored risk factors that cause adverse maternal and neonatal outcomes in the ART population.

2. Methods

2.1. Study design

This was a retrospective cohort study conducted at a large tertiary hospital in China, where we recruited subjects who underwent in vitro fertilization-embryo transfer (IVF-ET) and delivered one live fetus between January 2018 and October 2021. The embryo culture was performed by the same laboratory with identical operating specifications used throughout, showing little heterogeneity. Donor oocytes, frozen-thawed oocytes and preimplantation genetic testing (PGT) were excluded. Personal information, ovulation-induction regimens, embryo culture, and transfer information, pregnancy complications, and delivery and neonatal information derived from the IVF and SC groups were automatically matched and extracted from the IVF electronic medical records system as well as the obstetric electronic medical records system (Fig. 1).

Patients who had undergone IVF-ET were classified into fresh ET and FET groups for comparison with the SC group. Additionally, the outcomes between fresh ET and FET groups were compared, and potential risk factors were further analyzed for the entire IVF-ET population.

2.2. Ovarian stimulation and IVF/ICSI

The controlled ovarian stimulation (COS) protocol, monitoring, and oocyte collection were performed as previously described in detail [10,11]. Oocytes were inseminated by conventional IVF methods or ICSI four to 6 h after follicular aspiration based upon sperm quality. Embryos were transferred or cryopreserved after three to five days of in vitro culture, and the transfer of frozen-thawed embryos was performed 2 h after embryos were warmed.

2.3. Outcomes

The obstetricians recorded maternal complications during pregnancy and delivery according to the International Classification of Diseases, 10th revision (ICD-10). The maternal outcomes included pregnancy-induced hypertension (PIH, ICD-10 code O13), pre-eclampsia (PE, ICD-10 code O14.0, O14.1, and O14.9), gestational diabetes mellitus (GDM, ICD-10 code O24.400), cesarean section (code O82), and postpartum hemorrhage (PPH, ICD-10 code 072.1). We also analyzed placenta-related indicators, including placental abruption (PA, ICD-10 code O45), and placenta accreta spectrum (PAS, ICD-10 code O43.2). The neonatal outcomes included small for gestational age (SGA, birth weight$<$10th percentile or two standard deviations below the mean, adjusted for gestational age and infant sex), macrosomia (birth weight$>$4000 g), low birthweight (LBW, birth weight $<$2500 g), very LBW (vLBW, birth weight $<$1,500 g), iatrogenic and spontaneous preterm birth ($<$37 weeks), and birth defects (ICD-10 code Q00-Q99). The detailed definitions were shown in Supplementary Table S1. For naturally conceived babies, gestational age was estimated based upon the date of the mother's last menstrual period. For IVF pregnancies, gestational age was estimated based on the date of the embryo transfer. All clinical diagnoses were made by the obstetrician.

2.4. Statistical analysis

In the study, continuous variables were described by means and standard deviations, while categorical variables were presented as absolute numbers and percentages. We performed logistic regression to analyze the outcomes between IVF and SC groups adjusted for maternal age, pre-pregnancy body mass index (BMI), gravidity, primigravida, chronic hypertension, uterine fibroids, scarred uterus, hypothyroidism, presence of polycystic ovary syndrome (PCOS), smoking history, drinking history, and year of delivery. For comparisons between FET and fresh ET group, we adjusted for additional factors, including duration of infertility, infertility factors, Gn days, Gn dosage, endometrial thickness on the day of embryo transfer, ovulation-induction regimens, fertilization methods (IVF/ICSI), infertility type, and duration of embryo culture. In describing our data, we employed crude and adjusted odds ratios (AOR) and 95 % confidence intervals (*CI*). It is considered to have a statistical difference if the *95 % CI* do not contain 1. We considered $P < 0.05$ to be statistically significant. Statistical analyses were conducted using IBM SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

2.5. Post-hoc power calculation

For preterm births, we compared 3203 IVF patients (1745 patients with FET and 1458 patients with fresh ET) with 41,956 natural pregnancies. With an incidence of spontaneous preterm birth at 3.49 % and an alpha level 0.05, the statistical power values for the detection of ORs of 1.47, 1.24, and 1.75 were more than 90 %.

3. Results

3.1. Study subjects

A total of 3203 IVF patients and 41,956 spontaneous pregnancies were included in this study. The distributions of age, pre-pregnancy BMI, gravidity, primigravida, chronic hypertension, uterine fibroids, scarred uterus, hypothyroidism, and year of delivery were significantly different between the two groups ($P < 0.05$) (Table 1). In addition, there were 1458 (45.52 %) fresh ET patients and 1745 (54.48 %) FET patients in the IVF group, with the distributions of basic characteristics shown in Supplementary Table S2.

4. Maternal and neonatal outcomes

4.1. IVF vs SC

We uncovered no significant differences regarding SGA, and macrosomia between the IVF group and the SC group. However, compared with SC, the IVF group was associated with an increased risk of PIH (AOR, 1.67, *95 % CI*, 1.34–2.08**)**, PE (AOR, 1.84, *95 % CI*, 1.55–2.18), GDM (AOR, 1.70, *95 % CI*, 1.56–1.85), PA (AOR, 1.39, *95 % CI*, 1.01–1.91), PAS (AOR, 2.72, *95 % CI*, 2.42–3.07), PPH (AOR, 2.66, *95 % CI*, 2.22–3.18), cesarean section (AOR, 2.95, *95 % CI*, 2.71–3.21**)**, LBW (AOR, 1.95, *95 % CI*, 1.66–2.28), vLBW (AOR, 4.59, *95 % CI*, 3.15–6.69), iatrogenic preterm birth (AOR, 2.40, *95 % CI*, 1.96–2.94), spontaneous preterm birth (AOR, 1.47, *95 % CI*, 1.24–1.75), and birth defects (AOR, 1.96, *95 % CI*, 1.60–2.40) (Table 2 and Supplementary Table S3). Furthermore, we analyzed the indications for cesarean sections between the groups, and the result showed that pregnancy complications, fetal distress, and placenta-related factors were the main reasons in the IVF group, while scarred uterus and fetal distress were the primary factors in the SC group, as illustrated in Supplemental Fig. S1.

4.2. FET vs SC

The distributions of maternal and neonatal outcomes among FET, fresh ET, and SC groups are depicted in Supplementary Table S2. We did not find any increased risk of PA and SGA in the FET group compared with the SC group after adjusting for multiple factors (Table 3). However, the risks of PIH (AOR, 1.97; *95 % CI*, 1.51–2.57), PE (AOR, 2.28; *95 % CI*, 1.86–2.80), GDM (AOR, 1.71, *95 % CI*, 1.53–1.91), PAS (AOR, 3.89, *95 % CI*, 3.39–4.46), PPH (AOR, 3.46, *95 % CI*, 2.76–4.34), cesarean section (AOR, 4.03, *95 % CI*, 3.58–4.54), macrosomia (AOR, 1.53, *95 % CI*, 1.25–1.86), LBW (AOR, 1.67, *95 % CI*, 1.35–2.07), vLBW (AOR, 4.68, *95 % CI*, 2.95–7.43), iatrogenic preterm birth (AOR, 2.26, *95 % CI*, 1.73–2.94), spontaneous preterm birth (AOR, 1.32, *95 % CI*, 1.04–1.66), and birth defects (AOR, 2.03, *95 % CI*, 1.57–2.63) were increased in the FET group (Table 3).

Table 1
Maternal characteristics of infertile women and naturally conceiving women.

Parameter	IVF group(n = 3203)	SC group(n = 41,956)	*P*
Age, mean (SD), year	31.89(3.78)	29.48(3.91)	<0.001
Age, n (%)			<0.001
<35	2451(76.52)	37531(89.45)	
≥35	752(23.48)	4425(10.55)	
Pre-pregnancy BMI, mean (SD)	21.71(2.76)	21.09(2.76)	<0.001
Pre-pregnancy BMI, n (%)			<0.001
<18.5	300(9.37)	6609(15.75)	
18.5–23.9	2281(71.21)	29539(70.40)	
24.0–27.9	537(16.77)	4949(11.80)	
≥28.0	85(2.65)	859(2.05)	
PCOS, n (%)	273(8.52)	544(1.30)	<0.001
Gravidity, mean (SD)	0.99(1.28)	1.15(1.35)	<0.001
Primigravida, n (%)	2910(90.85)	29223(69.65)	<0.001
Diabetes, yes, n (%)	20(0.62)	260(0.62)	0.974
Chronic hypertension, yes, n (%)	24(0.75)	120(0.29)	<0.001
Uterine fibroids, yes, n (%)	243(7.59)	1353(3.22)	<0.001
[a]Scarred uterus, yes, n (%)	259(8.09)	6473(15.43)	<0.001
Hyperthyroidism, yes, n (%)	11(0.34)	139(0.33)	0.908
Hypothyroidism, yes, n (%)	391(12.21)	3621(8.63)	<0.001
Year of delivery, n (%)			<0.001
2018	962(30.03)	5331(12.71)	
2019	740(23.10)	13603(32.42)	
2020	775(24.20)	12929(30.82)	
2021	726(22.67)	10093(24.06)	
Smoking history, n (%)	39(1.22)	535(1.28)	0.779
Drinking history, n (%)	47(1.47)	693(1.65)	0.428

[a] Scarred uterus: Scarred uterus refers to uterine scarring from previous caesarean section and other uterine surgery.

Table 2
Maternal and neonatal outcomes between IVF and SC groups.

Outcome	IVF group (n = 3203)	SC group (n = 41956)	Crude OR (*95 % CI*)	Adjusted OR (95 %)
Pregnancy–induced hypertension, n (%)	112(3.50)	715(1.70)	**2.09(1.71–2.56)**	**1.67(1.34–2.08)**
Preeclampsia, n (%)	197(6.15)	1017(2.42)	**2.64(2.25–3.09)**	**1.84(1.55–2.18)**
Gestational diabetes mellitus, n (%)	978(30.53)	7319(17.44)	**2.08(1.92–2.25)**	**1.70(1.56–1.85)**
Placental abruption, n (%)	47(1.47)	435(1.04)	**1.42(1.05–1.92)**	**1.39(1.01–1.91)**
Placenta accreta spectrum, n (%)	445(13.89)	2362(5.63)	**2.70(2.43–3.01)**	**2.72(2.42–3.07)**
Postpartum hemorrhage[a], n (%)	169(5.28)	1309(3.12)	**1.73(1.47–2.04)**	**2.66(2.22–3.18)**
Cesarean section, n (%)	2264(70.68)	18688(44.54)	**3.00(2.78–3.25)**	**2.95(2.71–3.21)**
Small for gestational age, n (%)	49(1.53)	496(1.18)	1.30(0.97–1.75)	1.18(0.86–1.61)
Macrosomia, n (%)	169(5.28)	1926(4.59)	1.16(0.99–1.36)	1.11(0.94–1.31)
Low birth weight, n (%)	220(6.87)	1309(3.12)	**2.29(1.98–2.65)**	**1.95(1.66–2.28)**
Very low birth weight, n (%)	48(1.50)	122(0.29)	**5.22(3.73–7.30)**	**4.59(3.15–6.69)**
Iatrogenic preterm birth, n (%)	136(4.25)	689(1.64)	**2.66(2.20–3.20)**	**2.40(1.96–2.94)**
Spontaneous preterm birth, n (%)	175(5.46)	1466(3.49)	**1.60(1.36–1.88)**	**1.47(1.24–1.75)**
Birth defects, n (%)	127(3.97)	886(2.11)	**1.91(1.58–2.31)**	**1.96(1.60–2.40)**

Adjustments were made for age, pre-pregnancy BMI, gravidity, primigravida, chronic hypertension, uterine fibroids, scarred uterus, hypothyroidism, PCOS, smoking history, drinking history, and year of delivery.

[a] In addition to the variables mentioned above, an additional adjustment was made for cesarean section.

Table 3
Maternal and neonatal outcomes after fresh ET, FET, and SC.

Outcome	FET vs SC		Fresh ET vs SC		FET vs Fresh ET[a]	
	Crude OR (*95 % CI*)	Adjusted OR (*95 % CI*)	Crude OR (*95 % CI*)	Adjusted OR (*95 % CI*)	Crude OR (*95 % CI*)	Adjusted OR (*95 % CI*)
Pregnancy-induced hypertension	**2.45(1.91–3.14)**	**1.97(1.51–2.57)**	**1.67(1.21–2.30)**	1.34(0.97–1.87)	1.47(0.99–2.17)	**1.68(1.03–2.72)**
Preeclampsia	**3.29(2.73–3.98)**	**2.28(1.86–2.80)**	**1.88(1.45–2.43)**	1.30(0.99–1.70)	**1.75(1.29–2.38)**	**1.61(1.11–2.33)**
Gestational diabetes mellitus	**2.10(1.89–2.33)**	**1.71(1.53–1.91)**	**2.06(1.84–2.31)**	**1.67(1.48–1.88)**	1.02(0.88–1.19)	1.06(0.88–1.28)
Placental abruption	0.77(0.45–1.32)	0.72(0.41–1.24)	**2.21(1.55–3.16)**	**2.19(1.51–3.18)**	**0.35(0.19–0.66)**	**0.39(0.17–0.90)**
Placenta accreta spectrum	**3.88(3.42–4.41)**	**3.89(3.39–4.46)**	**1.46(1.21–1.77)**	**1.46(1.19–1.79)**	**2.65(2.12–3.32)**	**2.23(1.70–2.92)**
Postpartum hemorrhage[b]	**1.95(1.58–2.39)**	**3.46(2.76–4.34)**	**1.47(1.14–1.90)**	**1.90(1.46–2.48)**	1.32(0.96–1.82)	**2.09(1.39–3.14)**
Cesarean section, n (%)	**3.95(3.54–4.42)**	**4.03(3.58–4.54)**	**2.24(2.01–2.50)**	**2.12(1.88–2.38)**	**1.77(1.51–2.06)**	**2.07(1.68–2.54)**
Small for gestational age	0.97(0.62–1.52)	0.86(0.54–1.37)	**1.70(1.16–2.48)**	**1.56(1.06–2.31)**	0.57(0.32–1.01)	**0.42(0.19–0.91)**
Macrosomia	**1.59(1.32–1.92)**	**1.53(1.25–1.86)**	**0.66(0.49–0.89)**	**0.63(0.46–0.85)**	**2.40(1.70–3.40)**	**2.87(1.89–4.35)**
Low birth weight	**2.03(1.66–2.49)**	**1.67(1.35–2.07)**	**2.61(2.14–3.19)**	**2.24(1.82–2.77)**	0.78(0.59–1.02)	**0.63(0.44–0.89)**
Very low birth weight	**5.39(3.54–8.20)**	**4.68(2.95–7.43)**	**5.01(3.14–7.99)**	**4.31(2.59–7.16)**	1.08(0.61–1.91)	0.60(0.28–1.29)
Iatrogenic preterm birth, n (%)	**2.54(1.98–3.26)**	**2.26(1.73–2.94)**	**2.79(2.16–3.62)**	**2.60(1.98–3.41)**	0.91(0.64–1.28)	0.74(0.48–1.14)
Spontaneous preterm birth, n (%)	**1.45(1.16–1.81)**	**1.32(1.04–1.66)**	**1.77(1.42–2.21)**	**1.61(1.28–2.03)**	0.82(0.60–1.11)	0.71(0.48–1.04)
Birth defects, n (%)	**1.94(1.51–2.48)**	**2.03(1.57–2.63)**	**1.89(1.44–2.48)**	**1.88(1.42–2.50)**	1.03(0.72–1.47)	0.71(0.44–1.14)

Adjustments were made for age, pre-pregnancy BMI, gravidity, primigravida, chronic hypertension, uterine fibroids, scarred uterus, hypothyroidism, PCOS, smoking history, drinking history, and year of delivery.

[a] In addition to the variables mentioned above, additional adjustments were made for infertility factors, Gn days, Gn dosage, endometrial thickness on the day of embryo transfer, duration of infertility, ICSI, blastocyst, infertility type, and ovulation-induction regiments.

[b] In addition to the variables mentioned above, an additional adjustment was made for cesarean section.

4.3. Fresh ET vs SC

The risks of PIH and PE were not statistically different between the fresh ET group and the SC group (Table 3). However, compared with the SC group, **the** fresh ET group exhibited increased risks of GDM (AOR, 1.67, *95 % CI*, 1.48–1.88), PA (AOR, 2.19, *95 % CI*, 1.51–3.18), PAS (AOR, 1.46, *95 % CI*, 1.19–1.79), PPH (AOR, 1.90, *95 % CI*, 1.46–2.48), cesarean section (AOR, 2.12, *95 % CI*, 1.88–2.38), SGA (AOR, 1.56, *95 % CI*, 1.06–2.31), LBW (AOR, 2.24, *95 % CI*, 1.82–2.77), vLBW (AOR, 4.31, *95 % CI*, 2.59–7.16), iatrogenic preterm birth (AOR, 2.60, *95 % CI*, 1.98–3.41), spontaneous preterm birth (AOR, 1.61, *95 % CI*, 1.28–2.03), and birth defects (AOR, 1.88, *95 % CI*, 1.42–2.50**), and attenuated risk of** macrosomia (AOR, 0.63, *95 % CI*, 0.46–0.85) (Table 3).

4.4. FET vs fresh ET

We further analyzed the factors that affect the maternal and neonatal outcomes in the IVF-ET population (Table 3 and Supplementary Tables S4–S17). We observed that FET was associated with an increased risk of PIH (AOR, 1.68, *95 % CI*, 1.03–2.72), PE (AOR, 1.61, *95 % CI*, 1.11–2.33), PAS (AOR, 2.23, *95 % CI*, 1.70–2.92), PPH (AOR, 2.09, *95 % CI*, 1.39–3.14), cesarean section (AOR, 2.07,

95 % CI, 1.68–2.54), and macrosomia (AOR, 2.87, *95 % CI*, 1.89–4.35), and a reduced risk of PA (AOR, 0.39, *95 % CI*, 0.17–0.90), SGA (AOR, 0.42; *95 % CI*, 0.19–0.91), and LBW (AOR, 0.63; *95 % CI*, 0.44–0.89) (Table 3).

It should be noted that the biological characteristics of patients were also associated with PIH, PE, GDM, and PAS (Supplementary Table S4-S6 and S8). The risk of PIH was associated with gravidity (AOR, 1.22; *95 % CI*, 1.01–1.48) and PCOS (AOR, 2.32; *95 % CI*, 1.25–4.32); the risk of PE was associated with age (AOR, 1.45; *95 % CI*, 1.00–2.11), chronic hypertension (AOR, 4.66; *95 % CI*, 1.80–12.05), hypothyroidism (AOR, 1.62; *95 % CI*, 1.09–2.41), PCOS (AOR, 1.70; *95 % CI*, 1.00–2.89), and smoking history (AOR, 3.49; *95 % CI*, 1.07–11.44); the risk of GDM was associated with age (AOR, 1.46; *95 % CI*, 1.20–1.79), PCOS (AOR, 1.39; *95 % CI*, 1.02–1.89), drinking history (AOR, 2.09; *95 % CI*, 1.03–4.21), and duration of infertility (AOR, 1.04; *95 % CI*, 1.02–1.07); the risk of PAS was associated with gravidity (AOR, 1.15; *95 % CI*, 1.04–1.28), primigravida (AOR, 1.59; *95 % CI*, 1.03–2.44), uterine fibroids (AOR, 1.47; *95 % CI*, 1.04–2.08), and scarred uterus (AOR, 2.18; *95 % CI*, 1.49–3.20). Furthermore, BMI was associated with the risk of PIH, PE, GDM, cesarean section, and macrosomia (Supplementary Table S4-S10 and S12).

In addition, the risk of vLBW was associated with duration of embryo culture (cleavage stage vs. blastocyst stage: AOR, 0.39; *95 % CI*, 0.18–0.86) and endometrial thickness (AOR, 0.80; *95 % CI*, 0.65–0.99) (Supplementary Table S14), and the risk of iatrogenic preterm birth was associated with ICSI (AOR, 1.78; *95 % CI*, 1.14–2.79) (Supplementary Table S15), and the risk of birth defects was associated with age (AOR, 2.20; *95 % CI*, 1.39–3.47), and duration of embryo culture (cleavage stage vs. blastocyst stage: AOR, 0.51; *95 % CI*, 0.31–0.84) (Supplementary Table S17).

5. Discussion

These data suggested that embryo status was the main factor in the increased risk of adverse maternal and neonatal outcomes during ART treatments in addition to the patients' biological characteristics. FET was associated with the risk of PIH, PE, PAS, PPH, cesarean section, and macrosomia, while fresh ET was associated with PA, SGA, and LBW. Besides, the risk of vLBW, iatrogenic preterm birth and birth defects was associated with other ART-related treatment, such as insemination and duration of embryo culture. The risk of GDM was associated with the biological characteristics of patients.

FET was associated with increased risks of PIH and PE compared with both fresh cycles and the SC group, congruent with the results of other studies [12–14]. Intriguingly, several studies recently indicated that the absence of a corpus luteum (CL) was associated with an increased risk of PE, and they did not find a significant difference between the groups with a single CL and multiple CLs [15,16]. The increased risk of hypertensive disorders of pregnancy in patients undergoing FET might be related to the fact that the appearance of the dominant follicle was suppressed in programmed cycles, thus precluding the formation of a CL [17]. In our study, 97.1 % (1695/1745) of patients participated in programmed cycles for FET.

The CL secretes not only progesterone and estradiol, but also relaxin and vasoactive and angiogenic substances that play vital roles in the initial stages of pregnancy [18]. The CL is the key regulator of endometrial function, inducing endometrial decidualization in the secretory phase of the menstrual cycle and in early pregnancy [19]. Relaxin was not detected in pregnant women with luteal deficiency, which may affect cardiovascular and kidney adaptation in the early stages of pregnancy [20]. Conrad et al. found extensively dysfunctional cardiovascular function in women who conceived by IVF in the absence of a CL [21,22]. In addition, although hyperreactio luteinalis is a rare condition following ART treatment [23], we could not ignore its role in the mechanism of PE. A review reported that PE occurred in 24 % of patients with hyperreactio luteinalis [24]. Luteal function is thus critical to the prevention of PE. Moreover, we found that hypothyroidism, high BMI, and PCOS were associated with an increased risk of PE. Obesity is a common feature in women with PCOS and could exacerbate pregnancy-related metabolic disorders [25]. Hyperandrogenism in women with PCOS might activate vascular endothelial cells and cause damage, which could contribute to elevated blood pressure [26]. Similarly, hypothyroidism might increase the risk of PE also by causing endothelial cell dysfunction with impaired vasodilation [27].

Interestingly, although the results showed that the risk of GDM was significantly higher in the IVF group compared to the SC group, the impact of ART treatments on this risk was not observed. Women with PCOS have intrinsic insulin resistance and compensatory hyperinsulinemia, which may increase the risk of GDM [28]. Besides, alcohol exposure induces oxidative stress in placental tissues, and elevated oxidative stress is linked to an increased risk of GDM [29].

IVF-ET was an independent risk factor for PA [30], which was congruent with our findings, although some studies showed no significant association between FET and PA [31,32]. Johnson et al. reported that frozen cycles reflected a lower risk of ischemic placental disease compared with fresh cycles, but they did not find differences in the risks of PE and PA, which might be related to a limited sample size (n = 271 for frozen cycle) [33]. Furthermore, Elevated serum progesterone on the day of hCG administration in fresh cycles was associated with an increased risk of ischemic placental disease [34].

It was reported that the risk of PAS was significantly higher in the IVF-ET group than in the SC group [35]. Kaser et al. discerned that FET and endometrial thickness <9 mm were associated with increased risk for PAS in a case-control study [36], which was in line with the result of our study. Low progesterone level were suspected to be related to PAS due to failure of normal decidualization and over–invasion by extravillous trophoblasts [37,38]. The research on the association between PAS and FET remains limited, and its mechanisms still require further exploration.

Reports on neonatal outcomes are still debatable. A recent study reported that the risk of iatrogenic preterm birth after IVF/ICSI was significantly greater than that occurring in the SC group [39], with similar results observed in twin pregnancies as well [40]. Additionally, a small prospective cohort reported that the risk of spontaneous preterm birth was significantly lower in pregnancies from fresh day-3 embryo transfer compared with frozen-thawed day-5 embryo transfer (fresh ET, n = 276; FFT, n = 133), which was inconsistent with our findings [41]. However, most studies did not differentiate between iatrogenic and spontaneous preterm birth in the analyses, resulting in a lack of research on the association between fresh ET and either type of preterm birth.

In addition, Maheshwari et al. showed that fresh ET was associated with an increased risk of LBW, while Raja et al. reported that fresh ET was associated with a higher risk of preterm birth, SGA, and congenital anomaly [42,43], However, we did not find a similar association between fresh ET and birth defects in the study. Cavoretto et al. found that FET had a lower mean uterine artery pulsatility index, with greater fetal growth and a lower risk of SGA compared with fresh ET [44]. Thawed blastocyst transfer presents a greater crown-rump length compared with fresh blastocyst transfer in early pregnancy, which partially explains the birth weight difference observed in FET versus fresh ET pregnancies [45]. Moreover, unified modeling showed that the mean estimated fetal weight z-scores were significantly higher in the FET group compared to the fresh ET group, and this difference remained consistent from 19 weeks to birth [46]. We speculated that ovarian hormonal stimulation causes a state of hyper-estrogenism in fresh cycles, which then leads to abnormal endometrial angiogenesis and subsequent abnormal placentation, whereas the effect of hormonal stimulation tends to diminish with time in frozen cycles [47–49].

The choice of embryo transfer remains a controversial topic in clinical practice. Some reproductive medical centers have promoted "freeze-all strategy" in recent years due to the low risk of ovarian hyperstimulation syndrome and the advantages of selective single embryo transfer. We recommend that the method of embryo transfer might be determined after a comprehensive assessment of the mother's status. Furthermore, the mechanisms underlying PAS and PA remain arcane, and we recommend that future studies focus on placental function within different subgroups of the IVF-ET population.

The data in this study were derived from the electronic medical records system of a triple-A hospital, and the diagnosis was objective, accurate, and comprehensive. The embryo culture was performed by the same laboratory with identical operating specifications used throughout, showing little heterogeneity. However, there were some limitations to this study. This study was conducted in a single tertiary hospital, which might lead to selections bias, as the included patients were more attentive to prenatal care, potentially resulting in an underestimation of the impact of ART treatment on maternal and neonatal outcomes. In addition, data from electronic medical record systems might contain missing or inaccurate information, but we verified the indicators by comparing records from different sources to ensure completeness and accuracy. Moreover, we could not evaluate the impact of endometrial preparation protocols on the outcomes of the frozen cycles. Furthermore, the present study was also retrospective in nature and conducted only in a Chinese population, and results should be interpreted with caution.

6. Conclusion

In conclusion, compared with SC, IVF-ET exhibited a higher risk for adverse maternal and neonatal outcomes. Fresh ET was chiefly related to the risk of PA, SGA, and LBW, while FET was primarily related to the risks of PIH, PE, PAS, PPH, cesarean section, and macrosomia. The risks for vLBW, iatrogenic preterm birth and birth defects were associated with a variety of factors related to ART treatments, and GDM may be linked to maternal characteristics.

Ethical approval statement

Permission for this study was granted by the Ethics Committee Review Board of the Chongqing Health Center for Women and Children (ethics code, 2022-RGI-08). Informed written consent was not obtained, because our data were extracted from electronic medical records and the data did not include any personally identifiable parameters.

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Data availability

Data will be made available on request.

CRediT authorship contribution statement

Qi Zhang: Writing – original draft, Methodology, Funding acquisition, Data curation, Conceptualization. **Xiaoni Guo:** Writing – original draft, Visualization, Formal analysis, Data curation. **Feng Zhou:** Formal analysis, Data curation. **Qian Luo:** Supervision, Investigation. **Deying He:** Supervision, Investigation. **Xi Qian:** Methodology, Conceptualization. **Li Hong Wu:** Investigation, Data curation. **Xiaodong Zhang:** Writing – review & editing, Project administration, Methodology. **Guoning Huang:** Writing – review & editing, Project administration, Funding acquisition. **Wei Zhou:** Writing – review & editing, Supervision, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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