Maternal characteristics and pregnancy outcomes of Chinese women with infertility undergoing assisted reproductive technology treatment: a retrospective cohort study

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Abstract

Background: To examine differences in the maternal characteristics and pregnancy outcomes of Chinese women with various causes of infertility who underwent assisted reproductive technology (ART) treatment.

Methods: This retrospective cohort study included women with various causes of infertility who used ART. Data on demographic characteristics, medical history, laboratory tests, and delivery were reviewed. Logistic regression analysis was performed to calculate odds ratios and 95% confidence intervals for pregnancy and perinatal complications and neonatal outcomes. The multivariable model was adjusted for age, gravidity, parity, pre-pregnancy obesity, birth plurality, and history of previous caesarean section.

Results: The ART treatment group was divided into 5 subgroups according to infertility cause as follows: ovulation disorder, tubal disease, male infertility, endometriosis, and mixed infertility. Among singleton pregnancies, compared with spontaneous pregnancies, ART pregnancies were associated with significant increases in the rates of the following: gestational diabetes mellitus (GDM), preeclampsia, preterm preeclampsia, postpartum haemorrhage, intrahepatic cholestasis of pregnancy, preterm premature rupture of membranes, preterm birth, low birthweight, macrosomia, and neonatal intensive care unit (NICU) admission in the ovulation disorder group; GDM, placenta previa, placenta accreta, postpartum haemorrhage, macrosomia and 5-minute Apgar score ≤7 in the tubal disease group; placenta previa, abnormal placental cord insertion, small for gestational age, macrosomia and NICU admission in the endometriosis group; placenta previa and placenta accreta in the male infertility group; and GDM, placenta previa, placental abruption, chorioamnionitis, preterm birth, and 1-minute Apgar score ≤7 in the mixed infertility group. Among multiple pregnancies, most of the differences that were significant in singleton pregnancies were less extensive or had disappeared.

Conclusions: During the perinatal period, maternal characteristics, in particular type of infertility, appears an additional risk factor for abnormal pregnancy outcomes besides use of IVF techniques. Lower risk is found in male infertility and higher risk for ovulation disorders.
Background
The number of pregnancies and births after ART has increased exponentially over the past 40 years. In China, ART contributes to 1% of all births[1]. Indeed, ART has become among the most important treatments for infertility. However, in recent years, evidence has emerged that ART pregnancies are at an increased risk of maternal complications and adverse pregnancy outcomes, including pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), placenta previa, placental abruption, postpartum haemorrhage, preterm birth, low birth weight, and small for gestational age, both in multiple pregnancies and singleton pregnancies[2-7]. In addition, some research has shown that infants conceived after ART have a higher prevalence of certain birth defects. Assisted hatching and the diagnosis of an ovulation disorder are marginally associated with increased risks for nonchromosomal birth defects[8-10]. Other research has shown that ART is associated with a slightly elevated risk of birth defects and that the risks vary depending on the exposure[11]. Despite the widespread application of ART, concerns about potential health implications remain, and the results of previous studies are controversial, partly because of their different study designs, ethnic group compositions, ART protocols and techniques used, and maternal biometric characteristics.

The reasons for the increase in adverse pregnancy outcomes with ART are unknown. It is difficult to identify whether the adverse outcomes observed with ART are the direct result of the procedure itself or a result of the underlying subfertility of the parents. One hypothesis is that an infertility-related diagnosis in a woman undergoing ART contributes directly to adverse outcomes, and excess perinatal morbidities have been associated with the infertility-related diagnosis in both ART-treated and non-ART-treated women[12]. However, after adjustments for maternal characteristics, other studies have reported few cases in which underlying infertility directly contributed to adverse outcomes[13]. Another possibility is that adverse outcomes result from the ART procedure itself, including the artificial induction of ovulation; exposure of oocytes, sperm, and embryos to the environment outside of the body; and freezing and manipulation of oocytes and embryos. In several prior studies, age-matching of patients between the ART and spontaneous conception groups was not performed.
Knowledge of ART pregnancy outcomes in China is limited, and few studies have examined the relationship between infertility causes and pregnancy outcomes.

We therefore conducted this retrospective cohort study to explore the characteristics of adverse pregnancy and birth outcomes among infertile women with different infertility diagnosis after ART treatment to explore relationships between the reason for ART and adverse outcomes.

Methods
Data source and study sample

We conducted a large retrospective, hospital-based cohort study in couples who underwent ART treatment at Beijing Obstetrics and Gynecology Hospital between January 2009 and May 2018. All ART-derived pregnancies were randomly matched to a sample of spontaneous pregnancies for maternal age and birth year. The inclusion criteria were as follows: 1) all patients were Chinese; 2) all patients in each group had live births and a gestational age of ≥28 weeks; 3) the ART method was in vitro fertilization and embryo transfer (IVF-ET), and the IVF-ET method was frozen-embryo transfer of the early cleavage-stage embryos; and 4) the infertility diagnosis was an ovulation disorder, tubal disease, endometriosis, male infertility, or mixed infertility (means multiple infertility-related diagnosis). The exclusion criteria were as follows: 1) the use donor oocytes/sperm or embryos, to ensure that all embryos transferred were autologous; 2) the use of preimplantation genetic testing (PGT); 3) the existence of chronic pre-pregnancy complications, to ensure that only patients with complications that occurred during pregnancy were studied; or 4) women who smoked or consumed alcohol during pregnancy, to prevent confounding effects on outcomes by these factors. Overall, a total of 8773 deliveries were subjected to this retrospective analysis. Among the women, 21% (1843) had received ART treatment. The ART group consisted of 1241 singleton and 602 gemellary pregnancies. The spontaneously conceived group consisted of 6832 singleton and 98 gemellary pregnancies. All data, including infertility diagnosis, ART method, and pregnancy, obstetric and neonatal outcomes, were obtained from records of the patients' visits to hospitals. The demographic and selected maternal characteristics, pregnancy and labour complications and neonatal outcomes were compared between the two groups.
Variables of interest, and definition of main outcomes

The selected maternal and pregnancy characteristics and pregnancy outcomes included the following: gestational hypertension (BP ≥ 140/90 mmHg after 20 weeks in previously normotensive women), preeclampsia (hypertension and proteinuria, evidence of other maternal organ dysfunction, or uteroplacental dysfunction), preterm pre-eclampsia (if preeclampsia occurred at <37 gestational weeks)[14], GDM (diabetes diagnosed during pregnancy)[15], delivery method, intrahepatic cholestasis of pregnancy (ICP, characterized by an underlying elevation in circulating bile acids and liver derangement)[16], placenta previa (lower placenta edge within 2 cm from the internal os)[17], placenta accreta (a spectrum disorder ranging from abnormally adherent to deeply invasive placental tissue)[17], placental abruption (a premature separation of the placenta before delivery)[18], preterm premature rupture of membranes (pPROM, membranes rupture before labour and before 37 weeks of gestation)[19], chorioamnionitis (histological or clinical)[20], postpartum haemorrhage (an estimated blood loss in excess of 500 ml after a vaginal birth or a loss of greater than 1000 ml after a caesarean birth)[21], abnormal umbilical cord insertion (the umbilical cord was inserted in the placenta noncentrally), polyhydramnios (US assessment showing a largest deepest pool of AF greater than 8 cm or an amniotic fluid index greater than 25 cm), oligohydramnios (US assessment showing a largest deepest pool of AF less than 2 cm or an amniotic fluid index less than 2 cm)[22], preterm birth (PB, delivery after at least 28 weeks gestation but no more than 37 weeks gestation)[23], low birthweight (LBW, birthweight <2500 g)[23], macrosomia (birth weight≥4000 g)[24], small for gestational age (SGA, defined as birth weight below the 10th percentile of a standard optimal reference population for a given gestational age and sex)[25], Apgar score at 1 minute, Apgar score at 5 minutes and neonatal intensive care unit (NICU) admission.

Ethical approval

This study was approved by the local institutional ethics committee, namely, The Beijing Obstetrics and Gynaecology Hospital committee (ethics approval number: 2019-KY-024-01) and is being
conducted in accordance with the Declaration of Helsinki. Due to the retrospective study design, consent for participation was not required. Nevertheless, private information was well protected during the study.

Statistical analysis

SPSS statistical software (version 20.0) was used for data analysis. We first compared baseline characteristics between ART and natural pregnancies. Quantitative data are presented as the mean and SD (mean ± SD). Fisher’s exact tests, t tests and Pearson’s chi-square tests were performed to evaluate differences in the proportions of categorical variables between two or more groups. Second, we assessed the effect of infertility diagnosis on adverse perinatal and neonatal outcomes by comparing the prevalence of adverse perinatal and neonatal outcomes in different infertility diagnosis subgroups and natural pregnancies. Logistic regression analysis was conducted to calculate approximate relative risks of adverse outcomes and to identify possible predictors of pregnancy complications. The multivariable model was adjusted for maternal age, gravidity, parity, and pre-pregnancy obesity (body mass index ≥ 28 kg/m²) [26], birth plurality, and history of previous caesarean section; the results are reported as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). P values of less than 0.05 were considered statistically significant. The methods were carried out in accordance with approved guidelines.

Results

Figure 1 shows the flow chart of the participants who were either included in the main analysis or excluded for failing to meet the inclusion criteria. The diagnosis for ART-treated deliveries included ovulation disorders (N=404), tubal disease (N=803), endometriosis (N=107), male infertility (N=403), and mixed infertility (N=126). The number of natural pregnancies was 6930. Table 1 summarizes the background characteristics of the women who were included in the main analysis. Women with ART pregnancies were more likely to have significantly higher rates of pre-pregnancy obesity, caesarean section, and multiple pregnancy and a lower rate of previous caesarean delivery than women with spontaneous pregnancies (P<0.001). The spontaneous pregnancy group also had a significantly
higher number of second gravidity and pregnancies than the ART group ($P<0.001$).

Table 2 shows the pregnancy and perinatal complications due to infertility for singleton pregnancies and multiple pregnancies. Table 3 shows the neonatal outcomes by cause of infertility among singleton pregnancies and multiple pregnancies. The associations between each cause of infertility and maternal/perinatal complication or adverse outcomes were assessed using a logistic regression, with women who conceived spontaneously serving as a reference (Table 4 and Table 5). Among singleton pregnancies, women with ovulation disorders who conceived by ART had a higher risk of preeclampsia (aOR 2.60 [95% CI 1.61-4.20]), preterm preeclampsia (aOR 4.52 [95% CI 2.03-10.06]), GDM (aOR 1.76 [95% CI 1.33-2.33]), ICP (aOR 3.84 [95% CI 1.06-13.94]), pPROM (aOR 2.11 [95% CI 1.17-3.81]), postpartum haemorrhage (aOR 1.57 [95% CI 1.04-2.36]), PB (aOR 1.95 [95% CI 1.26-3.01]), low birthweight (aOR 1.90 [95% CI 1.13-3.20]), macrosomia (aOR 1.53 [95% CI 1.03-2.27]), and NICU admission (aOR 1.69 [95% CI 1.22-2.34]) than those who conceived spontaneously. Additionally, women with tubal disease who conceived by ART had a higher risk of GDM (aOR 1.50 [95% CI 1.21-1.86]), placenta previa (aOR 2.70 [95% CI 1.59-4.59]), placenta accreta (aOR 1.78 [95% CI 1.10-2.89]), postpartum haemorrhage (aOR 1.61 [95% CI 1.19-2.18]), macrosomia (aOR 1.60 [95% CI 1.21-2.13]), and a 5-minute Apgar score≤7 (aOR 4.09 [95% CI 1.04-16.08]) than those who conceived spontaneously.

Women with endometriosis who conceived by ART had a higher risk of placenta previa (aOR 9.33 [95% CI 4.22-20.62]), abnormal placental cord insertion (aOR 2.74 [95% CI 1.16-6.46]), SGA (aOR 2.29 [95% CI 1.04-5.08]), macrosomia (aOR 2.00 [95% CI 1.02-3.95]), and NICU admission (aOR 2.35 [95% CI 1.35-4.09]) than those who conceived spontaneously. Women with male infertility who conceived by ART had a higher risk of placenta previa (aOR 4.14 [95% CI 2.23-7.68]) and placenta accreta (aOR 2.05 [95% CI 1.08-3.87]). Women with mixed infertility who conceived by ART had a higher risk of GDM (aOR 1.85 [95% CI 1.15-2.98]), placenta previa (aOR 4.73 [95% CI 1.83-12.21]), placental abruption (aOR 3.39 [95% CI 1.20-9.56]), chorioamnionitis (aOR 2.93 [95% CI 1.04-8.26]), PB (aOR 2.69 [95% CI 1.41-5.15]), and a 1-minute Apgar score≤7 (aOR 4.68 [95% CI 1.62-13.51]) than those who conceived spontaneously. However, when gemellary pregnancies were compared with spontaneous pregnancies, only the rates of the following were significantly increased:
GDM in the ovulation disorder and mixed infertility groups and 1-minute Apgar score ≤7 in the mixed infertility group; the other differences that were significantly higher in the singleton pregnancy cohort had narrowed or disappeared in the gemellary pregnancy cohort.

Discussion

As the use of ART increases and newer technologies continue to push the boundaries of science, it is important to consider the clinical safety of these approaches. Through this retrospective, hospital-based cohort study of pregnant Chinese women, we verified that ART pregnancies are related to increased risks of pregnancy complications, perinatal complications and poor neonatal outcomes. Furthermore, diagnostic categories within the ART population were found to affect maternal and neonatal outcomes among all births. As summarized in Table 4 and Table 5, infertility caused by an ovulation disorder had the worst prognosis. In fact, ovulation disorders were associated with higher risks of preeclampsia (3-fold), GDM (2-fold), pPROM (2-fold), postpartum haemorrhage (2-fold), PB (2-fold), low birthweight (2-fold), macrosomia (1.5-fold), and NICU admission (2-fold), which is consistent with prior studies[12, 27, 28]. One possible explanation is that a high proportion of women with ovulation disorders have polycystic ovarian syndrome (PCOS), and many of them have multiple metabolic abnormalities. Growing evidence demonstrates that PCOS has a negative impact on fertility and pregnancy outcomes, such as GDM, gestational hypertensive disorders, and PB[29]. GDM is evidently related to the delivery of an infant with macrosomia, so the incidence of macrosomia is significantly higher for pregnant women with PCOS[28]. In addition, neonates of women with PCOS are at greater risk of neonatal complications, including perinatal mortality, prematurity, SGA, lower birth weight and higher NICU admission[30]. Current evidence also suggests that pre-pregnancy hormonal dysfunction, including hyperandrogenism, progesterone resistance and hyperinsulinism, impairs uterine placentation mechanisms, which may lead to a greater risk of adverse obstetric and neonatal outcomes[30].

Compared to spontaneous pregnancies, ART pregnancies in patients who had tubal infertility had an increased risk of GDM (1.5-fold), placenta previa (3-fold), placenta accreta (2-fold), postpartum haemorrhage (2-fold), macrosomia (2-fold), and a 5-minute Apgar score≤7 (4-fold). One study
reported that infertility, particularly due to an ovulatory disorder or tubal blockage, was associated with an increased GDM risk; specifically, women with a history of infertility due to tubal blockage had an 83% greater risk[31], consistent with our results. GDM is closely related to the birth of an infant with macrosomia, so the rate of macrosomia in tubal infertility is also significantly increased. Tubal-factor infertility is always associated with reproductive inflammation, which may lead to an imbalance in immune-endocrine crosstalk among the endometrium, myometrium and cervix and between the decidua and trophoblasts, predisposing patients to pregnancy complications, such as placenta previa, placenta accreta and postpartum haemorrhage, which could affect neonatal outcomes.

Our data showed that endometriosis was significantly associated with placenta previa, SGA, and NICU admission, similar to the findings of previous studies[32-35]. Endometriosis is a common reason for infertility and may cause chronic inflammation and adhesions in the pelvis of reproductive-aged women. Moreover, women with endometriosis exhibit defective deep placentation because of defective remodelling of the spiral arteries[36]. These factors may explain why endometriosis is possibly a crucial factor for increased negative outcomes in ART pregnancy. However, Benaglia L found that women with endometriosis who conceived via in vitro fertilization (IVF) do not face an increased risk of preterm birth[37], similar to our finding. In addition, we found that ART pregnancies in patients with endometriosis had a higher rate of macrosomia (2-fold) than those who conceived naturally. Regrettably, we have not found any literature on the relationship between endometriosis and macrosomia. This controversial result still needs to be further studied by expanding the sample size.

In the male infertility subgroup, the rates of placenta previa and placenta accreta were also increased, but this has not been universally reported. One possible explanation is that the increased risk of placenta previa and placenta accreta is caused by factors related to ART[38, 39]. Indeed, the intrauterine operation and manipulation of embryonic cells in ART might induce uterine contraction, leading to higher frequencies of implantation in the lower uterine segment, which may increase the risk of placenta previa. The changes to the endometrium wrought by IVF treatment protocols, and the use of hormone therapy to promote embryo implantation, may increase the risk of placenta accreta.
In this research, the risk of placenta previa increased in all subgroups except for the ovarian disorder subgroup, which was similar to previous research[38]. Interestingly, there were no significant differences in neonatal outcomes between ART and spontaneous conception in the male infertility subgroup. Vannuccini S found that in uncomplicated term pregnancies following ART, infants born after ART had a similar birthweight, Apgar score and arterial blood pH to those of spontaneously conceived infants[40]. This finding might indicate that the factors associated with infertility are more likely to be associated with adverse neonatal complications rather than the ART procedure itself, which is consistent with a previous study[41]. Overall, the results require further analysis in larger cohorts, adjustments for as many confounders as possible and further preclinical studies.

Our study also showed an increased risk for GDM, placenta previa, chorioamnionitis, PB, and a 1-minute Apgar score≤7 in the mixed infertility subgroup compared with corresponding controls. When there are mixed reasons for parental infertility, pregnancy complications and parental and neonatal outcomes might differ, but perinatal morbidities will always increase. In addition, in gemellary pregnancies, the differences in perinatal and neonatal outcomes between ART pregnancies and natural pregnancies mostly narrowed or disappeared. This may indicate that pregnancy outcomes are greatly affected by multiple pregnancies, regardless of whether they are ART pregnancies or natural pregnancies. This finding may also be the result of a small number of cases.

The major strength of our study is not only the comparison of perinatal and neonatal outcomes of ART and spontaneous conception but also the assessment of the impact of different infertility diagnosis on pregnancy characteristics and outcomes in China. China has abolished the “one child” policy, and since 2016, it has entered into an era of the two-child policy. As a result, the number of infants is expected to increase greatly, which may promote the demand for ART[42]. Our findings have extremely important clinical implications and may provide guidance for couples and obstetricians in determining whether ART is useful as a first-line treatment or as a last resort. Moreover, these findings may help in identifying likely perinatal and neonatal complications and provide information for the underlying pathogenic mechanisms.

There are, however, a few limitations of this study. First, the numbers of stillbirths and neonatal
deaths were few; hence, these figures were not included in the main analysis, which may have given rise to the possibility of residual confounding in our results. Therefore, we could not accurately determine the severity of the effects of different infertility diagnosis on neonatal outcomes, nor can we identify the high-risk factors related to the long-term prognosis of the newborn. Another gap in the data that were available was the severity and treatment process of infertility. For example, data on the stage of endometriosis, baseline endocrine level, body mass index, duration of infertility, and ovarian stimulation protocol were incomplete. In addition, some information about environmental exposure (educational level, income level) was not included in this study, which may lead to bias. Further studies, particularly systematic reviews of observational studies such as the current study and prospective studies with adjustments for important confounders, will be required to confirm these initial findings.

Conclusions
Taken together, these findings indicate that maternal characteristics, in particular type of infertility, appears an additional risk factor for abnormal pregnancy outcomes besides use of IVF techniques. Lower risk is found in male infertility and higher risk for ovulation disorders. Doctors should fully inform patients of possible adverse pregnancy outcomes before they receive ART. In addition, obstetricians should not only be aware of the increased risk of adverse outcomes with ART but also pay attention to the specific complications related to the cause of infertility and provide timely treatment. Further studies, including prospective studies, are needed to confirm the role of the underlying infertility-related diagnosis and severity of infertility in the increase in adverse outcomes with ART after adjusting for important confounders.

Abbreviations
ART: Assisted reproductive technology
BMI: Body mass index
GDM: Gestational diabetes mellitus
ICP: Intrahepatic cholestasis of pregnancy
pPROM: Preterm premature rupture of membranes
PB: Preterm birth
LBW: Low birthweight
SGA: Small for gestational age
NICU: Neonatal Intensive Care Unit
CI: Confidence interval
aOR: Adjusted odds ratio
NC: Not calculated due to low numbers

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were approved by the local institutional ethics committee–The Beijing Obstetrics and Gynecology Hospital committee (ethics approval number: 2019-KY-024-01). Due to the retrospective study design, consent for participation was not required. Nevertheless, private information was well protected during the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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This study was not funded.

Authors’ contributions

JXW and JMC contributed to the study conception and design. QWL, BED and FC examined the data integrity and accuracy. JXW and XWL performed the data analysis. JXW drafted the manuscript, and JMC revised the manuscript, and JMC revised the manuscript. All the authors read and approved the final manuscript.
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Tables
Table 1. Maternal and pregnancy characteristics of the ART and spontaneous pregnancy groups.

|                         | Ovulation disorder | Tubal disease | Endometriosis | Male infertility | Mixed infertility | All ART | Controls | P value* |
|-------------------------|--------------------|---------------|---------------|------------------|-------------------|---------|----------|----------|
| Number of patients      | 404                | 803           | 107           | 403              | 126               | 1843    | 6930     |          |
| Maternal age            | 33.6 ± 4.1         | 33.33 ± 3.10  | 34.11 ± 3.58  | 33.41 ± 3.50     | 33.27 ± 3.50      | 33.40   | 33.39 ± 2.96 | 0.11     |
| Gravidity               | G1                 | G2            |               |                  |                   |         |          | <0.001   |
|                         | 258 (63.9%)        | 146 (42.9%)   | 74 (54.3%)    | 289 (69.2%)      | 75 (71.7%)        | 1132    | 711      |          |
|                         | (54.3%)            | (69.2%)       | (71.7%)       | (59.5%)          | (61.4%)           |         |          |          |
|                         | G2                 |               |               |                  |                   |         |          |          |
|                         | 114 (71.4%)        | 33 (18.4%)    | 51 (30.9%)    | 114 (71.4%)      | 33 (18.4%)        | 711     | 4048     |          |
|                | P1          | P≥2         |
|----------------|-------------|-------------|
|                | (382, 762) | (22, 41)   |
|                | (104, 389) | (3, 14)    |
|                | (124, 1761)| (2, 82)    |
|                | (5055)     | (1872)     |
|                | (94.1%)    | (5.4%)     |
|                | (97.2%)    | (2.8%)     |
|                | (96.5%)    | (3.5%)     |
|                | (98.4%)    | (1.6%)     |
|                | (95.6%)    | (4.4%)     |
|                | (73%)      | (27%)      |

| Pre-pregnancy obesity |            |
|-----------------------|------------|
| Yes                   | (15, 389) |
|                       | (13, 790) |
|                       | (1, 106)  |
|                       | (7, 396)  |
|                       | (4, 122)  |
|                       | (40, 1803)|
|                       | (61, 6869)|
|                       | (3.7%)    |
|                       | (1.6%)    |
|                       | (0.9%)    |
|                       | (1.7%)    |
|                       | (3.2%)    |
|                       | (2.2%)    |
|                       | (0.9%)    |

| Birth plurality |            |
|-----------------|------------|
| Singleton       | (271, 133)|
|                 | (542, 261)|
|                 | (74, 33)  |
|                 | (267, 136)|
|                 | (87, 39)  |
|                 | (1241, 602)|
|                 | (6832)    |
|                 | (67.1%)   |
|                 | (67.5%)   |
|                 | (69.2%)   |
|                 | (66.3%)   |
|                 | (69%)     |
|                 | (67.3%)   |
|                 | (98.6%)   |

|                |            |
|----------------|------------|
|                | (22, 133) |
|                | (41, 261) |
|                | (3, 33)   |
|                | (14, 136) |
|                | (2, 39)   |
|                | (82, 602) |
|                | (1872)    |
|                | (5.4%)    |
|                | (5.1%)    |
|                | (2.8%)    |
|                | (3.5%)    |
|                | (1.6%)    |
|                | (4.4%)    |
|                | (27%)     |

(36, 76) (30.8%) (28.3%) (40.5%) (38.5%) (58.4%) 1%)
(45.7%)  

Parity  

P1  382 762 104 389 124 1761 5055

(94.1%) (94.9%) (97.2%) (96.5%) (98.4%) (95.6%) (73%) 6%

P≥2 22 41 3 14 2 82 1872

(5.4%) (5.1%) (2.8%) (3.5%) (1.6%) (4.4%) (27%)

Pre-pregnancy obesity  

Yes 15 13 1 7 4 40 61

(3.7%) (1.6%) (0.9%) (1.7%) (3.2%) (2.2%) (0.9%)

No 389 790 106 396 122 1803 6869

(96.3%) (98.4%) (99.1%) (98.3%) (96.8%) (97.8%) (99.1%)

Birth plurality  

Singleton 271 542 74 267 87 1241 6832

(67.1%) (67.5%) (69.2%) (66.3%) (69%) (67.3%) (98.6%)

(1%)  

Multiple 133 261 33 136 39 602 98
(32.9% (32.5%) (30.8%) (33.7% (31%) (32.7% (1.4%)

9%)

Previous caesarean delivery <0.001

|       | Yes       | No       |
|-------|-----------|----------|
|       | 6 (1.5%)  | 398 (98.5%) |
|       | 17 (2.1%) | 786 (97.9%) |
|       | 3 (2.8%)  | 104 (97.2%) |
|       | 6 (1.5%)  | 397 (98.5%) |
|       | 2 (1.6%)  | 124 (98.4%) |
|       | 34 (1.8%) | 1809 (98.2%) |
|       | 772 (11.1%) | 6158 (88.9%) |

Delivery method <0.001

|                   | Vaginal delivery | Caesarean section | Operative vaginal delivery |
|-------------------|------------------|-------------------|---------------------------|
|                   | 115 (28.5%)      | 261 (64.6%)       | 28 (6.9%)                 |
|                   | 227 (28.3%)      | 538 (67%)         | 38 (4.7%)                 |
|                   | 24 (22.4%)       | 75 (70.1%)        | 8 (7.5%)                  |
|                   | 115 (28.5%)      | 276 (68.5%)       | 12 (3%)                   |
|                   | 27 (21.4%)       | 91 (72.2%)        | 8 (6.3%)                  |
|                   | 508 (27.6%)      | 1241 (67.3%)      | 8 (5.1%)                  |
|                   | 3547 (51.2%)     | 3100 (44.7%)      | 94 (4.1%)                 |

Number of embryos transferred

|       | 1       | 274     | 545     | 74      | 271     | 89 |
|-------|---------|---------|---------|---------|---------|----|
Note: Data are presented as means±SDs for continuous variables and n (%) for dichotomous variables.

Mixed infertility refers to a multiple infertility-related diagnosis.

*Pearson's chi-square test, Fisher's exact test or the t test, was used as appropriate; Obesity means BMI≥28 kg/m².

Table 2. Pregnancy and delivery outcomes among specific infertility causes compared to spontaneous pregnancies

| Maternal outcomes | Control | Ovulation disorder | Tubal disease | Endometriosis | Male |
|-------------------|---------|--------------------|---------------|---------------|------|
| Singleton pregnancies | N       | %                  | N             | %             | N    | %       | N    |
| Maternal outcomes | 6832    | 271                | 542           | 74            | 26   |
| Gestational       | 271     | 4                  | 13            | 4.8           | 18   | 3.3     | 3    | 4.1  | 18   |
| Hypertension      |         |                    |               |               |      |
| Preeclampsia      | 193     | 2.8                | 22            | 8.1*          | 23   | 4.2     | 2    | 2.7  | 9    |
| Mild              | 63      | 0.9                | 8             | 3*            | 7    | 1.3     | 0    | 0    | 2    |
| Severe            | 130     | 1.9                | 14            | 5.2*          | 16   | 3       | 2    | 2.7  | 7    |
| Preterm preeclampsia | 46     | 0.7                | 8             | 3*            | 5    | 0.9     | 0    | 0    | 3    |
| Condition                          | N  | %   | N  | %   | N  | %   | N  | %   | N  | %   |
|-----------------------------------|----|-----|----|-----|----|-----|----|-----|----|-----|
| **GDM**                           | 1132 | 16.6 | 76 | 28* | 129 | 23.8* | 15 | 20.3 | 57 |  |
| **ICP**                           | 16 | 0.2 | 3 | 1.1^ | 4 | 0.7^ | 0 | 0 | 1 |  |
| Placenta previa                   | 94 | 1.4 | 3 | 1.1 | 18 | 3.3^ | 8 | 10.8^ | 13 |  |
| Placental abruption               | 92 | 1.3 | 7 | 2.6 | 7 | 1.3 | 2 | 2.7 | 2 |  |
| pPROM                             | 154 | 2.3 | 13 | 4.8^ | 19 | 3.5 | 3 | 4.1 | 11 |  |
| Abnormal placental cord insertion| 186 | 2.7 | 10 | 3.7 | 24 | 4.4^ | 6 | 8.1^ | 11 |  |
| Placenta accreta                  | 148 | 2.2 | 7 | 2.6 | 20 | 3.7^ | 3 | 4.1 | 11 |  |
| Postpartum                        | 574 | 8.4 | 31 | 11.4 | 59 | 10.9^ | 6 | 8.1 | 21 |  |
| **haemorrhage**                   |     |     |     |     |     |     |     |     |     |     |
| Polyhydramnios                    | 61 | 0.9 | 4 | 1.5 | 7 | 1.3 | 1 | 1.4 | 5 |  |
| Oligohydramnios                   | 247 | 3.6 | 14 | 5.2 | 18 | 3.3 | 4 | 5.4 | 12 |  |
| Chorioamnionitis                  | 91 | 1.4 | 7 | 2.6 | 10 | 1.8 | 2 | 2.7 | 3 |  |
| Gemellary                         | N | %  | N | %  | N | %  | N | %  | N |  |
| **pregnancies**                   |     |     |     |     |     |     |     |     |     |     |
| Maternal outcomes                 | 98 | 133 | 261 | 33 | 13 |  |
| Gestational                       | 5 | 5.1 | 12 | 9 | 17 | 6.5 | 1 | 3 | 10 |  |
| **hypertension**                  |     |     |     |     |     |     |     |     |     |     |
| Preeclampsia                      | 10 | 10.2 | 19 | 14.3 | 27 | 10.3 | 2 | 6.1 | 16 |  |
| Mild                              | 2 | 2 | 4 | 3 | 6 | 2.3 | 1 | 3 | 2 |  |
| Severe                            | 8 | 8.2 | 15 | 11.3 | 21 | 8 | 1 | 3 | 14 |  |
| Preterm eclampsia                 | 7 | 7.1 | 8 | 3 | 19 | 7.3 | 1 | 3 | 12 |  |

**Note**: N = Number, % = Percentage
| Condition                          | Control | Ovulation disorder | Tubal disease | Endometriosis |
|-----------------------------------|---------|--------------------|---------------|---------------|
| Singleton                         | N       | %                  | N             | %             |

Note: GDM= Gestational diabetes mellitus; ICP=intrahepatic cholestasis of pregnancy; pPROM=preterm premature rupture of membranes; Mixed infertility refers to multiple infertility-related diagnosis. Data are presented as n (%) for dichotomous variable, and Pearson’s chi-square or Fisher’s exact test was used as appropriate; P≤0.001=∗; P<0.05=^ . Nonsignificant numbers have not symbol.

Table 3. Neonatal outcomes among specific infertility causes compared to spontaneous pregnancies
|                         | N  | %   | N  | %   | N  | %   | N  | %   |
|-------------------------|----|-----|----|-----|----|-----|----|-----|
| Pregnancies             |    |     |    |     |    |     |    |     |
|                         | 6832 |      | 271 |      | 542 |      | 74 |      |
| Gestational weeks       | 38.8±1.5 |     | 38.3±1.8 |     | 38.5±1.6* |     | 38.3±1.8 |     |
| Preterm birth           | 355 | 5.2 | 25 | 9.2^ | 36 | 6.6 | 7 | 9.5 |
| 34≤PTD<37 wk            | 267 | 3.9 | 17 | 6.3 | 29 | 5.4 | 5 | 6.8 |
| 28≤PTD<34 wk            | 88 | 1.3 | 8 | 3^ | 7 | 1.3 | 2 | 2.7 |
| Birthweight, g          | 3370±47 |     | 3379±58 |     | 3382±498 |     | 3244±50 |     |
| <2500 g                 | 236 | 3.5 | 17 | 6.3^ | 21 | 3.9 | 4 | 5.4 |
| <1500 g                 | 38 | 0.6 | 4 | 1.5 | 3 | 0.6 | 0 | 0 |
| SGA                     | 281 | 4.1 | 18 | 6.6^ | 21 | 3.9 | 7 | 9.5^ |
| Macrosomia              | 521 | 7.6 | 31 | 11.4^ | 64 | 11.8* | 10 | 13.5 |
| Body length, cm         | 50.55±4 |     | 49.85±2. |     | 50.02±1.8 |     | 49.73±2. |     |
| 1-Minute Apgar score≤7  | 64 | 0.9 | 5 | 1.8 | 4 | 0.7 | 0 | 0 |
| 5-Minute Apgar score≤7  | 10 | 0.1 | 1 | 0.4 | 3 | 0.6* | 0 | 0 |
| NICU admission          | 728 | 10.7 | 48 | 17.7* | 72 | 13.3 | 17 | 23* |
| Gemellary               | N | % | N | % | N | % | N | % |
| Pregnancies             |    |     |    |     |    |     |    |     |
|                          | 98          | 133         | 161         | 33          |
|--------------------------|-------------|-------------|-------------|-------------|
| **Gestational weeks**    | 35.6±2.4    | 35.8±2      | 36.2±1.8^   | 36.2±2.1    |
| **Preterm birth**        | 54          | 55.1        | 70          | 52.6        | 99          | 37.9^       | 11          | 33.3^       |
| 34≤PTD<37 wk             | 39          | 39.8        | 54          | 40.6        | 78          | 29.9        | 9           | 27.3        |
| 28≤PTD<34 wk             | 15          | 15.3        | 16          | 12          | 20          | 7.7^        | 2           | 6.1         |
| **Birthweight, g**       | 2413.5±     | 2537±48     | 2580±419    | 2557±45     |
|                          | 464.6       | 6^          | *           | 3           |
| <2500 g                  | 61          | 62.2        | 71          | 53.4        | 132         | 50.6^       | 17          | 51.5        |
| <1500 g                  | 10          | 10.2        | 8           | 6           | 13          | 5           | 2           | 6.1         |
| **SGA**                  | 33          | 33.7        | 36          | 27.1        | 80          | 30.7        | 10          | 30.3        |
| **Macrosomia**           | 0           | 0           | 0           | 0           | 0           | 0           | 0           | 0           |
| **Body length, cm**      | 45.82±3.    | 46.70±3.    | 46.96±2.5   | 46.65±3.    |
|                          | 43          | 05^         | 6^          | 00          |
| **1-Minute Apgar score ≤7** | 2          | 2           | 5           | 3.8         | 4           | 1.5         | 2           | 6.1         |
| **5-Minute Apgar score ≤7** | 0          | 0           | 2           | 1.5         | 1           | 0.4         | 0           | 0           |
| **NICU admission**       | 53          | 54.1        | 78          | 58.6        | 139         | 53.3        | 15          | 45.5        |

Note: PTD=preterm delivery; **SGA**=small for gestational age (birthweight below the 10th percentile for gestational age); Macrosomia=birth weight ≥4000g;

Mixed infertility refers to multiple infertility-related diagnosis.

Data are presented as means±SDs for continuous variables and n (%) for dichotomous variables.
Pearson’s chi-square test, Fisher’s exact test or the t test was used as appropriate; P≤0.001=*. P<0.05=^. Nonsignificant numbers have not symbol

Table 4. aOR and 95% CIs of pregnancy and delivery outcomes among specific infertility causes compared to spontaneous pregnancies

|                | Ovulation disorder | Tubal disease | Endometriosis | Male infert |
|----------------|--------------------|---------------|---------------|-------------|
|                | aOR    | 95% CI      | aOR    | 95% CI      | aOR    | 95% CI      | aOR |
| SP             |        |             |        |             |        |             |     |
| GH             | 0.93   | 0.52 - 1.68 | 0.72   | 0.44 - 1.19 | 0.90   | 0.28 - 2.89 | 1.49 |
| Preeclampsia   | 2.60   | 1.61 - 4.20 | 1.40   | 0.89 - 2.21 | 0.90   | 0.22 - 3.74 | 1.10 |
| Mild           | 2.67   | 1.23 - 5.79 | 1.20   | 0.54 - 2.68 | NC     | NC           | NC  |
| Severe         | 2.46   | 1.36 - 4.44 | 1.51   | 0.88 - 2.59 | 1.42   | 0.34 - 5.92 | 1.36 |
| PPE            | 4.52   | 2.03 - 10.06| 1.38   | 0.54 - 3.54 | NC     | NC           | NC  |
| Condition          | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 |
|--------------------|----|----|----|----|----|----|----|----|----|----|----|----|
| GDM                | 1.76 | 1.33 | 2.33 | 1.50 | 1.21 | 1.86 | 1.20 | 0.67 | 2.13 | 1.31 | 0.0 |
| ICP                | 3.84 | 1.06 | 13.94 | 2.77 | 0.89 | 8.60 | NC  | NC  | NC  | 1.36 | 0.0 |
| Placenta previa    | 0.93 | 0.29 | 3.00  | 2.70 | 1.59 | 4.59 | 9.33 | 4.22 | 20.62 | 4.14 | 2.0 |
| Placental abruption| 1.89 | 0.86 | 4.17  | 0.92 | 0.42 | 2.01 | 1.90 | 0.46 | 7.97  | 0.55 | 0.0 |
| pPROM              | 2.11 | 1.17 | 3.81  | 1.52 | 0.93 | 2.49 | 1.76 | 0.55 | 5.70  | 1.79 | 0.0 |
| APCI               | 1.14 | 0.59 | 2.21  | 1.50 | 0.96 | 2.34 | 2.74 | 1.16 | 6.46  | 1.36 | 0.0 |
| Placenta accreta   | 1.29 | 0.59 | 2.80  | 1.78 | 1.10 | 2.89 | 2.00 | 0.62 | 6.48  | 2.05 | 1.0 |
| PH                 | 1.57 | 1.04 | 2.36  | 1.61 | 1.19 | 2.18 | 1.11 | 0.46 | 2.68  | 1.17 | 0.0 |
| Condition          | aOR | 95% CI | aOR | 95% CI | aOR | 95% CI | aOR | 95% CI |
|--------------------|-----|--------|-----|--------|-----|--------|-----|--------|
| Polyhydramnios     | 1.72| 0.60   | 4.89| 1.56   | 0.70| 3.48   | 1.79| 0.24   | 13.24| 2.27   | 0.    |
| Oligohydramnios    | 1.19| 0.68   | 2.10| 0.75   | 0.46| 1.22   | 1.17| 0.42   | 3.25 | 1.01   | 0.    |
| Chorioamnionitis   | 1.64| 0.74   | 3.63| 1.19   | 0.61| 2.32   | 1.76| 0.42   | 7.38 | 0.75   | 0.    |
| GP                 |     |        |     |        |     |        |     |        |      |        |      |
| GH                 | 3.36| 0.96   | 11.82| 2.38  | 0.69| 8.16   | 0.99| 0.10   | 9.92 | 2.67   | 0.    |
| Preeclampsia       | 0.94| 0.37   | 2.38| 0.64   | 0.26| 1.55   | 0.37| 0.07   | 1.90 | 0.78   | 0.    |
| Mild               | 0.74| 0.11   | 4.89| 0.56   | 0.09| 3.28   | 0.73| 0.06   | 9.65 | 0.33   | 0.    |
| Severe             | 1.07| 0.38   | 3.07| 0.71   | 0.26| 1.95   | 0.27| 0.03   | 2.41 | 1.04   | 0.    |
|               | Mean | SD  | CI   | Mean | SD  | CI   | Mean | SD  | CI   | Mean | SD  | CI   |
|---------------|------|-----|------|------|-----|------|------|-----|------|------|-----|------|
| PPE           | 1.38 | 0.48| 3.95 | 0.68 | 0.24| 1.93 | 0.28 | 0.03| 2.54 | 0.88 | 0.24| 1.93 |
| GDM           | 3.74 | 1.73| 8.09 | 1.23 | 0.58| 2.63 | 1.61 | 0.55| 4.72 | 1.62 | 0.55| 2.63 |
| ICP           | 0.54 | 0.11| 2.80 | 0.54 | 0.12| 2.41 | NC   | NC  | NC   | 0.48 | 0.09| NC   |
| Placenta previa| 0.23 | 0.02| 3.39 | 0.55 | 0.08| 3.90 | 1.65 | 0.17| 16.23| 0.21 | 0.17| 16.23|
| Placental abruption| 0.12 | 0.01| 1.51 | 0.08 | 0.01| 0.87 | NC   | NC  | NC   | 0.12 | 0.01| NC   |
| pPROM         | 2.13 | 0.88| 5.13 | 1.26 | 0.54| 2.97 | 0.69 | 0.13| 3.52 | 1.80 | 0.13| 3.52 |
| APCI          | 0.25 | 0.08| 0.84 | 0.33 | 0.12| 0.89 | NC   | NC  | NC   | 0.42 | 0.14| NC   |
| Placenta accreta| NC | NC  | NC   | NC | NC | NC | NC | NC | NC | NC | NC | NC |
| PH            | 1.45 | 0.63| 3.35 | 1.76 | 0.82| 3.80 | 2.78 | 0.91| 8.47 | 2.10 | 0.91| 8.47 |
| Condition          | aOR  | 95% CI       | p Value | NC  | NC  | NC  | NC  | aOR  | 95% CI       |
|--------------------|------|--------------|---------|-----|-----|-----|-----|------|--------------|
| Polyhydramnios     | 0.43 | 0.08         | 2.23    | 0.14| 0.02| 0.89| NC  | NC  | 0.38         |
| Oligohydramnios    | 0.33 | 0.03         | 4.22    | 0.09| 0.01| 1.52| NC  | NC  | 0.18         |
| Chorioamnionitis   | 1.39 | 0.08         | 22.88   | 0.26| 0.01| 6.51| NC  | NC  | NC           |

Note: *Logistic regression analysis was adjusted for age, gravidity, parity, pre-pregnancy obesity, birth plurality, and history of previous caesarean section. CI=confidence interval; aOR=adjusted odds ratio. Mixed infertility refers to multiple infertility-related diagnosis; SP=singleton pregnancies; GP=gestational pregnancies; GH=gestational hypertension; PPE=preterm preeclampsia; GDM=gestational diabetes mellitus; ICP=intrahepatic cholestasis of pregnancy; pPROM=preterm premature rupture of membranes; APCI= abnormal placental cord insertion, PH=postpartum haemorrhage.

Bold indicates significant differences; NC=not calculated due to low numbers.

Table 5. aOR and 95% CIs of neonatal outcomes among specific infertility causes compared to spontaneous pregnancies
|                  | aOR | 95% CI     | aOR | 95% CI     | aOR | 95% CI     | aOR | 95% CI     | aOR |
|------------------|-----|------------|-----|------------|-----|------------|-----|------------|-----|
| Singleton        |     |            |     |            |     |            |     |            |     |
| Pregnancies      |     |            |     |            |     |            |     |            |     |
| Preterm birth    | 1.95| 1.26       | 3.01| 1.33       | 1.91| 1.97       | 0.89| 4.34       | 1.52|
| 34≤PTD<37 wk     | 1.73| 1.03       | 2.89| 1.42       | 0.95| 2.11       | 1.83| 0.73       | 4.61|
| 28≤PTD<34 wk     | 2.49| 1.17       | 5.29| 1.06       | 0.48| 2.31       | 2.24| 0.53       | 9.38|
| Birthweight      | 1.90| 1.13       | 3.20| 1.12       | 0.71| 1.78       | 1.59| 0.57       | 4.42|
| <2500 g          |     |            |     |            |     |            |     |            |     |
| Birthweight      | 3.31| 1.34       | 9.60| 1.09       | 0.33| 3.59       | NC  | NC         | NC  |
| <1500 g          |     |            |     |            |     |            |     |            |     |
| SGA              | 1.60| 0.97       | 2.65| 0.90       | 0.57| 1.42       | 2.29| 1.04       | 5.08|
| Macrosomia       | 1.53| 1.03       | 2.27| 1.60       | 1.21| 2.13       | 2.00| 1.02       | 3.95|
| 1-Minute Apgar   | 1.84| 0.72       | 4.73| 0.77       | 0.28| 2.15       | NC  | NC         | NC  |
| score≤7          |     |            |     |            |     |            |     |            |     |
| 5-Minute Apgar   | 2.39| 0.27       | 20.34| 4.09       | 1.04| 16.08      | NC  | NC         | NC  |
| score≤7          |     |            |     |            |     |            |     |            |     |
| NICU admission   | 1.69| 1.22       | 2.34| 1.24       | 0.95| 1.61       | 2.35| 1.35       | 4.09|
| Gemellary        | aOR | 95% CI     | aOR | 95% CI     | aOR | 95% CI     | aOR |
| Pregnancies      |     |            |     |            |     |            |     |            |     |
| Preterm birth    | 1.33| 0.72       | 2.47| 0.74       | 0.42| 1.31       | 0.66| 0.27       | 1.63|
| 34≤PTD<37 wk     | 1.01| 0.54       | 1.89| 0.63       | 0.35| 1.14       | 0.58| 0.23       | 1.47|
| 28≤PTD<34 wk     | 2.05| 0.76       | 5.51| 1.26       | 0.49| 3.24       | 1.23| 0.23       | 6.65|
| Birthweight      | 0.86| 0.47       | 1.60| 0.76       | 0.43| 1.36       | 0.86| 0.36       | 2.05|
| <2500 g          |     |            |     |            |     |            |     |            |     |
| Birthweight <1500 g |
|---------------------|
| 1.03 0.31 3.42 0.84 0.28 2.53 1.32 0.23 7.62 1.32 0 |

| SGA | 0.62 0.32 1.20 0.72 0.39 1.32 0.74 0.29 1.88 0.57 0 |

| 1-Minute Apgar score≤7 |
|------------------------|
| 6.88 0.81 58.29 3.07 0.35 26.69 20.50 1.66 253.72 10.61 1 |

| NICU admission |
|---------------|
| 1.66 0.90 3.09 1.34 0.75 2.37 1.07 0.45 2.55 1.62 0 |

Note: *Logistic regression analysis was adjusted for age, gravidity, parity, pre-pregnancy obesity, birth plurality, and history of previous caesarean section. CI=confidence interval; aOR=adjusted odds ratio.

Mixed infertility refers to multiple infertility-related diagnosis; PTD=preterm delivery; **SGA=small for gestational age** (birthweight below the 10th percentile for gestational age); NICU= neonatal intensive care unit Macrosomnia=birth weight≥4000g

Bold indicates significant differences; NC=not calculated due to low numbers.
Figure 1

Flow chart of participants in the analysis