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Adverse Obstetric Outcomes Associated With In Vitro Fertilization in Singleton Pregnancies: A Prospective Cohort Study

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Abstract

Objective: To compare the obstetric outcomes of women treated with in vitro fertilization (IVF), women with indicators of subfertility but without assisted reproductive technologies, and fertile women with singleton pregnancies. **Methods:** A prospective cohort study was conducted from March 2013 to February 2016 at the Hunan Provincial Maternal and Child Health Hospital in China. Finally, 1260 eligible mothers were recruited into the IVF group, 1899 into the subfertile group, and 2480 into the fertile group. **Results:** Compared to the fertile group, gestational diabetes mellitus (adjusted odds ratio [aOR] = 2.36; 95% confidence interval [CI]: 1.67-3.34), pregnancy-induced hypertension (aOR = 2.23; 95% CI: 1.37-3.64), placenta previa (aOR = 4.11; 95% CI: 2.12-7.96), premature rupture of membranes (aOR = 4.60; 95% CI: 2.71-7.81), anemia in pregnancy (aOR = 2.17; 95% CI: 1.42-3.31), preterm birth (PTB; aOR = 2.19; 95% CI: 1.59-3.02), low birth weight (aOR = 2.82; 95% CI: 2.02-3.94), perinatal mortality (aOR = 2.72; 95% CI: 1.67-4.03), and congenital malformations (aOR = 6.07; 95% CI: 3.14-11.72) were evidently increased in the IVF group, while placenta previa (aOR = 1.67; 95% CI: 1.05-2.67), PTB (aOR = 1.31; 95% CI: 1.05-1.64), low birth weight (aOR = 1.42; 95% CI: 1.12-1.81), and congenital malformations (aOR = 2.03; 95% CI: 1.28-3.21) were also increased in the subfertile group. Additionally, the IVF group compared to the subfertile group was at a higher risk of gestational diabetes mellitus (aOR = 1.40; 95% CI: 1.08-1.83), premature rupture of membranes (aOR = 1.45; 95% CI: 1.00-2.10), PTB (aOR = 1.26; 95% CI: 1.01-1.58), low birth weight (aOR = 1.75; 95% CI: 1.36-2.24), perinatal mortality (aOR = 1.95; 95% CI: 1.02-3.46), and congenital malformations (aOR = 1.81; 95% CI: 1.12-2.92). **Conclusion:** An increased risk of adverse outcomes in IVF pregnancies may be a result of the IVF procedures themselves and the infertility itself together.

Keywords

assisted reproductive technology, in vitro fertilization, maternal complications, adverse pregnancy outcomes, cohort study

Introduction

Assisted reproductive technology (ART) is a group of medical procedures for treating infertility in which both male and female gametes are handled outside the body to achieve conception. Today, in the context of high incidence of infertility,[1] an increasing number of couples require ART, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), to build their family.[2] Up to now, the ART has contributed to the birth of more than 5 million infants worldwide.[3] Children conceived with ART currently constitute as much as 3.3% of all births in Australia, 4.2% in Israel, 1.5% in Japan, 1.6% in the United States, 5.9% in Denmark, and 1.7% to 2.2% in the largest European countries (Germany, France, United Kingdom, and Italy).[4-9]

Although ART may help infertile couples achieve pregnancy, the growth in the use of ART has raised concerns because of the reported associations with pregnancy-related complications and adverse pregnancy outcomes (APOs).[10]

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Much of the increased risk with ART results from multiple pregnancies,[11] however, risks are increased even in singleton pregnancies.[12-16] The underlying mechanisms in the association between ART and adverse outcomes are uncertain. One hypothesis is that ART procedures themselves bring about increased risks of poor outcomes in the ART pregnancies.[4,17-20] Additionally, it has been hypothesized that ART procedures are not responsible for adverse outcomes, and the underlying infertility-related diagnoses of the women who undergo ART contribute directly to the adverse outcomes.[21-23] Distinguishing between these possibilities is complicated by the fact that most studies compare ART pregnancies with those of fertile women rather than with those of infertile women who did not undergo ART,[24,25] which causes the effect of ART procedures could not be distinguished from that of underlying infertility. Besides, in the Chinese context, a comparison group of births to women with indicators of subfertility without ART has not been available in the past studies.

The IVF as one of forms of ART is the most common procedure for infertility treatment in China. Our study aimed at addressing the question whether IVF procedures themselves or underlying infertility or a combination of these bring about increased risks of adverse outcomes in the IVF singleton pregnancies. We used a hospital-based prospective cohort design to develop a comparison group of singleton pregnancies with indicators of subfertility who did not receive ART, thus permitting the examination of underlying risks associated with infertility and providing a more refined assessment of unique impact of IVF on obstetric outcomes.

Methods

Recruitment of Study Participants

Recruitment was conducted by the Hunan Provincial Maternal and Child Health Hospital from March 13, 2013, to February 25, 2016. The Hunan Provincial Maternal and Child Health Hospital was founded in 1947 and is one of the oldest Maternal and Child Health Hospitals in China. Study participants were recruited from the Gynecology and Obstetrics Department, Infertility Clinic, and Reproductive Center in this hospital. All pregnant women visiting this hospital were recruited after giving informed consent when they first participated in prenatal care. We performed this study that accorded with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[26] The recruitment got assistance from the China Postdoctoral Science Foundation, Hunan Provincial Science and Technology Plan Project Foundation, and Hunan Provincial Natural Science Foundation. The study was approved by the ethics committee of the Hunan Provincial Maternal and Child Health Hospital, and written informed consent was obtained from all participants.

Inclusion Criteria and Grouping

The study population comprised eligible pregnant women, their live-born and stillborn infants, and their spouses. For this evaluation, we included participating women who (1) provided informed consent to be in the evaluation; (2) belonged to singleton pregnancies; (3) participated in the follow-up process and had a complete case report form (CRF); and (4) had a pregnancy outcome that could be clearly evaluated. We excluded deliveries of women younger than 15 years and women older than 60 years because of the lack of comparable ART and non-ART groups, respectively. Births of higher order multiplicity (twin, triplet, and quadruplet) were excluded because appropriate size references do not exist. We also excluded the vanishing twins and pregnant women undergoing egg donation.

The eligible pregnant women were further classified into 3 groups including the IVF group, the subfertile group, and the fertile group. The IVF group consisted of pregnant women who had a history of infertility and IVF treatment. The subfertile group included pregnant women who had a recorded diagnosis of infertility but not associated with assisted conception treatment, such as donor oocyte procedures, gamete intrafallopian transfer, IVF with fresh or frozen embryo cycles, and ICSI with fresh or frozen embryo cycles, and were pregnant by minimal medical intervention, ovulation induction (OI) and intrauterine insemination only. The fertile group comprised those who were pregnant by spontaneous conception and had no history of infertility in their records and no infertility treatment.

Outcome Measures

The main outcomes of interest were pregnancy-related complications and APOs. The maternal complications involved were gestational diabetes mellitus, pregnancy-induced hypertension, placenta previa, placental abruption, premature rupture of membranes, and anemia in pregnancy. The APOs involved were preterm birth (PTB; defined as birth at <37 weeks of gestation), very PTB (VPTB; defined as birth at <32 weeks of gestation), low birth weight (LBW; defined as birth weight <2500 g), very LBW (VLBW; defined as birth weight <1500 g), perinatal mortality (defined as stillbirth, fetal death, or neonatal death), and congenital malformations (defined as all major and minor malformations).

Information Collection

All women were followed up every month during their pregnancy. Their spouses were invited to participate in this study and to provide some basic information. These children were followed up until birth outcomes were clearly diagnosed. A standardized CRF developed by experts was used to collect information by specially trained nurses. For participating women, we collected data regarding their sociodemographic characteristics (ie, age, race, education, occupation, family's monthly income per person in the past 1 year, and body mass index [BMI] before pregnancy), behavioral characteristics in the past 6 months before pregnancy (ie, smoking condition, alcohol use, and cocaine/crack use), previous obstetric characteristics (ie, gravidity, parity, and previous pregnancy loss and

related complications), characteristics of personal illness history before pregnancy (ie, sexually transmitted diseases, hysteromyoma, hypertension, hepatitis, diabetes mellitus, congenital malformations, and Mediterranean anemia), dietary and behavioral characteristics during pregnancy (ie, folic acid use, active smoking, passive smoking, alcohol use, whether the diet is balanced or not, and workloads), and incidence of pregnancy-related complications. We also collected data (ie, age, education, occupation, race, BMI, and behavioral characteristics including smoking, alcohol use, and cocaine/crack use) for spouses. For infants, we evaluated birth outcomes.

Data Analysis

We first compared the IVF and subfertile groups with the fertile group as a reference and then compared the IVF group directly with the subfertile group as a reference. Categorical variables were described using frequencies and percentages, and the continuous variables were described using means $\pm$ standard deviation. In this study, all continuous variables were also transformed into categorical variables. Proportions were compared using χ^2 and Fisher exact test, as appropriate. Incidence of adverse outcomes and their 95% confidence intervals (CIs) were calculated. Odds ratios (ORs) and their 95% CI were used to demonstrate the level of association. The unadjusted ORs and adjusted ORs (aORs) were calculated by logistic regression. All factors that were significantly different between the groups in the univariate analysis were included in the multivariable logistic regression. A P value of <.05 was considered statistically significant, except where otherwise specified. All analyses were performed using SAS v9.1 (SAS Institute Inc, Cary, North Carolina).

Results

Recruitment of Study Participants

From March 13, 2013, to February 25, 2016, a total of 7023 pregnant women were recruited when they first participated in prenatal care. Of these, 257 (3.7%) women selected the termination of pregnancy by artificial abortion or induced labor, 722 (10.3%) were still pregnant at the time of follow-up, 298 (4.2%) were lost to follow-up, and 107 (1.5%) lacked complete CRF. Finally, 5639 eligible women were included in this study. Of these, 2480 women were recruited into the fertile group that consisted of pregnant women with no history of infertility and no infertility treatment, 1899 women into the subfertile group that included pregnant women with a recorded diagnosis of infertility without ART, and 1260 women into the IVF group that comprised pregnant women with a history of infertility and IVF treatment.

Sociodemographic and Behavioral Characteristics in the 3 Groups

Remarkable statistical differences were observed between the groups for age, education level, and smoking condition and alcohol use in the past 6 months before pregnancy (Table 1). Overall, women in the IVF group were older ($\chi^2 = 283.112$, $P = .000$), had a lower education level ($\chi^2 = 188.497$, $P = .000$), and had a higher proportions of smoking ($\chi^2 = 32.893$, $P = .000$) and alcohol use ($\chi^2 = 16.656$, $P = .000$) in the past 6 months before pregnancy than either the subfertile group or the fertile group.

Obstetric Characteristics in the 3 Groups

There were significant statistical differences in the 3 groups for obstetric characteristics including gravidity, parity, and history of induced abortion, ectopic pregnancy, APOs, and pregnancy-related complications (Table 2). Generally speaking, the IVF group was more likely to be nulliparous ($\chi^2 = 1508.652$, $P = .000$) and have a history of induced abortion ($\chi^2 = 45.934$, $P = .000$), ectopic pregnancy ($\chi^2 = 304.232$, $P = .000$), APOs ($\chi^2 = 79.716$, $P = .000$), and pregnancy-related complications ($\chi^2 = 48.293$, $P = .000$), when compared with the other groups.

Characteristics of Personal Illness History Before Pregnancy in the 3 Groups

Significant statistical differences were found for a history of hepatitis, diabetes mellitus, and congenital malformations before pregnancy in the 3 groups (Table 3). Overall, the incidence of personal illness including hepatitis ($\chi^2 = 52.465$, $P = .000$), diabetes mellitus ($\chi^2 = 19.816$, $P = .000$), and congenital malformations ($\chi^2 = 13.028$, $P = .001$) before pregnancy were evidently higher in the IVF group than in the remaining groups.

Dietary and Behavioral Characteristics During Pregnancy in the 3 Groups

The distribution of dietary and behavioral characteristics during pregnancy observably differed in the 3 groups (Table 4). Overall, the IVF group had a significantly increased proportion of folic acid use ($\chi^2 = 13.940$, $P = .001$), active smoking ($\chi^2 = 21.734$, $P = .000$), and passive smoking ($\chi^2 = 8.176$, $P = .017$) during pregnancy but a lower proportion of alcohol use ($P = .025$), dietary bias ($\chi^2 = 34.726$, $P = .000$), and heavy workloads ($\chi^2 = 75.754$, $P = .000$), when compared with the other groups.

Spouse's Sociodemographic and Behavioral Characteristics in the 3 Groups

Spouse's age, education level, and history of alcohol use significantly differed in the 3 groups (Table 5). As a whole, spouses in the IVF group were more likely to be older ($\chi^2 = 220.787$, $P = .000$), have a lower education level ($\chi^2 = 111.132$, $P = .000$), and have a lower proportion of alcohol use ($\chi^2 = 46.534$, $P = .000$), when compared with those in the other groups.

Table 1. Percentage Distribution of Sociodemographic and Behavioral Characteristics in the 3 Groups.[a,b]

Characteristics	Fertile Group (n = 2480)	Subfertile Group (n = 1899)	IVF Group (n = 1260)	Univariable Analysis	Unadjusted ORs (95% CI)		
					IVF vs Fertile	Subfertile vs Fertile	IVF vs Subfertile
Age (years)	28.8 ± 4.2	29.72 ± 4.3	31.3 ± 3.8		1.85 (1.70-2.01)[c]	1.25 (1.17-1.34)[c]	1.48 (1.36-1.61)[c]
<25	330 (13.3%)	182 (9.6%)	30 (2.4%)	$\chi^2 = 283.112$, $P = .000$	1	1	1
25-30	1224 (49.4%)	830 (43.7%)	450 (35.7%)		4.04 (2.74-5.97)[c]	1.23 (1.01-1.50)[c]	3.29 (2.20-4.92)[c]
30-35	681 (27.5%)	618 (32.5%)	510 (40.5%)		8.24 (5.57-12.18)[c]	1.65 (1.33-2.03)[c]	5.01 (3.34-7.50)[c]
35-40	203 (8.2%)	239 (12.6%)	255 (20.2%)		13.82 (9.11-20.96)[c]	2.14 (1.65-2.77)[c]	6.47 (4.23-9.90)[c]
≥40	42 (1.7%)	30 (1.6%)	15 (1.2%)		3.93 (1.96-7.90)[c]	1.30 (0.78-2.14)	3.03 (1.46-6.30)[c]
Race							
Han	2411 (97.2%)	1840 (96.9%)	1223 (97.1%)	$\chi^2 = 0.400$, $P = .819$	1	1	1
Minority	69 (2.8%)	59 (3.1%)	37 (2.9%)		1.06 (0.71-1.59)	1.12 (0.79-1.59)	0.94 (0.62-1.43)
Education level					0.70 (0.64-0.75)	0.89 (0.83-0.96)[c]	0.79 (0.73-0.86)[c]
Junior high school or below	242 (9.8%)	269 (14.2%)	315 (25.0%)	$\chi^2 = 188.497$, $P = .000$	1	1	1
Senior middle school	615 (24.8%)	466 (24.5%)	300 (23.8%)		0.37 (0.30-0.45)	0.67 (0.54-0.82)[c]	0.55 (0.44-0.68)[c]
Bachelor degree	1429 (57.6%)	1007 (53.0%)	540 (42.9%)		0.28 (0.24-0.34)	0.62 (0.52-0.75)[c]	0.46 (0.38-0.55)[c]
Master degree	177 (7.1%)	132 (7.0%)	75 (6.0%)		0.32 (0.23-0.44)	0.66 (0.50-0.87)[c]	0.48 (0.35-0.67)[c]
Missing	17 (0.7%)	25 (1.3%)	30 (2.4%)		2.17 (2.01-2.34)[c]	1.24 (1.17-1.31)[c]	1.71 (1.58-1.85)[c]
Family monthly income per person in the past 1 year (RMB)							
≤2500	395 (15.9%)	215 (11.3%)	30 (2.4%)	$\chi^2 = 534.068$, $P = .000$	1	1	1
2500-5000	783 (31.6%)	537 (28.3%)	240 (19.0%)		4.04 (2.71-6.01)[c]	1.26 (1.03-1.54)[c]	3.20 (2.12-4.83)[c]
>5000	510 (20.6%)	306 (16.1%)	105 (8.3%)		2.71 (1.77-4.15)[c]	1.10 (0.89-1.37)	2.46 (1.58-3.83)[c]
Missing	792 (31.9%)	841 (44.3%)	885 (70.2%)		14.71 (10.03-21.59)[c]	1.95 (1.61-2.37)[c]	7.54 (5.09-11.18)[c]
Body mass index before pregnancy							
Standard body weight[d]	1652 (66.6%)	1274 (67.1%)	840 (66.7%)	$\chi^2 = 0.120$, $P = .942$	1	1	1
Underweight, overweight or obese[e]	828 (33.4%)	625 (32.9%)	420 (33.3%)		1.00 (0.86-1.15)	0.98 (0.86-1.11)	1.02 (0.88-1.19)
Smoking condition in the past 6 months before pregnancy							
No	2465 (99.4%)	1872 (98.6%)	1223 (97.1%)	$\chi^2 = 32.893$, $P = .000$	1	1	1
Yes	15 (0.6%)	27 (1.4%)	37 (2.9%)		4.97 (2.72-9.09)[c]	2.37 (1.26-4.47)[c]	2.10 (1.27-3.46)[c]
Alcohol use in the past 6 months before pregnancy							
No	2445 (98.6%)	1861 (98.0%)	1217 (96.6%)	$\chi^2 = 16.656$, $P = .000$	1	1	1
Yes	35 (1.4%)	38 (2.0%)	43 (3.4%)		2.47 (1.57-3.88)[c]	1.43 (0.90-2.27)	1.73 (1.11-2.69)[c]
History of cocaine/crack use in the past 6 months before pregnancy							
No	2480 (100.0%)	1899 (100.0%)	1260 (100.0%)				
Yes	0	0	0				

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; IVF, in vitro fertilization; OR, odd ratio.

[a]N = 5639.

[b]The fertile group consisted of women with no history of infertility and no infertility treatment; the subfertile group included women with indicators of subfertility without ART; the IVF group comprised women with a history of infertility and IVF treatment.

[c]Statistically significant ($\alpha = .05$).

[d]BMI with a range from 18.5 to 23.9.

[e]BMI ≥24 or <18.5.

Table 2. Percentual Distribution of Obstetric Characteristics in the 3 Groups.[a,b]

Characteristics	Fertile Group (n = 2480)	Subfertile Group (n = 1899)	IVF Group (n = 1260)	Univariable Analysis	Unadjusted ORs (95% CI)		
					IVF vs Fertile	Subfertile vs Fertile	IVF vs Subfertile
Gravidity	2.10 ± 1.81	2.16 ± 1.70	2.20 ± 1.23		1.17 (1.09-1.24)[c]	1.06 (1.01-1.12)[c]	1.10 (1.03-1.17)[c]
1	1153 (46.5%)	811 (42.7%)	465 (36.9%)	$\chi^2 = 33.549$, $P = .000$	1	1	1
2	629 (25.4%)	505 (26.6%)	360 (28.6%)		1.42 (1.20-1.68)[c]	1.14 (0.99-1.32)	1.24 (1.04-1.48)[c]
3	363 (14.6%)	311 (16.4%)	240 (19.0%)		1.64 (1.35-1.99)[c]	1.22 (1.02-1.45)[c]	1.35 (1.10-1.65)[c]
≥4	335 (13.5%)	272 (14.3%)	195 (15.5%)		1.44 (1.17-1.78)[c]	1.15 (0.96-1.39)	1.25 (1.01-1.55)[c]
Parity							
Nulliparous	643 (25.9%)	1432 (75.4%)	1020 (81.0%)	$\chi^2 = 1508.652$, $P = .000$	1	1	1
Parous	1837 (74.1%)	467 (24.6%)	240 (19.0%)		0.08 (0.07-0.10)[c]	0.11 (0.10-0.13)[c]	0.72 (0.61-0.86)[c]
History of induced abortion							
No	1750 (70.6%)	1267 (66.7%)	750 (59.5%)	$\chi^2 = 45.934$, $P = .000$	1	1	1
Yes	730 (29.4%)	632 (33.3%)	510 (40.5%)		1.63 (1.42-1.88)[c]	1.20 (1.05-1.36)[c]	1.36 (1.18-1.58)[c]
History of adverse pregnancy outcomes							
No	1416 (57.1%)	980 (51.6%)	525 (41.7%)	$\chi^2 = 79.716$, $P = .000$	1	1	1
Yes	1064 (42.9%)	919 (48.4%)	735 (58.3%)		1.86 (1.62-2.14)[c]	1.25 (1.11-1.41)[c]	1.49 (1.29-1.72)[c]
History of ectopic pregnancy							
No	2439 (98.3%)	1776 (93.5%)	1050 (83.3%)	$\chi^2 = 304.232$, $P = .000$	1	1	1
Yes	41 (1.7%)	123 (6.5%)	210 (16.7%)		11.90 (8.45-16.76)[c]	4.12 (2.88-5.90)[c]	2.89 (2.28-3.65)[c]
History of pregnancy-related complications							
No	1809 (72.9%)	1328 (69.9%)	780 (61.9%)	$\chi^2 = 48.293$, $P = .000$	1	1	1
Yes	671 (27.1%)	571 (30.1%)	480 (38.1%)		1.66 (1.44-1.92)[c]	1.16 (1.02-1.32)[c]	1.43 (1.23-1.66)[c]

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; IVF, in vitro fertilization; OR, odd ratio.
[a]N = 5639.
[b]The fertile group consisted of women with no history of infertility and no infertility treatment; the subfertile group included women with indicators of subfertility without ART; the IVF group comprised women with a history of infertility and IVF treatment.
[c]Statistically significant ($\alpha = .05$).

Table 3. Percentual Distribution of Characteristics of Personal Illness History Before Pregnancy in the 3 Groups.[a,b]

Characteristics	Fertile Group (n = 2480)	Subfertile Group (n = 1899)	IVF Group (n = 1260)	Univariable Analysis	Unadjusted ORs (95% CI)		
					IVF vs Fertile	Subfertile vs Fertile	IVF vs Subfertile
History of sexually transmitted diseases							
No	2472 (99.7%)	1896 (99.8%)	1260 (100.0%)	$P = .083$ (Fisher exact test)		1	
Yes	8 (0.3%)	3 (0.2%)	0		0.49 (0.13-1.85)		
History of hysteromyoma							
No	2461 (99.2%)	1879 (98.9%)	1245 (98.8%)	$\chi^2 = 1.862$, $P = .394$	1	1	1
Yes	19 (0.8%)	20 (1.1%)	15 (1.2%)		1.56 (0.79-3.08)	1.38 (0.73-2.59)	1.13 (0.58-2.22)
History of hypertension							
No	2470 (99.6%)	1895 (99.8%)	1256 (99.7%)	$P = .568$ (Fisher exact test)	1	1	1
Yes	10 (0.4%)	4 (0.2%)	4 (0.3%)		0.79 (0.25-2.51)	0.52 (0.16-1.67)	1.51 (0.38-6.04)
History of hepatitis							
No	2386 (96.2%)	1798 (94.7%)	1140 (90.5%)	$\chi^2 = 52.465$, $P = .000$	1	1	1
Yes	94 (3.8%)	101 (5.3%)	120 (9.5%)		2.67 (2.02-3.53)[c]	1.43 (1.07-1.90)[c]	1.87 (1.42-2.47)[c]
History of diabetes mellitus							
No	2476 (99.8%)	1892 (99.6%)	1245 (98.8%)	$\chi^2 = 19.816$, $P = .000$	1	1	1
Yes	4 (0.2%)	7 (0.4%)	15 (1.2%)		7.46 (2.47-22.52)[c]	2.29 (0.67-7.84)	3.26 (1.32-8.01)[c]
History of congenital malformations							
No	2474 (99.8%)	1887 (99.4%)	1245 (98.8%)	$\chi^2 = 13.028$, $P = .001$	1	1	1
Yes	6 (0.2%)	12 (0.6%)	15 (1.2%)		4.97 (1.92-12.84)[c]	2.62 (0.98-7.00)	1.90 (0.88-4.06)
History of Mediterranean anemia							
No	2463 (99.3%)	1888 (99.4%)	1245 (98.8%)	$\chi^2 = 4.087$, $P = .130$	1	1	1
Yes	17 (0.7%)	11 (0.6%)	15 (1.2%)		1.75 (0.87-3.51)	0.84 (0.39-1.81)	2.07 (0.95-4.52)

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; IVF, in vitro fertilization; OR, odd ratio.

[a]N = 5639.

[b]The fertile group consisted of women with no history of infertility and no infertility treatment; the subfertile group included women with indicators of subfertility without ART; the IVF group comprised women with a history of infertility and IVF treatment.

[c]Statistically significant ($\alpha = .05$).

Table 4. Percentual Distribution of Dietary and Behavioral Characteristics During Pregnancy in the 3 Groups.[a,b]

Characteristics	Fertile Group (n = 2480)	Subfertile Group (n = 1899)	IVF Group (n = 1260)	Univariable Analysis	Unadjusted ORs (95% CI)		
					IVF vs Fertile	Subfertile vs Fertile	IVF vs Subfertile
Folic acid use during pregnancy							
Yes	2401 (96.8%)	1854 (97.6%)	1245 (98.8%)	$\chi^2 = 13.940$, $P = .001$	1	1	1
No	79 (3.2%)	45 (2.4%)	15 (1.2%)		0.37 (0.21-0.64)[c]	0.74 (0.51-1.07)	0.50 (0.28-0.89)[c]
Active smoking during pregnancy							
No	2478 (99.9%)	1889 (99.5%)	1245 (98.8%)	$\chi^2 = 21.734$, $P = .000$	1	1	1
Yes	2 (0.1%)	10 (0.5%)	15 (1.2%)		14.93 (3.41-65.38)[c]	6.56 (1.44-29.97)[c]	2.28 (1.02-5.08)[c]
Passive smoking during pregnancy							
No	697 (28.1%)	520 (27.4%)	300 (23.8%)	$\chi^2 = 8.176$, $P = .017$	1	1	1
Yes	1783 (71.9%)	1379 (72.6%)	960 (76.2%)		1.25 (1.07-1.46)[c]	1.04 (0.91-1.19)	1.21 (1.02-1.42)[c]
Alcohol use during pregnancy							
No	2468 (99.5%)	1891 (99.6%)	1260 (100.0%)	$P = .025$ (Fisher exact test)		1	
Yes	12 (0.5%)	8 (0.4%)	0		0.87 (0.36-2.13)		
Dietary bias during pregnancy							
No	2182 (88.0%)	1716 (90.4%)	1185 (94.0%)	$\chi^2 = 34.726$, $P = .000$	1	1	1
Yes	298 (12.0%)	183 (9.6%)	75 (6.0%)		0.46 (0.36-0.60)[c]	0.78 (0.64-0.95)[c]	0.59 (0.45-0.78)[c]
Workloads during pregnancy							
Light	1850 (74.6%)	1498 (78.9%)	1095 (86.9%)	$\chi^2 = 75.754$, $P = .000$	1	1	1
Heavy	630 (25.4%)	401 (21.1%)	165 (13.1%)		0.44 (0.37-0.53)[c]	0.79 (0.68-0.91)[c]	0.56 (0.46-0.69)[c]

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; IVF, in vitro fertilization; OR, odd ratio.

[a]n = 5639.

[b]The fertile group consisted of women with no history of infertility and no infertility treatment; the subfertile group included women with indicators of subfertility without ART; the IVF group comprised women with a history of infertility and IVF treatment.

[c]Statistically significant ($\alpha = .05$).

Table 5. Percentual Distribution of Spouse's Sociodemographic and Behavioral Characteristics in the 3 Groups.[a,b]

Characteristics	Fertile Group (n = 2480)	Subfertile Group (n = 1899)	IVF Group (n = 1260)	Univariable Analysis	Unadjusted ORs (95% CI)		
					IVF vs Fertile	Subfertile vs Fertile	IVF vs Subfertile
Age, years	31.2 ± 5.2	32.2 ± 5.3	33.9 ± 4.7		1.45 (1.36-1.55)[c]	1.17 (1.10-1.23)[c]	1.24 (1.16-1.33)[c]
<25	127 (5.1%)	66 (3.5%)	0	$\chi^2 = 220.787$, $P = .000$	1	1	1
25-30	930 (37.5%)	553 (29.1%)	210 (16.7%)		0.43 (0.32-0.56)[c]	0.80 (0.63-1.01)	0.54 (0.40-0.72)[c]
30-35	796 (32.1%)	638 (33.6%)	435 (34.5%)		1.03 (0.79-1.34)	1.07 (0.85-1.36)	0.96 (0.73-1.27)
35-40	388 (15.6%)	412 (21.7%)	375 (29.8%)		1.82 (1.38-2.40)[c]	1.42 (1.10-1.83)[c]	1.28 (0.96-1.71)
≥40	168 (6.8%)	148 (7.8%)	135 (10.7%)		1.52 (1.09-2.10)[c]	1.18 (0.87-1.60)	1.29 (0.91-1.81)
Missing	71 (2.9%)	82 (4.3%)	105 (8.3%)		0.87 (0.83-0.91)[c]	0.96 (0.93-1.00)	0.90 (0.86-0.95)[c]
Education level							
Junior high school or below	270 (10.9%)	219 (11.5%)	195 (15.5%)	$\chi^2 = 111.132$, $P = .000$	1	1	1
Senior middle school	576 (23.2%)	475 (25.0%)	345 (27.4%)		0.83 (0.66-1.04)	1.02 (0.82-1.26)	0.82 (0.64-1.04)
Bachelor degree	1353 (54.6%)	952 (50.1%)	510 (40.5%)		0.52 (0.42-0.64)[c]	0.87 (0.71-1.06)	0.60 (0.48-0.75)[c]
Master degree	196 (7.9%)	145 (7.6%)	90 (7.1%)		0.64 (0.47-0.87)[c]	0.91 (0.69-1.21)	0.70 (0.50-0.97)[c]
Missing	85 (3.4%)	108 (5.7%)	120 (9.5%)				
Body mass index							
Standard body weight[d]	1226 (49.4%)	890 (46.9%)	555 (44.0%)	$\chi^2 = 2.492$, $P = .288$	1	1	1
Underweight, overweight, or obese[e]	1163 (46.9%)	904 (47.6%)	585 (46.4%)		1.11 (0.97-1.28)	1.07 (0.95-1.21)	1.04 (0.90-1.20)
Missing	91 (3.7%)	105 (5.5%)	120 (9.5%)				
History of smoking							
No	1104 (44.5%)	843 (44.4%)	525 (41.7%)	$\chi^2 = 3.113$, $P = .211$	1	1	1
Yes	1376 (55.5%)	1056 (55.6%)	735 (58.3%)		1.12 (0.98-1.29)	1.01 (0.89-1.13)	1.12 (0.97-1.29)
History of alcohol use							
No	1068 (43.1%)	872 (45.9%)	690 (54.8%)	$\chi^2 = 46.534$, $P = .000$	1	1	1
Yes	1412 (56.9%)	1027 (54.1%)	570 (45.2%)		0.63 (0.55-0.72)[c]	0.89 (0.79-1.01)	0.70 (0.61-0.81)[c]
History of cocaine/crack use							
No	2473 (99.7%)	1896 (99.8%)	1260 (100.0%)	$P = .142$ (Fisher exact test)		1	
Yes	7 (0.3%)	3 (0.2%)	0		0.56 (0.14-2.17)		

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; IVF, in vitro fertilization; OR, odd ratio.

[a]N = 5639.

[b]The fertile group consisted of women with no history of infertility and no infertility treatment; the subfertile group included women with indicators of subfertility without ART; the IVF group comprised women with a history of infertility and IVF treatment.

[c]Statistically significant ($\alpha = .05$).

[d]BMI with a range from 18.5 to 23.9.

[e]BMI ≥24 or <18.5.

Incidence of Adverse Outcomes in the 3 Groups

Table 6 shows the unadjusted incidence of cesarean sections, pregnancy-related complications, and APOs in the 3 groups. There were significant statistical differences for the incidence of cesarean sections, gestational diabetes mellitus, pregnancy-induced hypertension, placenta previa, placental abruption, premature rupture of membranes, PTB, LBW, VLBW, perinatal mortality, and congenital malformations in the 3 groups ($\chi^2 \geq 13.104$, all $P \leq .001$).

The IVF group compared with the fertile group was more likely to have cesarean sections (53.2% vs 23.7%), gestational diabetes mellitus (13.1% vs 8.8%), pregnancy-induced hypertension (7.0% vs 3.3%), placenta previa (4.0% vs 1.5%), placental abruption (1.5% vs 0.3%), premature rupture of membranes (6.8% vs 2.8%), PTB (17.6% vs 7.9%), LBW (16.9% vs 6.2%), VLBW (2.4% vs 1.0%), perinatal mortality (18.3‰ vs 5.6‰), and congenital malformations (5.2% vs 1.4%).

The subfertile group compared with the fertile group was at a higher incidence of cesarean sections (35.6% vs 23.7%), pregnancy-induced hypertension (4.6% vs 3.3%), placenta previa (2.4% vs 1.5%), premature rupture of membranes (4.1% vs 2.8%), PTB (12.8% vs 7.9%), LBW (11.4% vs 6.2%), and congenital malformations (2.9% vs 1.4%).

The IVF group compared with the subfertile group had a significantly increased incidence of cesarean sections (53.2% vs 35.6%), gestational diabetes mellitus (13.1% vs 10.0%), pregnancy-induced hypertension (7.0% vs 4.6%), placenta previa (4.0% vs 2.4%), placental abruption (1.5% vs 0.6%), premature rupture of membranes (6.8% vs 4.1%), PTB (17.6% vs 12.8%), LBW (16.9%% vs 11.4%), VLBW (2.4% vs 1.1%), perinatal mortality (18.3‰ vs 8.4‰), and congenital malformations (5.2% vs 2.9%).

Findings From the Multiple Logistic Regression Analysis

Table 7 displays the aORs and 95% CIs for adverse outcomes of the 3 fertility groups, controlling for the covariates noted. We compared the IVF and subfertile groups with the fertile group as a reference and then compared the IVF group directly with the subfertile group as a reference.

The IVF group compared with the fertile group had an evidently higher risk of gestational diabetes mellitus (aOR = 2.36; 95% CI: 1.67-3.34), pregnancy-induced hypertension (aOR = 2.23; 95% CI: 1.37-3.64), placenta previa (aOR = 4.11; 95% CI: 2.12-7.96), premature rupture of membranes (aOR = 4.60; 95% CI: 2.71-7.81), anemia in pregnancy (aOR = 2.17; 95% CI: 1.42-3.31), PTB (aOR = 2.19; 95% CI: 1.59-3.02), LBW (aOR = 2.82; 95% CI: 2.02-3.94), perinatal mortality (aOR = 2.72; 95% CI: 1.67-4.03), and congenital malformations (aOR = 6.07; 95% CI: 3.14-11.72).

The subfertile group compared with the fertile group significantly increased the risk of placenta previa (aOR = 1.67; 95% CI: 1.05-2.67), PTB (aOR = 1.31; 95% CI: 1.05-1.64), LBW (aOR = 1.42; 95% CI: 1.12-1.81), and congenital malformations (aOR = 2.03; 95% CI: 1.28-3.21).

The IVF group compared with the subfertile group was at a higher risk of gestational diabetes mellitus (aOR = 1.40; 95% CI: 1.08-1.83), premature rupture of membranes (aOR = 1.45; 95% CI: 1.00-2.10), PTB (aOR = 1.26; 95% CI: 1.01-1.58), LBW (aOR = 1.75; 95% CI: 1.36-2.24), perinatal mortality (aOR = 1.95; 95% CI: 1.02-3.46), and congenital malformations (aOR = 1.81; 95% CI: 1.12-2.92).

Discussion

In recent years, available evidence has emerged that ART pregnancies are at an increased risk of poor outcomes when compared with those conceived naturally. However, most studies of outcomes of ART have not distinguished the effect of ART from that of underlying infertility because of the absence of appropriate control groups.[24,25] The outcomes of ART pregnancies have been analyzed and compared with spontaneous conceptions,[2,5,6,27-32] across different treatment parameters[22,33] and within women themselves across different pregnancies[4,17,34] and within a survey population,[35] to measure the delay in becoming pregnant. However, in the Chinese context, a comparison group of pregnancies with indicators of subfertility without ART has not been available in the past.

Our study has addressed several of the major problems that have limited past research efforts to examine obstetric outcomes, most notably the inability to distinguish between outcomes that may be the result of ART and those resulting from underlying infertility. The results demonstrated that many of the adverse outcomes of IVF were also seen in the subfertile pregnancies without ART treatment, which indicated that underlying infertility can result in poor outcomes and that these occurred even in the absence of ART treatment. In the present study, the women's sociodemographic characteristics, behavioral characteristics in the past 6 months before pregnancy, obstetric history, personal illness history before pregnancy, and dietary and behavioral characteristics during pregnancy, as well as spouses' sociodemographic and behavioral characteristics were compared between the groups. We found that many risk factors for infertility, such as advanced maternal age, obesity, smoking, alcohol use, and previous pregnancy loss, were also strong for adverse obstetric outcomes resulting in very strong confounding by indication. However, we have controlled these confounding factors using multiple logistic regression analysis.

After adjusting for a wide range of potential confounders, we observed that gestational diabetes mellitus (aOR = 2.36), pregnancy-induced hypertension (aOR = 2.23), placenta previa (aOR = 4.11), premature rupture of membranes (aOR = 4.60), anemia in pregnancy (aOR = 2.17), PTB (aOR = 2.19), LBW (aOR = 2.82), perinatal mortality (aOR = 12.17), NRDS (aOR = 1.69), and congenital malformations (aOR = 6.07) were increased among the IVF pregnancies compared with spontaneously conceived pregnancies in a fertile population, but that placenta previa (aOR = 1.67), PTB (aOR = 1.31), LBW (aOR = 1.42), and congenital malformations (aOR = 2.03) were also increased in a subfertile population. Besides, the IVF pregnancies compared with those with indicators of

Table 6. Incidence of Adverse Outcomes in the 3 Groups.[a,b]

Outcomes	Fertile Group (n = 2480)	Subfertile Group (n = 1899)	IVF Group (n = 1260)	Univariable Analysis	Unadjusted ORs (95% CI)		
					IVF vs Fertile	Subfertile vs Fertile	IVF vs Subfertile
Cesarean sections	23.7% (95% CI: 22.1-25.4)	35.6% (95% CI: 33.5-37.8)	53.2% (95% CI: 50.4-55.9)	$\chi^2 = 324.050$, $P = .000$	1.91 (1.78-2.06)[c]	1.78 (1.56-2.03)[c]	2.05 (1.78-2.38)[c]
Pregnancy-related complications							
Gestational diabetes mellitus	8.8% (95% CI: 7.8-10.0)	10.0% (95% CI: 8.7-11.4)	13.1% (95% CI: 11.4-15.1)	$\chi^2 = 16.782$, $P = .000$	1.25 (1.12-1.39)[c]	1.14 (0.93-1.40)	1.36 (1.09-1.70)[c]
Pregnancy-induced hypertension	3.3% (95% CI: 2.7-4.1)	4.6% (95% CI: 3.8-5.7)	7.0% (95% CI: 5.7-8.5)	$\chi^2 = 25.906$, $P = .000$	1.48 (1.27-1.73)[c]	1.42 (1.05-1.93)[c]	1.55 (1.14-2.10)[c]
Placenta previa	1.5% (95% CI: 1.1-2.0)	2.4% (95% CI: 1.8-3.2)	4.0% (95% CI: 3.0-5.2)	$\chi^2 = 23.348$, $P = .000$	1.68 (1.35-2.08)[c]	1.65 (1.06-2.57)[c]	1.70 (1.13-2.56)[c]
Placental abruption	0.3% (95% CI: 0.2-0.6)	0.6% (95% CI: 0.4-1.1)	1.5% (95% CI: 1.0-2.4)	$\chi^2 = 17.241$, $P = .000$	2.18 (1.44-3.29)[c]	1.97 (0.80-4.82)	2.41 (1.17-4.98)[c]
Premature rupture of membranes	2.8% (95% CI: 2.2-3.6)	4.1% (95% CI: 3.3-5.0)	6.8% (95% CI: 5.6-8.4)	$\chi^2 = 33.838$, $P = .000$	1.59 (1.35-1.87)[c]	1.46 (1.05-2.02)[c]	1.73 (1.26-2.38)[c]
Anemia in pregnancy	7.0% (95% CI: 6.0-8.1)	7.1% (95% CI: 6.0-8.3)	7.5% (95% CI: 6.1-9.0)	$\chi^2 = 0.310$, $P = .858$	1.04 (0.91-1.18)	1.01 (0.80-1.28)	1.06 (0.81-1.40)
Adverse pregnancy outcomes							
Preterm birth	7.9% (95% CI: 6.9-9.1)	12.8% (95% CI: 11.4-14.4)	17.6% (95% CI: 15.6-19.8)	$\chi^2 = 79.411$, $P = .000$	1.58 (1.42-1.75)[c]	1.71 (1.40-2.09)[c]	1.46 (1.20-1.78)[c]
Very preterm birth	1.4% (95% CI: 1.0-1.9)	1.2% (95% CI: 0.8-1.8)	1.2% (95% CI: 0.7-2.0)	$\chi^2 = 0.452$, $P = .798$	0.93 (0.69-1.26)	0.84 (0.49-1.45)	1.03 (0.53-1.99)
Low birth weight	6.2% (95% CI: 5.3-7.2)	11.4% (95% CI: 10.0-12.9)	16.9% (95% CI: 14.9-19.1)	$\chi^2 = 106.411$, $P = .000$	1.75 (1.57-1.96)[c]	1.94 (1.56-2.41)[c]	1.59 (1.29-1.95)[c]
Very low birth weight	1.0% (95% CI: 0.7-1.5)	1.1% (95% CI: 0.7-1.7)	2.4% (95% CI: 1.7-3.4)	$\chi^2 = 13.104$, $P = .001$	1.55 (1.18-2.02)[c]	1.10 (0.61-1.97)	2.18 (1.24-3.83)[c]
Perinatal mortality	5.6‰ (95% CI: 3.3-9.4)	8.4‰ (95% CI: 5.2-13.6)	18.3‰ (95% CI: 12.2-27.3)	$\chi^2 = 14.558$, $P = .001$	1.81 (1.30-2.53)[c]	1.50 (0.73-3.07)	2.19 (1.15-4.16)[c]
Congenital malformations	1.4% (95% CI: 1.0-2.0)	2.9% (95% CI: 2.2-3.8)	5.2% (95% CI: 4.1-6.5)	$\chi^2 = 44.126$, $P = .000$	1.95 (1.58-2.40)[c]	2.08 (1.36-3.20)[c]	1.82 (1.26-2.63)[c]

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; IVF, in vitro fertilization; OR, odd ratio.

[a]N = 5639.

[b]The fertile group consisted of women with no history of infertility and no infertility treatment; the subfertile group included women with indicators of subfertility without ART; the IVF group comprised women with a history of infertility and IVF treatment.

[c]Statistically significant ($\alpha = .05$).

Table 7. Multiple Logistic Regression Analysis of the Risk for Pregnancy-Related Complications and Adverse Pregnancy Outcomes.[a]

Outcomes	Adjusted ORs (95% CI)		
	The IVF Group vs the Fertile Group[b]	The Subfertile Group vs the Fertile Group[c]	The IVF Group vs the Subfertile Group[d]
Pregnancy-related complications			
Gestational diabetes mellitus	2.36 (1.67-3.34)[e]	1.20 (0.96-1.49)	1.40 (1.08-1.83)[e]
Pregnancy-induced hypertension	2.23 (1.37-3.64)[e]	1.19 (0.85-1.66)	1.19 (0.84-1.68)
Placenta previa	4.11 (2.12-7.96)[e]	1.67 (1.05-2.67)[e]	1.62 (0.98-2.68)
Placental abruption	2.63 (0.68-10.14)	1.41 (0.52-3.82)	1.27 (0.57-2.83)
Premature rupture of membranes	4.60 (2.71-7.81)[e]	1.41 (0.99-2.01)	1.45 (1.00-2.10)[e]
Anemia in pregnancy	2.17 (1.42-3.31)[e]	1.20 (0.94-1.53)	1.34 (0.96-1.88)
Adverse pregnancy outcomes			
Preterm birth	2.19 (1.59-3.02)[e]	1.31 (1.05-1.64)[e]	1.26 (1.01-1.58)[e]
Very preterm birth	0.77 (0.36-1.65)	0.66 (0.36-1.21)	0.42 (0.11-1.61)
Low birth weight	2.82 (2.02-3.94)[e]	1.42 (1.12-1.81)[e]	1.75 (1.36-2.24)[e]
Very low birth weight	1.42 (0.64-3.17)	0.53 (0.26-1.09)	0.67 (0.24-1.87)
Perinatal mortality	2.72 (1.67-4.03)[e]	1.71 (0.95-3.08)	1.95 (1.02-3.46)[e]
Congenital malformations	6.07 (3.14-11.72)[e]	2.03 (1.28-3.21)[e]	1.81 (1.12-2.92)[e]

Abbreviations: APO, adverse pregnancy outcome; ART, assisted reproductive technology; CI, confidence interval; IVF, in vitro fertilization; OR, odd ratio.
[a]The fertile group consisted of women with no history of infertility and no infertility treatment; the subfertile group included women with indicators of subfertility without ART; the IVF group comprised women with a history of infertility and IVF treatment.
[b]Adjusted for maternal age, education level, family monthly income per person in the past 1 year, smoking condition and alcohol use in the past 6 months before pregnancy, gravidity, parity, history of induced abortion and ectopic pregnancy, history of APOs and pregnancy-related complications, personal illness history including hepatitis, diabetes mellitus and congenital malformations, folic acid use, active and passive smoking, and dietary bias and workloads during pregnancy, as well as paternal age, education level, and history of alcohol use; additionally, when assessing the risk of APOs, we also adjusted for current pregnancy-related complications.
[c]Adjusted for maternal age, education level, family monthly income per person in the past 1 year, smoking condition in the past 6 months before pregnancy, gravidity, parity, history of induced abortion and ectopic pregnancy, history of APOs and pregnancy-related complications, personal hepatitis history, active smoking, and dietary bias and workloads during pregnancy, as well as paternal age; additionally, when assessing the risk of APOs, we also adjusted for current pregnancy-related complications.
[d]Adjusted for maternal age, education level, family monthly income per person in the past 1 year, smoking condition and alcohol use in the past 6 months before pregnancy, gravidity, parity, history of induced abortion and ectopic pregnancy, history of APOs and pregnancy-related complications, personal illness history including hepatitis and diabetes mellitus, folic acid use, active and passive smoking, and dietary bias and workloads during pregnancy, as well as paternal age, education level and history of alcohol use; additionally, when assessing the risk of APOs, we also adjusted for current pregnancy-related complications.
[e]Statistically significant ($\alpha = .05$).

subfertility without ART were at a higher risk of gestational diabetes mellitus (aOR = 1.40), premature rupture of membranes (aOR = 1.45), PTB (aOR = 1.26), LBW (aOR = 1.75), perinatal mortality (aOR = 5.36), and congenital malformations (aOR = 1.81). Some studies have been conducted to examine the outcomes of mothers with subfertility indicators who were pregnant without ART treatment, but they have generally been based on non-Chinese data sources[21-23,35-38] or systematic reviews that primarily drew on non-Chinese studies.[39-40] In addition, these studies mainly focused on the APO except for congenital malformations and ignored the pregnancy-related complications. Previous studies generally found, as we did, an increased risk of PTB and LBW among pregnancies with subfertility indicators independent of ART.

The importance of the present work is to extend these comparisons to a Chinese population in which ART treatment parameters, including the amount of ovulation stimulation medication and number of embryos transferred, may be different than those of other countries. When comparing the obstetric outcomes of ART pregnancies with those conceived spontaneously, our findings were largely consistent with the past studies.[27-32] Our previous reviews[11,16] also suggested that the ART pregnancies compared with those conceived spontaneously in a fertile population experienced a significantly increased risk of pregnancy-induced hypertension, gestational diabetes mellitus, placenta previa, placental abruption, antepartum or postpartum hemorrhage, polyhydramnios or oligohydramnios, cesarean sections, PTB, VPTB, LBW, VLBW, small for gestational age, perinatal mortality, and congenital malformation.

The reasons for the increase in adverse outcomes with ART are uncertain and warrant further research. Previous reports[4,17,22,23,38] have indicated that an increased risk of poor outcomes in pregnancies generated with ART may be a result of the ART procedures themselves or the underlying infertility of couples seeking treatment. Whether one or a combination of these factors contributing to obstetric risk remains unclear. Some studies[4,17,18-20] suggested that factors associated with ART procedures themselves, such as the medications used to induce ovulation or to maintain the pregnancy in the early stages, the culture media composition, the length of time in culture, the freezing and thawing of embryos, the potential for polyspermic fertilization, the delayed fertilization of the oocyte, altered hormonal environment at the time of

implantation, and the manipulation of gametes and embryos or a combination of these, may increase the risk of adverse outcomes. However, some studies have concluded that the ART procedures associated with IVF and ICSI are not responsible for these adverse outcomes. This viewpoint is supported by studies of subfertile women who conceived without the aid of ART and yet exhibited an increased risk of PTB, [21-23,36,41-42] LBW,[22,36,41,42] perinatal mortality,[22] congenital malformations,[41] pregnancy-induced hypertension or preeclampsia,[36,41,42] gestational diabetes,[41] and cesarean delivery.[36,41,42] Our study confirmed that the ART procedures themselves and underlying infertility together contributed to poor outcomes in the ART pregnancies.

This study has several strengths. First, the data are comprehensive and unique as they include numerous variables related to both exposures and outcomes. We collected the maternal sociodemographic characteristics, behavioral characteristics in the past 6 months before pregnancy, obstetric history characteristics, personal illness history before pregnancy, dietary and behavioral characteristics during pregnancy, paternal sociodemographic and behavioral data, and neonatal data, which allow us to tightly control for potential confounding between the groups when assessing the risk of adverse outcomes. Accordingly, the data provide us with the opportunity to refine previous study questions and conduct novel analyses among distinct subgroups of the population. Second, we used a prospective cohort study design, which minimizes recall and selection biases. Moreover, the cohort study design allows for an assessment of several outcomes simultaneously, which is not only more comprehensive but also helps to assess the validity of the study findings. Third, our outcomes of interest were wide. We are not only concerned about the APOs but also concerned about pregnancy complications in the same population, which will provide basic data for the assessment of ART safety and its long-term risk. Fourth, all patients included in this study came from the same fertility center treated by essentially the same team of care providers who followed similar protocols and this reduced difficulties in the interpretation of results caused by differences in techniques across centers or among staff. Finally, outcomes in this study were assessed by a team consisting of epidemiologist, obstetrician, neonatologist, and research nurse using structured chart review. Charts for uncertain diagnoses were audited and adjudicated by the chart review team, and the final diagnosis was reached by the consensus of the team.

Potential limitations of this study should be considered. First, although a wide range of potential confounding factors have been adjusted, we still cannot rule out the possibility that residual confounding including environmental exposure before or during pregnancy, ethnic background, allogenic nature of the fetus, and pregnancy intention could affect the results, because these factors do not explain all of the obstetric risk. Second, the sample size was not large enough, especially for rare outcomes and analysis restricting study individuals with specific characteristics. Perceivable differences between crude and adjusted estimations have resulted because of the limited sample and the need to adjust for several important confounding factors simultaneously. Third, our study populations from the same fertility center treated by the same team of care providers and controls from the same catchment area could lead to increased internal validity,[2] which may affect the representativeness of samples, bring about a selection bias, and compromise the generalization of the study findings. Fourth, some women in the fertile group may have been exposed to hormones through non-ART OI or ovarian stimulation protocols. In addition, a small percentage of couples in the non-ART group may have experienced subfertility similar to the ART group but continued to attempt conception without ART and were then successful. This would possibly have the effect of weakening the ORs of poor outcomes related to infertility.[43] Additionally, we were also unable to determine definitively how long mothers in the subfertile group had been trying to conceive and whether they conceived spontaneously or used fertility drugs or other non-ART procedures to conceive. Longer infertile intervals have been associated with a greater risk for adverse outcome.[38] This may explain some of the differences between the ART and subfertile groups. Likewise, we were not able to assess time to pregnancy for women in the fertile group. However, our study question focused on the overall impact of the use of ART rather than an explicit comparison between the fertility drug use and ART.

In summary, the present study indicated that an increased risk of adverse outcomes in singleton pregnancies created with ART could be a result of the ART procedures themselves and the infertility itself together. Our study has provided a strong evidence for a significant role of underlying infertility-related diseases as a major contributing factor to increase the risk of maternal complications and APOs in the ART pregnancies. Future research on the subfertility group itself can yield important information through refinement of the subfertility measure and further exploration of poor outcomes in this population. An improved understanding of this topic will have important clinical implications, given the possibility that the clear results might be useful for counseling ART patients and properly designing the consent forms.

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References

1. Quintino-Moro A, Zantut-Wittmann DE, Tambascia M, Machado Hda C, Fernandes A. High prevalence of infertility among women with Graves' disease and Hashimoto's thyroiditis. *Int J Endocrinol*. 2014;2014:982705.
2. Wen SW, Leader A, White RR, et al. A comprehensive assessment of outcomes in pregnancies conceived by in vitro fertilization/intracytoplasmic sperm injection. *Eur J Obstet Gynecol Reprod Biol*. 2010;150(2):160-165.
3. Kissin DM, Jamieson DJ, Barfield WD. Monitoring health outcomes of assisted reproductive technology. *N Engl J Med*. 2014; 371(1):91-93.
4. Hansen M, Kurinczuk JJ, de Klerk N, Burton P, Bower C. Assisted reproductive technology and major birth defects in Western Australia. *Obstet Gynecol*. 2012;120(4):852-863.
5. Farhi A, Reichman B, Boyko V, Hourvitz A, Ron-El R, Lerner-Geva L. Maternal and neonatal health outcomes following assisted reproduction. *Reprod Biomed Online*. 2013;26(5): 454-461.
6. Fujii M, Matsuoka R, Bergel E, van der Poel S, Okai T. Perinatal risk in singleton pregnancies after in vitro fertilization. *Fertil Steril*. 2010;94(6):2113-2117.
7. Centers for Disease Control and Prevention. 2013 Assisted Reproductive Technology Fertility Clinic Success Rates Report. Web site. http://www.cdc.gov/art/reports/2013/fertility-clinic.html. Accessed June 25, 2016.
8. Malchau SS, Loft A, Larsen EC, et al. Perinatal outcomes in 375 children born after oocyte donation: a Danish National Cohort Study. *Fertil Steril*. 2013;99(6):1637-1643.
9. Kupka MS, Ferraretti AP, de Mouzon J, et al; European IVF-Monitoring Consortium, for the European Society of Human Reproduction and Embryology. Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. *Hum Reprod*. 2014;29(10):2099-2113.
10. International Committee for Monitoring Assisted Reproductive Technology, de Mouzon J, Lancaster P, Nygren KG, et al. World collaborative report on assisted reproductive technology, 2002. *Hum Reprod*. 2009;24(9):2310-2320.
11. Qin J, Wang H, Sheng X, Liang D, Tan H, Xia J. Pregnancy-related complications and adverse pregnancy outcomes in multiple pregnancies resulting from assisted reproductive technology: a meta-analysis of cohort studies. *Fertil Steril*. 2015;103(6): 1492-508.e1-e7.
12. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ*. 2004;328(7434):261.
13. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. *Obstet Gynecol*. 2004;103(3):551-563.
14. McDonald SD, Murphy K, Beyene J, Ohlsson A. Perinatal outcomes of singleton pregnancies achieved by in vitro fertilization: a systematic review and meta-analysis. *J Obstet Gynaecol Can*. 2005;27(5):449-459.
15. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18(5):485-503.
16. Qin J, Liu X, Sheng X, Wang H, Gao S. Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies. *Fertil Steril*. 2016;105(1): 73-85.e1-e6.
17. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *N Engl J Med*. 2002;346(10):725-730.
18. Tavaniotou A, Albano C, Smitz J, Devroey P. Impact of ovarian stimulation on corpus luteum function and embryonic implantation. *J Reprod Immunol*. 2002;55(1-2):123-130.
19. Johnson MR, Riddle AF, Grudzinskas JG, Sharma V, Collins WP, Nicolaides KH. Reduced circulating placental protein concentrations during the first trimester are associated with preterm labour and low birth weight. *Hum Reprod*. 1993;8(11): 1942-1947.
20. Haning RV Jr, Goldsmith LT, Seifer DB, et al. Relaxin secretion in in vitro fertilization pregnancies. *Am J Obstet Gynecol*. 1996; 174(1 pt 1):233-240.
21. Hayashi M, Nakai A, Satoh S, Matsuda Y. Adverse obstetric and perinatal outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used. *Fertil Steril*. 2012;98(4):922-928.
22. Marino JL, Moore VM, Willson KJ, et al. Perinatal outcomes by mode of assisted conception and sub-fertility in an Australian data linkage cohort. *PLoS One*. 2014;9(1):e80398.
23. Kapiteijn K, de Bruijn CS, de Boer E, et al. Does subfertility explain the risk of poor perinatal outcome after IVF and ovarian hyperstimulation? *Hum Reprod*. 2006;21(12): 3228-3234.
24. Buck Louis GM, Schisterman EF, Dukic VM, Schieve LA. Research hurdles complicating the analysis of infertility treatment and child health. *Hum Reprod*. 2005;20(1):12-18.
25. Barnhart KT. Assisted reproductive technologies and perinatal morbidity: interrogating the association. *Fertil Steril*. 2013; 99(2):299-302.
26. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. 2007;4(10):e296.
27. Halliday JL, Ukoumunne OC, Baker HW, et al. Increased risk of blastogenesis birth defects, arising in the first 4 weeks of pregnancy, after assisted reproductive technologies. *Hum Reprod*. 2010;25(1):59-65.
28. Wisborg K, Ingerslev HJ, Henriksen TB. IVF and stillbirth: a prospective follow-up study. *Hum Reprod*. 2010;25(5): 1312-1316.
29. Sagot P, Bechoua S, Ferdynus C, et al. Similarly increased congenital anomaly rates after intrauterine insemination and IVF

technologies: a retrospective cohort study. *Hum Reprod*. 2012; 27(3):902-909.
30. Davies MJ, Moore VM, Willson KJ, et al. Reproductive technologies and the risk of birth defects. *N Engl J Med*. 2012;366(19): 1803-1813.
31. Fedder J, Loft A, Parner ET, Rasmussen S, Pinborg A. Neonatal outcome and congenital malformations in children born after ICSI with testicular or epididymal sperm: a controlled national cohort study. *Hum Reprod*. 2013;28(1):230-240.
32. Poon WB, Lian WB. Perinatal outcomes of intrauterine insemination/clomiphene pregnancies represent an intermediate risk group compared with in vitro fertilisation/intracytoplasmic sperm injection and naturally conceived pregnancies. *J Paediatr Child Health*. 2013;49(9):733-740.
33. Schieve LA, Ferre C, Peterson HB, Macaluso M, Reynolds MA, Wright VC. Perinatal outcome among singleton infants conceived through assisted reproductive technology in the United States. *Obstet Gynecol*. 2004;103(6):1144-1153.
34. Romundstad LB, Romundstad PR, Sunde A, von During V, Skjaerven R, Vatten LJ. Increased risk of placenta previa in pregnancies following IVF/ICSI: a comparison of ART and non-ART pregnancies in the same mother. *Hum Reprod*. 2006;21(9): 2353-2358.
35. Brink Henriksen T, Day Baird D, Olsen J, Hedegaard M, Jørgen Secher N, Wilcox AJ. Time to pregnancy and preterm delivery. *Obstet Gynecol*. 1997;89(4):594-599.
36. Basso O, Baird DD. Infertility and preterm delivery, birthweight, and caesarean section: a study within the Danish National Birth Cohort. *Hum Reprod*. 2003;18(11):2478-2484.
37. Gaudoin M, Dobbie R, Finlayson A, Chalmers J, Cameron IT, Fleming R. Ovulation induction/intrauterine insemination in infertile couples is associated with low-birth-weight infants. *Am J Obstet Gynecol*. 2003;188(3):611-616.
38. Declercq E, Luke B, Belanoff C, et al. Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). *Fertil Steril*. 2015;103(4):888-895.
39. Pinberg A, Wennerholm U, Romundstad L, et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Hum Reprod Update*. 2013;19(2):87-104.
40. Messerlian C, Maclagan L, Basso O. Infertility and the risk of adverse pregnancy outcomes: a systematic review and meta-analysis. *Hum Reprod*. 2013;28(1):125-137.
41. Jaques AM, Amor DJ, Baker HW, et al. Adverse obstetric and perinatal outcomes in subfertile women conceiving without assisted reproductive technologies. *Fertil Steril*. 2010;94(7):2674-2679.
42. Thomson F, Shanbhag S, Templeton A, Bhattacharya S. Obstetric outcome in women with subfertility. *BJOG*. 2005;112(5):632-637.
43. Dunietz GL, Holzman C, McKane P, et al. Assisted reproductive technology and the risk of preterm birth among primiparas. *Fertil Steril*. 2015;103(4):974-979.e1.