Perinatal complications and live-birth outcomes following assisted reproductive technology: a retrospective cohort study

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Abstract

Background: With the development of assisted reproductive technology (ART) and its increasing success rate in the mainland of China, more attention has been paid to the safety of ART. In this study, we explored the associations between conception by ART and pregnancy/perinatal complications, and neonatal outcomes compared with similar outcomes following spontaneous conception.

Methods: This retrospective cohort study of pregnancies over a 3-year period (2013–2015) was performed at Beijing Obstetrics and Gynecology Hospital, Beijing, China. Subjects were divided into two groups: conception by ART ($n = 2256$) or spontaneous conception ($n = 6768$). According to different fertilization modes, the ART group was divided into *in vitro* fertilization (IVF, $n = 1873$) and intracytoplasmic sperm injection (ICSI, $n = 383$) subgroups. The ART group was also divided into two different embryo transfer methods; fresh embryo transfer (ET, $n = 1583$) and frozen embryo transfer (FET, $n = 673$) subgroups. Pregnancy complications, perinatal complications, and neonatal outcomes of the enrolled subjects were investigated and analyzed by univariate analysis and multivariate logistic regression.

Results: After adjustment for maternal age, gravidity, parity, maternal education, smoking, alcohol consumption, and body mass index (BMI), pregnancies conceived by ART were associated with a significantly increased incidence of gestational diabetes mellitus (GDM; OR 1.88, 95% CI 1.56–2.27), gestational hypertension (OR 2.18, 95% CI 1.83–2.60), and intrahepatic cholestasis of pregnancy (ICP) (OR 2.79, 95% CI 2.15–3.64), compared with spontaneous conception. These associations were similar for the singleton group. In the twin group, only the incidence of ICP was significantly higher than in controls. We found that pregnancies conceived by ART were associated with perinatal complications, including placental abruption (OR 2.14, 95% CI 1.33–3.45), premature rupture of membranes (PROM; OR 1.24, 95% CI 1.06–1.45), postpartum hemorrhage (OR 2.89, 95% CI 2.33–3.59) and polyhydramnios (OR 2.01, 95% CI 1.29–3.16). The singleton group had a similar result with placental abruption, but not with fetal membranes ruptures before labor and polyhydramnios. There were no significant differences in the incidence of these perinatal complications in the twin group. Some neonatal outcomes, including preterm labor (OR 4.29, 95% CI 3.84–4.80) and low birth weight (OR 1.72, 95% CI 1.42–2.08), were more likely to occur with singleton births after ART. However, there were no significant differences for these outcomes from twin pregnancies. Perinatal complications and neonatal outcomes were consistent between the IVF and ICSI subgroups. The FET and ET subgroups showed a similar increase in complications, except for the incidence of placental abruption. After taking into account the effects of parity, birth plurality and maternal age, the ART group still exhibited increased maternal and neonatal complications, although some differences narrowed or disappeared.

Conclusions: This retrospective cohort study demonstrated that patients who underwent ART were at increased risk of several adverse pregnancy outcomes compared with women who conceived spontaneously. These complications may be attributed in part to the relatively high multiple pregnancy rate after ART. Elective single embryo transfer should be promoted in China to reduce the obstetrical risks of ART pregnancy. Singletons of ART pregnancy exhibited increased maternal and neonatal complications as well, suggesting that underlying infertility or other maternal or parental factors may contribute to the adverse outcomes.

Keywords: Reproductive techniques, Assisted; fertilization in vitro; Sperm injections, Intracytoplasmic; Pregnancy complications

Introduction

Since the birth of Louise Brown in 1978, *in vitro* fertilization (IVF) has become an effective way to treat infertility and has produced millions of babies worldwide. The number of assisted reproductive technology (ART) births per year has increased worldwide, with the total number of IVFs approximately 5 million. IVF accounts for

1.7% to 4% of the total population in developing countries, and 1% of the Chinese population.[1-2] However, ART allows multiple eggs to mature simultaneously via controlled ovarian hyperstimulation, and fertilization and early embryo development are accomplished by *in vitro* culture and micromanipulation. These techniques interfere with the process of germ cell proliferation, fertilization, development, and differentiation and may have adverse effects on the embryo. More attention has been paid to the safety of ART worldwide.

Several studies have shown that ART increases the incidence of adverse pregnancy outcomes, including preeclampsia, gestational hypertension, placenta previa, gestational diabetes mellitus (GDM), preterm delivery, low birth weight, and birth defects.[3-8] Birth plurality is a post-treatment confounder; a variable that occurs after ART treatment that confounds the causal effect. Many studies have not examined mother's age and other mixed miscellaneous factors.[9-12] Does ART increase adverse pregnancy outcomes? Is the adverse pregnancy outcome due to multiple births or the ART technology itself? At present, opinions vary widely, and no unanimous conclusion can be drawn.

In the present study, we retrospectively investigated ART and natural pregnancies to explore the relationship between ART and adverse maternal and neonatal outcomes in China.

Methods

Data collection

This was a retrospective cohort study conducted at Beijing Obstetrics and Gynecology Hospital, Capital Medical University, between January 2013 and December 2015. All ART pregnancies were paired 1:3 with spontaneous pregnancies as the control group during the same time period at Beijing Obstetrics and Gynecology Hospital. The ART and control groups were compared for pregnancy complications, perinatal complications, and neonatal outcomes. Then, we conducted stratification analysis of birth plurality, maternal age, parity and the different types of ART. Only data from live newborns after the 28th week of gestation were included in the analysis. Donor oocytes/sperm or embryo recipients, ovulation induction or women applied preimplantation genetic diagnosis were excluded. Subjects were divided into two groups: conception by ART or spontaneous conception. Then, we conducted stratification analysis of birth plurality, maternal age, parity. According to different fertilization modes, the ART group was divided into IVF and intracytoplasmic sperm injection (ICSI) subgroups. The ART group was also divided into fresh embryo transfer (ET) and frozen embryo transfer (FET) subgroups according to different embryo transfer methods. All data were collected retrospectively from computer databases or telephone interviews.

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of the Beijing Obstetrics and Gynecology Hospital, Capital Medical University (No. 201592-015). Informed written consent was obtained from all patients in this study. Only data from 28 weeks after live neonatal births were included in the analysis. Methods were carried out in accordance with the approved guidelines.

Statistical analysis

Quantitative data are presented as the mean ± standard deviation (SD). Fisher exact and χ^2 tests were performed to test for differences in the proportions of categorical variables between two or more groups. Logistic regression analysis was done to identify possible predictors of pregnancy complications and the association of ART and spontaneous pregnancy. From this analysis, odd ratios (OR) with 95% confidence intervals (CI) were computed for all variables that were significantly associated with pregnancy complications and neonatal defects for ART relative to spontaneous conception. All statistical tests and P values were two-sided, and the limit of statistical significance was $P < 0.01$. SPSS statistical software (version 21, SPSS Inc., USA) was used for data analysis.

Results

Maternal characteristics of women who conceived by ART or spontaneously

From January 2013 to December 2015, 2256 ART-derived pregnancies and 6768 matched spontaneous pregnancies were enrolled in our study. The ART group consisted of 1453 singleton and 803 twin gestations, while the control group consisted of 6667 singleton and 101 twin gestations. According to different fertilization modes, the ART group was divided into IVF ($n = 1873$) and ICSI ($n = 383$) subgroups. The ART group was divided into ET ($n = 1583$) and FET ($n = 673$) subgroups by different embryo transfer methods. Table 1 summarizes the maternal characteristics. Women who conceived by ART were older than women who conceived spontaneously. The ART patients tended to be nulliparous. The cesarean section rate was significantly higher in the ART group.

Analysis of pregnancy/perinatal complications and neonatal outcomes in the ART and spontaneous pregnancy groups stratified by birth plurality

Pregnancy complications in the ART and spontaneous pregnant groups are described in Table 2. Regardless of the number of births, women undergoing ART were more likely to develop adverse pregnancy outcomes. Pregnancies after ART were 1.88 times more likely to develop GDM (OR 1.88, 95% CI 1.56–2.27), 2.18 times more likely to develop gestational hypertension (OR 2.18, 95% CI 1.83–2.60), and 2.79 times more likely to develop intrahepatic cholestasis of pregnancy (ICP, OR 2.79, 95% CI 2.15–3.64). Findings were similar in the singleton group. For the twin group, only the incidence of ICP was significantly higher than those in the controls (OR 3.19, 95% CI 2.55–4.00).

Table 1: Maternal characteristics among the ART and control groups.

Characteristics	ART ($n = 2256$)	Controls ($n = 6768$)	χ^2	P
Maternal age				
<35 years	871 (38.6)	4209 (62.2)	382.42	<0.01
≥35 years	1385 (61.4)	2559 (37.8)		
Pre-pregnancy BMI				
<24 kg/m^2	1647 (73.0)	5279 (78.0)	1.37	0.24
≥24 kg/m^2	609 (27.0)	1489 (22.0)		
Smoking				
Yes	13 (0.6)	59 (0.9)	1.87	0.17
No	2243 (99.4)	6709 (99.1)		
Alcohol consumption				
Yes	432 (19.1)	1270 (18.8)	1.56	0.15
No	1824 (80.9)	5498 (81.2)		
Diabetes history				
Yes	28 (1.2)	71 (1.0)	0.58	0.45
No	2228 (98.8)	6697 (99.0)		
Hypertension History				
Yes	18 (0.8)	59 (0.9)	0.11	0.74
No	2238 (98.8)	6709 (99.1)		
Maternal education				
≤Secondary school	1086 (48.1)	3469 (51.3)	6.76	0.03
College graduate	824 (36.5)	2345 (34.6)		
Post-graduate	346 (15.3)	954 (14.1)		
Gravidity				
0	1896 (84.0)	5535 (81.8)	5.95	0.02
≥1	360 (16.0)	1233 (18.2)		
Parity				
0	2053 (91.0)	5820 (86.0)	38.15	<0.01
≥1	203 (9.0)	948 (14.0)		
Birth plurality				
Singletons	1453 (64.4)	6667 (98.5)	109.28	<0.01
Twins	803 (35.6)	101 (1.5)		
Delivery mode				
Vaginal delivery	1278 (56.6)	4489 (66.30)	108.10	<0.01
Forceps assisted	7 (0.30)	114 (1.70)		
Cesarean delivery	971 (43.0)	2165 (32.0)		

Data are presented as n (%). ART: Assisted reproductive technology.

In the ART group, the incidence of most perinatal complications increased significantly [Table 2]. The incidence of placental abruption (OR 2.14, 95% CI 1.33–3.45), fetal premature rupture of membranes (PROM, OR 1.24, 95% CI 1.06–1.45), postpartum hemorrhage (OR 2.89, 95% CI 2.33–3.59) and polyhydramnios (OR 2.01, 95% CI 1.29–3.16), were more likely to occur after ART in all births. The findings were similar in the singleton group, except for PROM and polyhydramnios. There was no significant difference in the incidence of these perinatal complications in the twin group.

The incidences of poor newborn outcomes in the ART and spontaneous pregnancy groups are exhibited in Table 2. Neonatal outcomes included preterm labor, low birth weight, macrosomia, 1-min Apgar ≤ 7, and 5-min Apgar ≤ 7. Some neonatal outcomes, including preterm labor (OR 4.29, 95% CI 3.84–4.80), and low birth weight (OR 1.72,

95% CI 1.42–2.08), were more likely to occur after ART. In the singleton group, preterm labor (OR 1.85, 95% CI 1.24–2.78) and low birth weight (OR 1.74, 95% CI 1.39–2.17) were more likely to occur after ART. However, there was no significant difference in twins.

Analysis of pregnancy/perinatal complications and neonatal outcomes in the ART and spontaneous pregnancy groups stratified by nulliparous and multiparous

There were 2053 nulliparous women in the ART group, and 5820 nulliparous women in the natural conception group. The incidence of nulliparous women in the ART group was significantly higher than that in the natural conception group (91.0% $vs.$ 86.0%). We further studied the incidences of pregnancy, perinatal complications and neonatal outcomes for nulliparous and multiparous women [Table 3]. Nearly all the pregnancy and perinatal complications listed, including gestational hypertension

Table 2: Multivariate analysis of maternal and neonatal complications in ART and Controls stratified by birth plurality.

Items	Total				Singletons				Twins			
	ART (n = 2256)	Controls (n = 6768)	OR (95% CI)	P	ART (n = 1453)	Controls (n = 6667)	OR (95% CI)	P	ART (n = 803)	Controls (n = 101)	OR (95% CI)	P
Pregnancy complication												
Gestational hypertension	228 (10.1)	332 (4.9)	2.18 (1.83–2.60)	<0.01	138 (9.50)	321 (4.81)	2.25 (1.84–2.76)	<0.01	90 (11.2)	11 (10.9)	1.08 (0.83–1.99)	0.79
Preeclampsia												
Mild	72 (3.2)	152 (2.2)	1.44 (1.08–1.91)	>0.01	43 (3.0)	149 (2.2)	1.57 (1.14–2.17)	<0.01	29 (3.6)	3 (3.0)	1.53 (0.81–2.88)	0.19
Severe	29 (1.3)	99 (1.5)	0.88 (0.58–1.33)	0.54	16 (1.1)	97 (1.5)	0.82 (0.53–1.26)	0.36	13 (1.6)	2 (2.0)	0.78 (0.55–1.10)	0.16
GDM	187 (8.3)	311 (4.6)	1.88 (1.56–2.27)	<0.01	114 (7.9)	304 (4.6)	1.85 (1.24–2.78)	<0.01	73 (9.1)	7 (6.9)	1.52 (0.60–3.89)	0.38
ICP	110 (4.9)	122 (1.8)	2.79 (2.15–3.64)	<0.01	61 (4.2)	119 (1.8)	2.37 (1.73–3.24)	<0.01	49 (6.1)	3 (3.0)	3.19 (2.55–4.00)	<0.01
Perinatal complications												
Placental abruption	29 (1.3)	41 (0.6)	2.14 (1.33–3.45)	<0.01	15 (1.0)	39 (0.6)	1.87 (0.78–4.50)	0.05	14 (1.7)	2 (2.0)	0.89 (0.87–0.91)	0.260
Placenta Previa												
Complete	28 (1.2)	65 (1.0)	1.30 (0.83–2.02)	0.25	17 (1.2)	64 (1.0)	1.22 (0.71–2.09)	0.47	11 (1.4)	1 (1.0)	1.39 (0.18–10.87)	0.75
Partial	39 (1.7)	81 (1.2)	1.45 (0.99–2.13)	0.06	23 (1.6)	79 (1.2)	1.38 (0.87–2.19)	0.17	16 (2.0)	2 (2.0)	1.06 (0.13–8.13)	1.00
Marginal	100 (4.4)	271 (4.0)	1.11 (0.88–1.41)	0.38	71 (4.9)	266 (4.0)	1.24 (0.95–1.62)	0.12	29 (3.6)	5 (5.0)	0.72 (0.27–1.90)	0.38
PROM	233 (10.3)	576 (8.5)	1.24 (1.06–1.45)	<0.01	148 (10.2)	568 (8.5)	1.24 (1.03–1.50)	0.02	85 (10.6)	8 (7.9)	1.53 (0.69–3.40)	0.30
Placental adherence	186 (8.2)	47 (6.9)	1.20 (1.00–1.44)	0.04	119 (8.2)	462 (6.9)	1.24 (1.01–1.53)	0.04	67 (8.3)	8 (7.9)	1.14 (0.84–2.37)	0.19
Postpartum hemorrhage	167 (7.4)	182 (2.7)	2.89 (2.33–3.59)	<0.01	107 (7.4)	175 (2.6)	2.99 (2.35–3.82)	<0.01	60 (7.5)	7 (6.9)	1.07 (0.40–2.85)	0.89
Polyhydramnios	32 (1.4)	48 (0.7)	2.01 (1.29–3.16)	<0.01	19 (1.3)	47 (0.7)	1.62 (1.03–2.55)	0.04	13 (1.6)	1 (1.0)	1.59 (0.18–10.87)	0.75
Oligohydramnios	104 (4.6)	268 (4.0)	1.17 (0.93–1.49)	0.18	65 (4.5)	264 (4.0)	1.24 (0.95–1.62)	0.11	39 (4.9)	4 (4.0)	1.40 (0.42–4.65)	0.58
Neonatal outcomes												
Preterm labor	872/2256 (38.7)	866/6768 (12.8)	4.29 (3.84–4.80)	<0.01	262/1453 (18.0)	793/6667 (11.9)	1.85 (1.24–2.78)	<0.01	610/803 (76.0)	73/101 (73.7)	1.08 (0.65–1.71)	0.76
Low birth weight	1121/3059 (36.7)	871/6869 (12.7)	1.72 (1.42–2.08)	<0.01	319/1453 (22.0)	775/6667 (11.6)	1.74 (1.39–2.17)	<0.01	802/1606 (49.9)	96/202 (47.5)	1.35 (1.24–2.65)	0.42
Macrosomia	131/3059 (4.3)	405/6869 (5.9)	9.97 (0.79–1.19)	0.76	83/1453 (5.7)	400/6667 (6.0)	0.95 (0.74–1.21)	0.68	48/1606 (3.0)	5/202 (2.5)	1.22 (0.47–3.14)	0.68
1 min Apgar score ≤7	122/3059 (4.0)	236/6869 (3.4)	1.14 (0.82–1.32)	0.36	53/1453 (3.7)	228/6667 (3.4)	1.15 (0.77–3.08)	0.52	69/1606 (4.3)	8/202 (4.0)	1.20 (0.92–1.58)	0.63
5 min Apgar score ≤7	34/3059 (1.1)	58/6869 (0.8)	1.27 (1.16–2.71)	0.15	13/1453 (0.9)	56/6667 (0.8)	1.00 (0.12–8.33)	0.91	21/1606 (1.8)	2/202 (1.0)	1.90 (0.25–14.57)	0.53

Data are shown as n (%). ART: Assisted reproductive technology; CI: Confidence interval; GDM: Gestational diabetes mellitus; ICP: Intrahepatic cholestasis of pregnancy; OR: Odds ratio; PROM: Premature rupture of membranes.

Table 3: Multivariate analysis of pregnancy outcomes in nulliparous and multiparous groups.

Items	Nulliparous group				Multiparous group			
	ART (n = 2053)	Controls (n = 5820)	OR (95%CI)	P	ART (n = 203)	Controls (n = 948)	OR (95%CI)	P
Pregnancy complication								
Gestational hypertension	198 (9.6)	281 (4.8)	2.18 (1.81–2.62)	<0.01	30 (14.8)	51 (5.4)	2.82 (1.21–8.72)	<0.01
Preeclampsia								
Mild	67 (2.3)	130 (2.2)	1.01 (0.85–1.90)	0.92	5 (2.5)	22 (2.3)	1.17 (0.53–4.06)	0.75
Severe	28 (1.4)	79 (1.4)	1.01 (0.65–1.55)	0.98	1 (0.5)	20 (2.1)	0.23 (0.03–1.72)	0.12
GDM	161 (7.8)	234 (4.0)	1.85 (1.60–2.38)	<0.01	17 (8.4)	77 (8.1)	1.03 (0.49–2.15)	0.95
ICP	110 (4.9)	103 (1.8)	2.87 (2.17–3.80)	<0.01	9 (4.4)	19 (2.0)	2.27 (1.01–5.09)	0.04
Perinatal complications								
Placental abruption	26 (1.3)	33 (0.6)	2.43 (1.46–4.02)	<0.01	3 (1.5)	8 (0.8)	1.48 (0.07–4.68)	0.51
Placenta Previa								
Complete	21 (1.0)	57 (1.0)	1.04 (0.61–1.67)	0.97	7 (3.5)	8 (0.8)	3.61 (1.86–16.87)	<0.01
Partial	36 (1.8)	69 (1.2)	1.16 (1.03–2.34)	0.05	3 (1.5)	12 (1.3)	0.93 (0.27–3.25)	0.91
Marginal	82 (4.0)	215 (3.7)	1.22 (0.88–1.44)	0.36	22 (10.8)	56 (5.9)	1.33 (0.41–2.13)	0.07
PROM	209 (10.2)	497 (8.5)	1.21 (1.02–1.44)	0.03	24 (11.8)	79 (8.3)	1.48 (0.91–2.39)	0.11
Placental adherence	168 (8.2)	406 (7.0)	1.19 (0.99–1.43)	0.07	18 (8.9)	64 (6.8)	1.34 (0.78–2.32)	0.29
Postpartum hemorrhage	151 (7.4)	109 (1.9)	3.85 (2.27–3.58)	<0.01	16 (7.9)	73 (7.7)	1.01 (0.64–6.27)	0.93
Polyhydramnios	29 (1.3)	38 (0.7)	2.16 (1.39–3.65)	0.01	3 (1.5)	10 (1.1)	1.23 (0.20–4.29)	0.83
Oligohydramnios	96 (4.7)	234 (4.0)	1.17 (0.92–1.49)	0.20	8 (3.9)	34 (3.6)	1.10 (0.50–2.42)	0.81
Neonatal outcomes								
Preterm labor	798/2053 (38.9)	753/5820 (12.9)	4.28 (3.81–4.81)	<0.01	74/203 (36.5)	113/948 (11.9)	4.24 (3.00–6.00)	<0.01
Low birth weight	1046/2833 (36.9)	768/5913 (13.0)	3.66 (2.35–3.04)	<0.01	75/226 (31.9)	103/956 (10.8)	2.984 (1.30–4.03)	<0.01
Macrosomia	121/2833 (4.3)	350/5913 (5.9)	0.95 (0.77–1.18)	0.66	10/226 (4.4)	55/956 (5.8)	0.74 (0.45–1.95)	0.63
1 min Apgar score ≤7	118/2833 (4.2)	212/5913 (3.6)	1.21 (0.76–1.89)	0.77	4/226 (3.9)	24/956 (2.5)	1.40 (0.50–2.42)	0.31
5 min Apgar score ≤7	32/2833 (1.2)	50/5913 (0.8)	1.32 (0.72–2.75)	0.64	2/226 (0.7)	8/956 (0.8)	0.75 (0.34–2.54)	0.61

Data are shown as n (%). Nulliparous ART group (2833 infants) consisted of 1273 cases of singleton gestation and 780 cases of twin gestation; Nulliparous control group (5913 infants) consisted of 5727 cases of singleton gestation and 93 cases of twin gestation; Multiparous ART group (226 infants) consisted of 180 cases of singleton gestation and 23 cases of twin gestation; Multiparous control group (956 infants) consisted of 940 cases of singleton gestation and eight cases of twin gestation. ART: Assisted reproductive technology; CI: Confidence interval; GDM: Gestational diabetes mellitus; ICP: Intrahepatic cholestasis of pregnancy; OR: Odds ratio; PROM: Premature rupture of membranes.

(OR 2.18, 95% CI 1.81–2.62), GDM (OR 1.85, 95% CI 1.60–2.38), ICP (OR 2.87, 95% CI 2.17–3.80), placental abruption (OR 2.43, 95% CI 1.46–4.02), postpartum hemorrhage (OR 3.85, 95% CI 2.27–3.58) and polyhydramnios (OR 2.16, 95% CI 1.39–3.65), were more likely occur after ART in nulliparous women. Gestational hypertension (OR 2.82, 95% CI 1.21–8.72) and complete placenta previa (OR 3.61, 95% CI 1.86–16.87) were significantly increased in multiparous women.

The incidences of poor neonatal outcomes in ART nulliparous and multiparous women are shown in Table 3. For nulliparous women, preterm labor (OR, 4.28, 95% CI 3.81–4.81) and low birth weight (OR, 3.66, 95%CI 2.54–

3.04) were significantly different between the two groups. The results were similar between the two groups in multiparous women.

Analysis of pregnancy/perinatal complications and neonatal outcomes in ART and spontaneous pregnancy groups stratified by maternal age

Women who conceived by ART were older than women who conceived spontaneously. The percentage of women ≥35 years old was higher in the ART-conceived group (61.4%) than in the spontaneously pregnant group (37.8%). Therefore, we conducted a maternal age stratification study on the incidences of pregnancy and perinatal complications in ART and control groups [Table 4]. The incidences of gestational hypertension (OR 1.80, 95% CI 1.37–2.39), GDM (OR 1.73, 95% CI 1.64–2.78), ICP (OR 3.03, 95% CI 2.09–4.41), postpartum hemorrhage (OR 2.52, 95% CI 1.83–3.47) were more likely occur after ART when women were younger than 35 years. The risk of gestational hypertension (OR 2.05, 95% CI 1.58–2.68), GDM (OR 1.80, 95% CI 1.37–2.39), ICP (OR 2.65, 95% CI 1.80–3.89), and postpartum hemorrhage (OR 3.37, 95% CI 2.45–4.64) was also markedly increased in advanced age parturient women after ART.

The adverse neonatal outcomes for the ART and control groups according to age stratification are shown in Table 4. Significant increases were observed for preterm labor (OR 4.25, 95% CI 3.61–5.01) and low birth weight (OR, 3.06,

95% CI 2.85–5.04) in the ART group when women were younger than 35 years. For women ≥35 years, the proportions with preterm labor (OR 4.25, 95% CI 3.61–5.01) and low birth weight (OR 3.06, 95% CI 2.85–5.04) were significantly higher for the ART compared with spontaneous group.

Pregnancy/perinatal complications and neonatal outcomes in IVF, ICSI, and spontaneous pregnancy groups

In addition to stratified analysis of maternal age, parity, and birth plurality, we also compared the incidences of pregnancy and perinatal complications, and neonatal outcomes related to different types of ART, including IVF and ICSI [Table 5]. Patients who underwent IVF were more likely to suffer from gestational hypertension (10.1% vs. 4.9%), GDM (8.2% vs. 4.6%), ICP (5.2% vs. 1.8%), placental abruption (1.3% vs. 0.6%), PROM (10.8% vs. 8.5%), postpartum hemorrhage (7.5% vs. 2.7%), polyhydramnios (1.3% vs. 0.7%), preterm labor (39.3% vs. 12.8%), and low birth weight (38.0% vs. 12.7%), compared with spontaneously conceived pregnancies. ICSI pregnancies showed a higher incidence of gestational hypertension (9.9% vs. 4.9%), GDM (8.6% vs. 4.6%), ICP (3.4% vs. 1.8%), placental abruption (1.0% vs. 0.6%), PROM (8.1% vs. 8.5%), postpartum hemorrhage (6.8% vs. 2.7%), polyhydramnios (1.8% vs. 0.7%), preterm labor (35.5% vs. 12.8%), and low birth weight (29.9% vs. 12.7%) than the control group. Differences became insignificant when comparing the incidence between the IVF and ICSI groups, except for PROM. In

Table 4: Multivariate analysis of pregnancy outcomes in ART and controls stratified by maternal age.

Items	Maternal age <35 years				Maternal age ≥35 years			
	ART (n = 871)	Controls (n = 4209)	OR (95% CI)	P	ART (n = 1385)	Controls (n = 2559)	OR (95%CI)	P
Pregnancy complication								
Gestational hypertension	74 (8.5)	198 (4.7)	1.80 (1.37–2.39)	<0.01	154 (11.1)	134 (5.2)	2.05 (1.58–2.68)	<0.01
Preeclampsia								
Mild	24 (2.8)	86 (2.0)	1.39 (1.03–2.46)	0.05	48 (3.5)	66 (2.6)	1.44 (0.84–1.83)	0.28
Severe	10 (1.2)	60 (1.4)	0.83 (0.50–1.74)	0.53	19 (1.4)	39 (1.5)	0.89 (0.48–1.51)	0.87
GDM	71 (8.2)	188 (4.5)	1.73 (1.64–2.78)	<0.01	116 (8.4)	123 (4.8)	1.80 (1.37–2.39)	<0.01
ICP	46 (5.3)	76 (1.8)	3.03 (2.09–4.41)	<0.01	64 (4.6)	46 (1.8)	2.65 (1.80–3.89)	<0.01
Perinatal complications								
Placental abruption	11 (1.3)	28 (0.7)	1.78 (0.89–3.57)	0.10	18 (1.3)	13 (0.5)	2.05 (1.44–6.48)	0.02
Placenta Previa								
Complete	9 (1.0)	35 (0.8)	1.25 (0.60–2.60)	0.56	19 (1.4)	30 (1.2)	1.17 (0.66–2.09)	0.59
Partial	13 (1.5)	52 (1.2)	1.21 (0.66–2.23)	0.54	26 (1.9)	29 (1.1)	1.67 (0.98–2.85)	0.06
Marginal	41 (4.7)	169 (4.0)	1.18 (0.83–1.68)	0.35	59 (4.3)	102 (4.0)	1.07 (0.77–1.49)	0.68
PROM	87 (10.0)	362 (8.6)	1.80 (0.92–1.51)	0.19	146 (10.5)	214 (8.4)	1.29 (1.04–1.61)	0.02
Placental adherence	69 (7.9)	285 (6.8)	1.185 (0.90–1.56)	0.07	117 (8.5)	185 (7.2)	1.18 (0.93–1.51)	0.17
Postpartum hemorrhage	60 (6.9)	120 (2.9)	2.52 (1.83–3.47)	<0.01	107 (7.7)	62 (2.4)	3.37 (2.45–4.64)	<0.01
Polyhydramnios	12 (1.4)	30 (0.7)	1.65 (0.99–3.82)	0.05	20 (1.4)	18 (0.7)	2.07 (1.09–3.92)	0.02
Oligohydramnios	41 (4.7)	160 (3.8)	1.24 (1.11–2.14)	0.11	63 (4.6)	108 (4.2)	1.12 (0.66–1.29)	0.07
Neonatal outcomes								
Preterm labor	333/871 (38.2)	535/4209 (12.7)	4.25 (3.61–5.01)	<0.01	539/1385 (38.9)	331/2559 (12.9)	4.29 (3.66–5.02)	<0.01
Low birth weight	516/1432 (36.0)	556/4275 (13.0)	3.06 (2.85–5.04)	<0.01	605/1627 (37.2)	325/2594 (12.5)	1.79 (1.36–2.36)	<0.01
Macrosomia	50/1432 (3.5)	250/4275 (5.9)	0.90 (0.69–1.35)	0.76	81/1627 (5.0)	155/2594 (6.0)	0.96 (0.73–1.27)	0.79
1 min Apgar score≤7	44/1432 (3.1)	135/4275 (3.2)	0.96 (0.73–1.55)	0.75	78/1627 (4.8)	104/2594 (4.0)	1.21 (0.46–3.00)	0.68
5 min Apgar score≤7	13/1432 (0.9)	33/4275 (0.8)	1.18 (0.57–3.49)	0.13	21/1627 (1.30)	25/2594 (1.0)	1.19 (0.94–3.22)	0.27

Data are shown as n (%). Maternal age <35 years ART (1432 infants) group consisted of 310 cases of singleton gestation and 561 cases of twin gestation; Maternal age <35 years control group (4275 infants) consisted of 4143 cases of singleton gestation and 66 cases of twin gestation; Maternal age ≥35 years ART group (1627 infants) consisted of 1143 cases of singleton gestation and 242 cases of twin gestation; Maternal age ≥35 years control group (2594 infants) consisted of 2524 cases of singleton gestation and 35 cases of twin gestation. ART: Assisted reproductive technology; CI: Confidence interval; GDM: Gestational diabetes mellitus; ICP: Intrahepatic cholestasis of pregnancy; OR: Odds ratio; PROM: Premature rupture of membranes.

Table 5: Chi-squared analysis of pregnancy outcomes in IVF, ICSI, and spontaneous pregnancy groups.

	ART ($n = 2256$)				
Items	IVF ($n = 1873$)	ICSI ($n = 383$)	Controls ($n = 6768$)	χ^2	P
Prenancy complication					
Gestational hypertension	190 (10.1)*	38 (9.9)*	332 (4.9)	78.66	<0.01
Preeclampsia					
Mild	61 (3.3)	11 (2.9)	152 (2.3)	6.45	0.04
Severe	23 (1.2)	6 (1.6)	99 (1.5)	0.64	0.73
GDM	154 (8.2)*	33 (8.6)*	311 (4.6)	44.37	<0.01
ICP	97 (5.2)*	13 (3.4)*	122 (1.8)	67.84	<0.01
Perinatal complications					
Placental abruption	25 (1.3)*	4 (1.0)*	41 (0.6)	10.50	<0.01
Placenta Previa					
Complete	25 (1.3)	3 (0.8)	65 (1.0)	2.26	0.32
Partial	30 (1.6)	9 (2.4)	81 (1.2)	5.01	0.08
Marginal	88 (4.7)	12 (3.1)	271 (4.0)	2.76	0.25
PROM	202 (10.8)*	31 (8.1)	576 (8.5)	9.67	<0.01
Placental adherence	158 (8.4)	28 (7.3)	470 (6.9)	4.84	0.09
Postpartum haemorrhage	141 (7.5)*	26 (6.8)*	182 (2.7)	101.57	<0.01
Polyhydramnios	25 (1.3)*	7 (1.8)*	48 (0.7)	10.57	<0.01
Oligohydramnios	91 (4.9)	13 (3.4)	268 (4.0)	3.53	0.17
Neonatal outcomes					
Preterm labor	736/1873 (39.3)*	136/383 (35.5)*	866/6768 (12.8)	730.40	<0.01
Low birth weight	967/2544 (38.0)*	154/515 (29.9)*	871/6869 (12.7)	31.13	<0.01
Macrosomia	102/2544 (4.0)	29/515 (5.6)	405/6869 (5.9)	2.67	0.26
1 min Apgar score≤7	102/2544 (4.0)	20/515 (3.9)	269/6869 (3.9)	0.73	0.70
5 min Apgar score≤7	27/2544 (1.1)	7/515 (1.4)	58/6869 (0.8)	7.33	0.02

Data are shown as n (%). ART: Assisted reproductive technology; CI: Confidence interval; GDM: Gestational diabetes mellitus; ICP: Intrahepatic cholestasis of pregnancy; ICSI: Intracytoplasmic sperm injection; IVF: *In vitro* fertilization; OR: Odds ratio; PROM: Premature rupture of membranes. * Significantly different from control group ($P < 0.01$). IVF (2544 infants) group consisted of 1202 cases of singleton gestation and 671 cases of twin gestation; ICSI group (515 infants) consisted of 251 cases of singleton gestation and 132 cases of twin gestation; control group (6869 infants) consisted of 6667 cases of singleton gestation and 101 cases of twin gestation.

the IVF group, 202 women had a pregnancy complicated by PROM (10.8%), compared with 31 women in ICSI group (8.1%, $P < 0.001$).

Pregnancy/perinatal complications and neonatal outcomes in fresh, FET and spontaneous pregnancy groups

In considering different ART methods, we also considered different embryo transfer methods. We further studied the incidences of pregnancy/perinatal complications and neonatal outcomes according to different embryo transfer methods, including Fresh and FET [Table 6]. Compared with the control group significantly increased incidences of gestational hypertension (10.0% *vs.* 4.9%), GDM (7.6% *vs.* 4.6%), ICP (4.9% *vs.* 1.8%), PROM (8.9% *vs.* 8.5%), postpartum hemorrhage (8.2% *vs.* 2.7%), polyhydramnios (1.8% *vs.* 0.7%), preterm labor (40.9% *vs.* 12.8%), and low birth weight (38.0% *vs.* 12.7%), were observed in both FET subgroup. Fresh subgroup showed a higher incidence of gestational hypertension (10.2% *vs.* 4.9%), GDM (7.6% *vs.* 4.6%), ICP (4.9% *vs.* 1.8%), PROM (10.9% *vs.* 8.5%), postpartum hemorrhage (7.1% *vs.* 2.7%), polyhydramnios (1.3% *vs.* 0.7%), preterm labor (37.7% *vs.* 12.8%), and low birth weight (36.1% *vs.* 12.7%) than the control group. It is worth mentioning there is only one insignificant difference between the FET

and ET groups. In the FET group, three women had a pregnancy complicated by placental abruption (0.5%), compared with 26 women in ET group (1.6%, $P < 0.001$).

Discussion

In the present retrospective cohort study, we observed the increased risks of perinatal complications and poor neonatal outcomes related to ART, such as GDM, hypertension during pregnancy, ICP, placental abruption, premature rupture of membranes, postpartum hemorrhage, polyhydramnios, premature delivery, and low birth weight. Previous studies have reported that ART has an increased incidence of hypertension during pregnancy, GDM, ICP, postpartum hemorrhage, premature delivery, and low birth weight,[13-16] which is consistent with our present results. The newest ART surveillance in USA reported 23.6% infants conceived with ART were born low birth weight and 29.9% of ART infants were preterm. Several studies have shown that twin pregnancy increased the incidence of adverse pregnancy and birth outcomes.[17-18] However, in our study the twin pregnancy rate in the ART group was over 20 times that in the spontaneous pregnancy group (35.6% *vs.* 1.5%). Are the adverse maternal and

Table 6: Chi-squared analysis of pregnancy outcomes in FET, ET, and spontaneous pregnancy groups.

Items	ART (n = 2256)		Controls (n = 6768)	X^2	P
	FET (n = 673)	ET (n = 1583)			
Pregnancy complication					
Gestational hypertension	67 (10.0)*	161 (10.2)*	332 (4.9)	78.67	<0.01
Preeclampsia					
Mild	20 (3.0)	52 (3.3)	152 (2.3)	6.44	0.04
Severe	9 (1.3)	20 (1.3)	99 (1.5)	0.40	0.82
GDM	51 (7.6)*	136 (8.6)*	311 (4.6)	45.21	<0.01
ICP	33 (4.9)*	77 (4.9)*	122 (1.8)	63.80	<0.01
Perinatal complications					
Placental abruption	3 (0.5)†	26 (1.6)*	41 (0.6)	18.94	<0.01
Placenta Previa					
Complete	10 (1.5)	18 (1.1)	65 (1.0)	1.88	0.39
Partial	9 (1.3)	30 (1.9)	81 (1.2)	4.77	0.09
Marginal	23 (3.4)	77 (4.9)	271 (4.0)	3.30	0.19
PROM	60 (8.9)	173 (10.9)	576 (8.5)	9.19	0.01
Placental adherence	59 (8.8)	127 (8.0)	470 (6.9)	4.63	0.10
Postpartum hemorrhage	55 (8.2)*	112 (7.1)*	182 (2.7)	102.63	<0.01
Polyhydramnios	12 (1.8)*	20 (1.3)	48 (0.7)	11.14	<0.01
Oligohydramnios	34 (5.1)	70 (4.4)	268 (4.0)	2.28	0.32
Neonatal outcomes					
Preterm labor	275/673 (40.9)*	597/1583 (37.7)*	866/6768 (12.8)	730.51	<0.01
Low birth weight	343/903 (38.0)*	778/2156 (36.1)*	871/6869 (12.7)	29.10	<0.01
Macrosomia	31/903 (3.4)	100/2156 (4.7)	405/6869 (5.9)	5.32	0.07
1 min Apgar score≤7	35/903 (3.9)	87/2156 (4.0)	269/6869 (3.9)	2.57	0.28
5 min Apgar score ≤7	8/903 (0.9)	26/2156 (1.2)	58/6869 (0.8)	2.37	0.29

Data are shown as n (%). ART: Assisted reproductive technology; CI: Confidence interval; ET: Embryo transfer; FET: Frozen embryo transfer; GDM: Gestational diabetes mellitus; ICP: Intrahepatic cholestasis of pregnancy; ICSI: Intracytoplasmic sperm injection; IVF: In vitro fertilization; OR: Odds ratio; PROM: Premature rupture of membranes. *Significantly different from control group (P < 0.01). †Significantly different from ET group (P < 0.01). FET group (903 infants) consisted of 443 cases of singleton gestation and 230 cases of twin gestation; ET group (2156 infants) consisted of 1010 cases of singleton gestation and 573 cases of twin gestation; control group (6869 infants) consisted of 6667 cases of singleton gestation and 101 cases of twin gestation.

live-birth outcomes of ART in our study due to twin pregnancies? To address this question, we performed further hierarchical analysis by birth plurality. Our study found that the incidence of some adverse pregnancy outcomes in the twin group was higher than that in the singleton group. For example, the incidence of GDM was higher in the twin ART group than in singleton ART group (9.10% vs. 7.69%). The incidence of hypertension during pregnancy in the twin ART group was higher than in singleton ART group (11.2% vs. 9.5%). These findings are consistent with a prospective cohort study by Moini et al.[10] This result suggested that twins are indeed an important factor leading to adverse pregnancy outcomes. Pregnancy, safe delivery, and good maternal and infant outcomes are the goals of successful ART. Single embryo transfer (SET) was first proposed in Sweden in 2003, and is considered the only effective method to avoid multiple pregnancies in ART. SET is on the rise globally, especially in Europe and Japan. In the United States, SET is recommended for patients under 35 years who experienced success with the first or previous ART and have good quality embryos. In China, more doctors are recommending SET for their patients, especially those already with a healthy child. However, ART is typically self-funded in China, and patients seek a higher pregnancy rate and tend to ignore multiple pregnancies and the associated risks. Therefore, the implementation of SET is challenging. As a simple, effective, and easy to implement method, SET can significantly reduce the incidence of multiple pregnancies and maternal/neonatal complications. Actively promoting SET should be standard trend for ART in China.

In our study, the increased risks were found in ART conceived singletons compared with spontaneously conceived singletons: gestational hypertension (2.25-fold), mild preeclampsia (1.57-fold), GDM (1.85-fold), ICP (2.37-fold), postpartum hemorrhage (2.99-fold), preterm labor (1.85-fold), low birth weight (1.74-fold). Although these rates were reduced when analyses were restricted to singletons, significant differences still remained. We conclude that infertility factors in women requiring ART procedures to conceive contribute to adverse obstetric and perinatal outcomes. Ovulatory disorders are a common cause of sterility. These patients may exhibit serious endocrine disorders, such as insulin resistance, and carry high risk factors for obstetrical diseases, such as GDM, and hypertensive disorder complicating pregnancy. Polycystic ovary syndrome is the most common endocrinopathy of infertile women. Kelley et al have suggested that in pregnancy, PCOS women experience increased risk of miscarriage, gestational diabetes, preeclampsia, and

extremes of fetal birth weight.[19] Some infertile patients have uterine damage due to uterine cavity operations. These patients more likely to have placental adhesions, placenta previa, postpartum hemorrhage and other perioperative complications after ART conception. A study by suggested that women with one previous induced abortion had higher rates of spontaneous preterm birth (adj. OR, 1.4; 95% CI, 1.0–1.9) and PROM (OR, 2.0; 95% CI, 1.4–3.0).[20] Some ART patients have infertility caused by endometriosis. The uterus of such patients often exhibit adenomyosis, which may lead to a large inflexible uterus and difficult obstetrical delivery, limited fetal growth, premature delivery, low birth weight, and other adverse maternal and infant outcomes. Our conclusions are consistent with some previous studies.[21-22] A meta-analysis revealed that endometriosis is associated with an increased risk of placenta previa in pregnancies achieved through ART (OR 2.96 (95% CI 1.25–7.03). They found that the frequencies of preterm birth and placenta previa were significantly increased in women with endometriosis, and the severity of endometriosis might have an adverse impact on ART pregnancy.[22] A retrospective cohort study in Japan also suggested that some causes of maternal infertility, and not the ART technique, may lead to the risk of poor obstetrics and perioperative outcomes.[23] Although these results should be interpreted with caution because the specificities of the subjects and database vary among studies, it seems that maternal factors associated with infertility may contribute to the adverse outcomes rather than the ART procedures themselves. However, the mechanisms leading to these adverse outcomes in infertile women remain unclear. These issues are worth further studying for elucidation. In future work, we will analyze the pregnancy outcomes of ART patients according to the different causes of sterility to reveal potential underlying mechanisms.

With the rapid development of ART technology, many new technologies have been born. Whether the pregnancy outcomes of different ART technology are different is also a hot topic that people are very concerned about. At present, the relevant research is limited, and the conclusions are inconsistent. In our study, differences became insignificant when comparing the incidence between the IVF and ICSI groups, except for PROM. Andrijasevic et al also found that ICSI was more prone to premature delivery and premature rupture of membranes in patients than IVF.[24] There is only one insignificant difference between the FET and ET groups, which is placental abruption. Our results in part complement a recent publication,[25] which demonstrated that although the increased risk of birth defects associated with IVF was no longer significant after adjustment for parental factors, the risk of birth defects associated with ICSI remained increased after multivariate adjustment. A retrospective study from the Centers for Disease Control and Prevention in the United States from 2007 to 2014 showed that transplantation patterns were closely related to infant birth weight in ART patients. The average birth weight of the FET group was 142 g higher than that of the ET group, and the risk of low birth weight in FET infants was significantly reduced.[26] Noguchi et al suggested that embryo transfer is a risk factor for severe postpartum hemorrhage.[27] The inconsistency of the

conclusion may be due to the small sample size of this study. In order to obtain more accurate conclusions, we will further expand the sample size in the next study. According to our study, we suggested that there is no significant difference in pregnancy outcomes between different ART techniques. Clinicians can flexibly adopt various ART techniques according to the actual situation of the patients.

There are several limitations to our study. First, due to the retrospective study design, data were extracted from the medical record system at a single center. The sample number is still relatively small. For getting a more creditable conclusion, we can consider multi-center, prospective studies, and expand the sample size in order to obtain higher level evidence. Second, since no data were collected on the particular cause of infertility, baseline endocrine level, as well as serum hormone levels during ovarian stimulation; therefore, we cannot analyze how these different factors may affect maternal and neonatal outcomes. The intrauterine insemination (IUI) is a relatively less invasive form of ART. However, the records of IUI outcomes are lacked in our database, and not included in the present study, which would lead to bias. It should be considered in future research plan.

To summarize, women who conceived by ART seem to have an increased risk for adverse obstetric and perinatal outcomes. Multiple pregnancies can partly explain this phenomenon. Elective single embryo transfer should be strongly promoted to reduce the perinatal risks of ART pregnancy. Infertility may contribute to the adverse perinatal outcomes. Further studies about how the cause of sterility affects the pregnancy outcome of ART are deserved.

Conflict of interest

None.

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