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

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Abstract
Background: To examine differences in maternal characteristics and pregnancy outcomes among Chinese women with infertility due to various reasons who underwent assisted reproductive technology (ART). Methods: This retrospective cohort study included women who used ART for various reasons. Demographics, medical history, laboratory tests, and delivery data were reviewed. Results: The ART treatment group was divided into 5 subgroups according to reason for infertility: ovulation disorder, tubal disease, male factor, endometriosis, multiple infertility-related diagnoses. Compared with spontaneous pregnancies, significant increases in the following were observed with ART: rates of gestational diabetes mellitus (GDM), preeclampsia, preterm premature rupture of membranes, postpartum hemorrhage, and chorioamnionitis in ovulation disorder; GDM, placenta previa and postpartum hemorrhage in tubal disease; placenta previa in endometriosis and male factor; and GDM, placenta previa and chorioamnionitis in multiple infertility-related diagnoses. Preterm birth, low birthweight, and small for gestational age were increased in all ART groups. Macrosomia and neonatal intensive care unit admission were increased in maternal factors with ART. Conclusions: During the perinatal period, women with different reasons for undergoing ART have different maternal characteristics and infant outcomes when compared with women not using ART, perinatal morbidities are higher in women undergoing ART for most reasons. The worst and best prognoses for infertility were found for that caused by ovulation disorder and male factor, respectively.

Background
The number of pregnancies and births after ART has increased exponentially over the past 40 years. To date, there have been more than 5 million infants born due to ART treatment globally[1]. ART contributes to 1.6% of all births in the United States [2], 2.7% in Australia and 1% in China[3, 4]. Indeed, ART has become among the most important treatments for infertility. Despite the widespread application of ART, concerns about potential health implications remain, and the results of previous studies are controversial, partly because of different study designs, populations and countries. The reasons for the increase in adverse pregnancy outcomes with ART are unknown. It is difficult to identify whether the adverse impacts observed in ART are the direct result of the procedure itself or a
result of the underlying subfertility of the parents. One hypothesis is that infertility-related diagnoses of women undergoing ART contribute directly to adverse outcomes, and excess perinatal morbidities have been associated with infertility-related diagnoses in both ART-treated and non-ART-treated women[5]. However, after adjustment for maternal characteristics, other studies have reported few cases of underlying infertility directly contributing to adverse outcomes[6]. Another possibility is that adverse outcomes result from the ART procedure itself, including artificial induction of ovulation, exposure of oocytes, sperm, and embryos outside of the body environment, and freezing and manipulation of oocytes and embryos. Many prior studies did not match the ages of ART and spontaneous conception groups, and knowledge on pregnancy outcomes of ART in China is limited. Besides, few literatures have examined the relationship between infertility causes and pregnancy outcomes. As a result, we conducted this retrospective cohort study to explore the characteristics of adverse pregnancy and birth outcomes in infertile women with different diagnoses after ART treatment to explore relationships between the reason for ART and adverse outcomes.

Methods

Cohort study

A large retrospective, hospital-based cohort study were conducted 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: 1) all groups were limited to live births, and gestational weeks were ≥28; 2) donor oocytes/sperm or embryo recipients or women who underwent preimplantation genetic diagnosis were excluded; 3) chronic complications of pre-pregnancy were excluded.

Main outcome Measures

Demographic and selected maternal characteristics, pregnancy and labor complications and neonatal outcomes were compared between the two groups. The selected maternal and pregnancy characteristics and pregnancy outcomes included gestational hypertension, preeclampsia, gestational
diabetes mellitus (GDM), delivery method, intrahepatic cholestasis of pregnancy (ICP), placenta previa, placental abruption, preterm premature rupture of membranes (pPROM), abnormal placental cord insertion, placental adherence or implantation, postpartum hemorrhage, polyhydramnios, oligohydramnios, preterm birth (PB), low birthweight (LBW), macrosomia, small for gestational age (SGA, defined as a birthweight below the 10th percentile for that gestational age), Apgar score at 1 minute, Apgar score at 5 minute and neonatal intensive care unit (NICU) admission. All diagnoses were based on the third edition of Chinese Obstetrics and Gynecology [7].

**Statistical Analysis**

SPSS statistical software (version 20.0) was used for data analysis. Quantitative data are presented as the mean and SD (mean ±SD). Fisher’s exact, t test and Pearson’s Chi-square tests were performed to evaluate differences in the proportions of categorical variables between two or more groups. 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, gravity, parity, pre-pregnancy body mass index (BMI), gestational week, birth plurality, and history of previous caesarean section; results are reported as adjusted odds ratio (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**

**Maternal Characteristics for Pregnancies Conceived by ART and Spontaneously**

A total of 8773 deliveries were subjected to retrospective analysis. Among the women, 21% (1843) had received ART treatment. The ART group consisted of 2651 singleton and 1185 gemellary pregnancies. The diagnoses for ART-treated deliveries, including ovulation disorder (N=404), tubal disease (N=803), endometriosis (N=107), male factor (N=403), and multiple infertility-related diagnoses (N=126). The spontaneously conceived group consisted of 6832 singleton and 98 gemellary pregnancies. The maternal characteristics for ART and spontaneous pregnancies were presented in Table 1. Compared with spontaneous pregnancies, women with ART pregnancies were
more likely to have higher BMIs and a lower rate of previous cesarean delivery. The spontaneous pregnancy group also had a significantly higher number of second gravidity and pregnancies compared with the ART group (\(P<0.001\)). In total, 1241 women (67.3%) who conceived via ART gave birth by cesarean section, 508 (27.6%) by vaginal delivery and only 94 (5.1%) by operative vaginal delivery; these numbers for women conceived spontaneously were 3100 (44.7%), 3547 (51.2%) and 283 (4.1%), respectively. The cesarean section rate was significantly higher in the ART pregnancy group than in the spontaneous pregnancy group (\(P<0.001\)), as was the multiple pregnancy rate (32.7% vs 1.4%).

**Pregnancy and Perinatal Complications Related with ART diagnoses categories**

As Table 2 shows, compared with spontaneous pregnancy, the subgroup of ovulation disorder conception was associated with an increased risk of preeclampsia (\(aOR 2.00, 95\%CI 1.32-3.03\)), GDM (\(aOR 2.06, 95\%CI 1.62-2.61\)), pPROM (\(aOR 2.10, 95\%CI 1.22-3.61\)), postpartum hemorrhage (\(aOR 1.47, 95\%CI 1.03-2.09\)), and chorioamnionitis (\(aOR 2.11, 95\%CI 1.05-4.24\)), and the subgroup of tubal disease conception was associated with an increased risk of GDM (\(aOR 1.35, 95\%CI 1.11-1.65\)), placenta previa (\(aOR 2.75, 95\%CI 1.66-4.57\)) and postpartum hemorrhage (\(aOR 1.57, 95\%CI 1.20-2.05\)). Additionally, subgroups of endometriosis and male factor conception were associated with an increased risk of placenta previa (\(aOR 7.78, 95\%CI 3.62-16.69; \ aOR 3.36, 95\%CI 1.78-6.35\)), and the subgroup of multiple infertility-related diagnosis conception was associated with an increased risk of GDM (\(aOR 1.97, 95\%CI 1.32-2.95\)), placenta previa (\(aOR 3.06, 95\%CI 1.13-8.30\)) and chorioamnionitis (\(aOR 3.04, 95\%CI 1.07-8.64\)). The results were similar for singleton and gemellary pregnancies.

**Neonatal Outcomes Related with ART diagnosis Categories**

Compared with spontaneous pregnancy, the risks of PB, LBW and SGA were significantly higher in all subgroups of ART, whereas the risks of macrosomia and NICU admission were increased in the subgroups of ovulation disorder, tubal disease and endometriosis; the risk of 1 minute Apgar\(\leq7\) was increased in the multiple infertility-related diagnosis subgroup, and the risk of 5 minute Apgar\(\leq7\) was
increased in the tubal disease subgroup (Table 2). However, after adjusting for parity, the differences narrowed or disappeared. Regarding singleton pregnancies, the risk of PB still increased in most subgroups of ART, except for male factor, despite no significant difference. Furthermore, the subgroup of ovulation disorder was associated with an increased risk of macrosomia (aOR 1.59, 95%CI 1.07-2.36), that of tubal disease conception with an increased risk of macrosomia (aOR 1.64, 95%CI 1.24-2.18), that of endometriosis with an increased risk of macrosomia (aOR 2.27, 95%CI 1.14-4.51), SGA (aOR 2.50, 95%CI 1.11-5.63) and NICU admission (aOR 2.46, 95%CI 1.31-4.63), and that of multiple infertility-related diagnoses with an increased risk of PB (aOR 3.15, 95%CI 1.41-7.02), and 1 minute Apgar≤7 (aOR 3.95, 95%CI 1.29-12.09). However, there were no significant differences in neonatal outcomes between ART and spontaneous conception in the subgroup of male factor.

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, diagnosis categories within the ART population were found to affect maternal and neonatal outcomes among all births. As summarized in Table 2, infertility caused by ovulation disorder had the worst prognosis. In fact, ovulation disorder was associated with higher risks of preeclampsia (2-fold), GDM (2.06-fold), pPROM (2.10-fold), postpartum hemorrhage (1.48-fold) and chorioamnionitis (2.11-fold), which is consistent with prior studies[5, 8]. One possible explanation is that a high proportion of the women with ovulation disorder 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[9]. 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 outcomes[10].
Compared to spontaneous pregnancies, ART pregnancies in patients having tubal infertility had an increased risk of GDM (1.35-fold), placenta previa (2.75-fold), and postpartum hemorrhage (1.57-fold). One study reported that infertility, particularly due to ovulatory disorder and 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[11], consistent with our results. Tubal factor infertility is always associated with reproductive inflammation, which may lead to imbalance in immune-endocrine crosstalk among the endometrium, myometrium and cervix and between the decidua and trophoblast, predisposing toward pregnancy complications, such as placenta previa and postpartum hemorrhage.

Our data showed that endometriosis was significantly associated with placenta previa, similar to the findings of previous studies[12-14]. 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 remodeling of the spiral arteries[15]. These factors may explain why endometriosis is possibly a crucial factor for increased negative outcomes in ART pregnancy.

Interestingly, in the male factor subgroup, the rate of placenta previa was also increased, but this has not been universally reported. One possible explanation is that the increased risk of placenta previa is caused by factors related to ART[16]. 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 and thereby increasing the risk of placenta previa. Therefore, the risk of placenta previa would increase in all subgroups except for ovarian disorder, similar to previous research[16].

In this retrospective study, we found that PB, LBW and SGA risks were significantly higher in all subgroups of ART. Regarding ART with female factor infertility, the risk of macrosomia increased. This finding might indicate that ART with female abnormality is more likely to be associated with adverse neonatal complications rather than the ART procedure itself, similar to a previous study[17]. Nonetheless, Galit Levi Dunietz et al. assert that preterm birth among ART singletons is increased
within each treatment type and all underlying infertility diagnoses, including male infertility[18], but Benaglia L found that women with endometriosis who conceived via in vitro fertilization (IVF) do not face an increased risk of preterm birth[19]. Overall, the results require further analysis in larger cohorts and control for as many confounders as possible and also further pre-clinical studies.

Our study also showed an increased risk for GDM, placenta previa, chorioamnionitis, and PB in the multiple infertility-related diagnosis sub-group compared with corresponding controls. When there are multiple infertility-related diagnoses for parental infertility, pregnancy complications, parental and neonatal outcomes might differ, but they will always increase perinatal morbidities.

The major strength of our study is not only the comparison of perinatal and neonatal outcomes of ART and spontaneous conception, but also assessment of the impact of different infertility diagnoses on pregnancy characteristics and outcomes in China. China has abolished the “one child” policy and since 2016 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[20]. Our findings have significantly 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 providing information for the underlying pathogenic mechanisms.

There are, however, a few limitations of this study. First, information about environmental exposure and risk behaviors (alcohol, tobacco use, educational level, income level) were not be included in this study, which may lead to bias. Another gap in the data that were available was the severity and treatment process of infertility. For example, the stage of endometriosis, baseline endocrine level and ovarian stimulation protocol were incomplete. Finally, this study represents results from a high-level specialty hospital in China, which may not be representative for other countries.

Conclusions

Taken together, women with different reasons for undergoing ART have different maternal characteristics, health issues and infant outcomes compared with women who conceive spontaneously. Perinatal morbidities are higher in ART-treated women. Infertility caused by ovulation
disorder and by male factor has the worst and best prognoses, respectively. Careful further studies are warranted to clarify the mechanism of these adverse events.

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 retrospective study design, consent for participation was not required. Nevertheless, the private information was well protected during the study.

**Consent for publication**

Not applicable

**Availability of data and material**

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 conflict of interest.

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**Author contributions**

JXW and JMC contributed to study conception and design. QWL,BED and FC examined the data integrity and accuracy. JXW and XWL performed data analysis. JXW drafted the manuscript and JMC revised the manuscript. All the authors read and approved the final manuscript.

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Not applicable

**Abbreviations**

ART: Assisted reproductive technology

BMI: Body mass index

GDM: Gestational diabetes mellitus

ICP: Intrahepatic cholestasis of pregnancy

pPROM: preterm Premature Rupture Of Membranes
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## Tables

### Table 1. Maternal and Pregnancy Characteristics in ART and Spontaneous Pregnancy Groups.

|                          | Ovulation disorder | Tubal disease | Endometriosis | Male factor | Multiple infertility-related diagnoses | ART | Controls | P value* |
|--------------------------|--------------------|---------------|---------------|-------------|----------------------------------------|-----|----------|----------|
| **numbers**              |                    |               |               |             |                                        |     |          |          |
| Mother's Age             |                    |               |               |             |                                        |     |          |          |
|                         | 404                | 803           | 107           | 403         |                                        | 1843| 6930     | 0.11     |
|                         | ±4.1 ±4.9          | ±3.10         | ±3.58         | ±3.50       |                                        |     |          |          |
| Gravidity                |                    |               |               |             |                                        |     |          | <0.001   |
| G1                       | 258 (63.9%)        | 436 (54.3%)   | 74 (69.2%)    | 289 (71.7%) |                                        | 1132| 2879     | (41.6%)  |
|                          |                    |               |               |             |                                        |     |          |          |
| G≥2                      | 146 (36.1%)        | 367 (45.7%)   | 33 (30.8%)    | 114 (28.3%) |                                        | 711 | 4048     | (58.4%)  |
| Parity                   |                    |               |               |             |                                        |     |          | <0.001   |
| P1                       | 382 (94.6%)        | 762 (94.9%)   | 104 (97.2%)   | 389 (96.5%) |                                        | 1761| 5055     | (73%)    |
|                          |                    |               |               |             |                                        |     |          |          |
| P≥2                      | 22 (5.4%)          | 41 (5.1%)     | 3 (2.8%)      | 14 (3.5%)   |                                        | 82  | 1872     | (27%)    |
| Obesity before pregnancy|                    |               |               |             |                                        |     |          | <0.001   |
| Yes                      | 15 (3.7%)          | 13 (1.6%)     | 1 (0.9%)      | 7 (1.7%)    |                                        | 40  | 61       | (0.9%)   |
|                         |                    |               |               |             |                                        |     |          |          |
| No                       | 389 (96.3%)        | 790 (98.4%)   | 106 (99.1%)   | 396 (98.3%) |                                        | 1803| 6869     | (99.1%)  |
| Birth plurality          |                    |               |               |             |                                        |     |          | <0.001   |
| Singleton                | 271 (67.1%)        | 542 (67.5%)   | 74 (69.2%)    | 267 (66.3%) |                                        | 87  | 1241     | (67.3%)  |
|                          |                    |               |               |             |                                        |     |          |          |
| Gemellary pregnancies    | 133 (32.9%)        | 261 (32.5%)   | 33 (30.8%)    | 136 (33.7%) |                                        | 39  | 602      | (32.7%)  |
|                         |                    |               |               |             |                                        |     |          | (1.4%)   |
| Previous cesarean delivery |                    |               |               |             |                                        |     |          | <0.001   |
| Yes                      | 6 (1.5%)           | 17 (2.1%)     | 3 (2.8%)      | 6 (1.5%)    |                                        | 34  | 772      | (11.1%)  |
|                         |                    |               |               |             |                                        |     |          |          |
| No                       | 398 (98.5%)        | 786 (97.9%)   | 104 (97.2%)   | 397 (98.5%) |                                        | 1809| 6158     | (88.9%)  |
| Delivery method          |                    |               |               |             |                                        |     |          | <0.001   |
| Vaginal delivery         | 115 (28.5%)        | 227 (28.3%)   | 24 (22.4%)    | 115 (28.5%) |                                        | 27  | 508      | (27.6%)  |
|                          |                    |               |               |             |                                        |     |          | (51.2%)  |

*P value significance levels: <0.001 indicates extremely significant, <0.01 indicates very significant, <0.05 indicates significant, and ≥0.05 indicates non-significant.
### Cesarean section

|        | 261 (64.6%) | 538 (67%) | 75 (70.1%) | 276 (68.5%) | 91 (72.2%) | 1241 (67.3%) | 3100 (44.7%) |

### Operative vaginal delivery

|        | 28 (6.9%) | 38 (4.7%) | 8 (7.5%) | 12 (3%) | 8 (6.3%) | 94 (5.1%) | 283 (4.1%) |

Note: Data are presented as mean±SD for continuous variables and n(%) for dichotomous variables.

*Pearson’s Chi-square or Fisher exact test or t test, as appropriate.

Table 2. Pregnancy and Delivery Outcomes Neonatal Outcomes with Specific Infertility Diagnosis and Spontaneous Pregnancy Groups.
| Outcome                                      | Control | Ovulation disorder | P Value* | aOR    | 95%CI | Tubal disease | P Value* | aOR    | 95%CI | Endometriosis | P Value* |
|----------------------------------------------|---------|--------------------|----------|--------|-------|--------------|----------|--------|-------|--------------|----------|
| Pregnancy and Delivery Outcomes             |         |                    |          |        |       |              |          |        |       |              |          |
| Gestational Hypertension                    | 276 (4%)| 25 (6.2%)          | 0.923    | 0.98   | 0.61-1.5 | 35 (4.4%)    | 0.269    | 0.80   | 0.54-1.1 | 4 (3.7%)  | 0.025    |
| Preeclampsia                                | 203 (2.9%)| 41 (10.1%)       | 0.001    | 2.00   | 1.32-3.30 | 50 (6.2%)    | 0.133    | 1.33   | 0.92-1.99 | 4 (3.8%)  | 0.006    |
| mild                                         | 65 (0.9%)| 12 (3%)           | 0.056    | 1.99   | 0.98-4.0 | 13 (1.6%)    | 0.611    | 1.19   | 0.61-2.3 | 4 (0.9%)  | 0.928    |
| severe                                       | 138 (2%)| 29 (7.2%)         | 0.006    | 2.01   | 1.22-3.3 | 37 (4.6%)    | 0.108    | 1.44   | 0.92-2.22 | 4 (2.8%)  | 1.953    |
| GDM                                          | 1147 (16.6%)| 127 (31.4%)     | <0.00    | 2.06   | 1.62-2.6 | 174 (21.7%)  | 0.003    | 1.35   | 1.11-1.6 | 5 (21.5%) | 0.278    |
| ICP                                          | 19 (0.3%)| 7 (1.7%)          | 0.269    | 1.83   | 0.63-5.3 | 12 (1.5%)    | 0.186    | 1.88   | 0.74-4.8 | 0 (NC)    | 1.292    |
| Placenta previa complete                     | 96 (1.4%)| 4 (1%)            | 0.666    | 0.79   | 0.26-2.3 | 23 (2.9%)    | <0.00    | 2.75   | 1.66-4.5 | 10 (<1%) | 1.473    |
| partial                                      | 49 (0.7%)| 1 (0.2%)         | 0.255    | 0.25   | 0.02-2.7 | 4 (0.5%)     | 0.767    | 0.85   | 0.28-2.5 | 5 (3.7%)  | 1.37     |
| marginal                                     | 47 (0.7%)| 4 (1%)           | 0.462    | 1.50   | 0.51-4.4 | 11 (1.4%)    | 0.022    | 2.30   | 1.13-4.6 | 2 (1.9%)  | 1.383    |
| Placental abruption pPROM                    | 95 (1.4%)| 8 (2%)           | 0.335    | 1.47   | 0.67-3.1 | 8 (1%)       | 0.507    | 0.77   | 0.36-1.6 | 5 (1.9%)  | 1.28     |
| Abnormal placental cord insertion            | 167 (2.4%)| 37 (9.2%)       | 0.007    | 2.10   | 1.22-3.6 | 49 (6.1%)    | 0.135    | 1.43   | 0.89-2.3 | 0 (1.9%)  | 0.415    |
| Placental adhesion or implantation           | 200 (2.9%)| 15 (3.7%)      | 0.595    | 0.86   | 0.48-5.5 | 37 (4.6%)    | 0.462    | 1.16   | 0.78-1.7 | 6 (5.6%)  | 0.83     |
| Postpartum haemorrhage                       | 597 (8.6%)| 50 (12.4%)      | 0.034    | 1.47   | 1.03-2.0 | 9 (12.3%)    | 0.001    | 1.57   | 1.20-2.0 | 5 (13.8%) | 0.03     |
| Polyhydramnios                               | 67 (1%) | 7 (1.7%)         | 0.437    | 1.41   | 0.59-3.3 | 9 (1.1%)     | 0.784    | 0.90   | 0.41-1.9 | 1 (0.9%)  | 1.16     |
| Oligohydramnios                              | 248 (3.6%)| 16 (4%)        | 0.291    | 1.34   | 0.78-2.2 | 19 (2.4%)    | 0.280    | 0.77   | 0.47-1.2 | 4 (3.7%)  | 1.17     |
| Chorioamnionitis Neonatal Outcomes           | 92 (1.3%)| 10 (2.5%)       | 0.036    | 2.11   | 1.05-4.2 | 11 (1.4%)    | 0.584    | 1.20   | 0.62-2.3 | 1 (1.9%)  | 1.05     |
| Preterm birth                                | 409 (5.9%)| 95 (23.5%)      | <0.00    | 4.82   | 3.41-6.7 | 3 (16.8%)    | <0.00    | 3.40   | 2.56-4.5 | 18 (16.8%) | 0.00     |
| Low Birthweight                              | 297 (4.3%)| 88 (21.8%)      | <0.00    | 3.40   | 2.33-4.9 | 3 (19.1%)    | <0.00    | 4.57   | 3.42-6.1 | 21 (19.6%) | 0.00     |
| Small for gestational age                    | 314 (4.5%)| 54 (13.4%)      | <0.00    | 2.74   | 1.97-0.8 | 2 (12.6%)    | <0.00    | 2.59   | 2.01-3.3 | 17 (15.9%) | 0.00     |
| Macrosomia                                   | 521 (7.5%)| 31 (7.7%)       | 0.010    | 1.70   | 1.14-2.5 | 4 (8%)       | <0.00    | 1.68   | 1.25-2.2 | 10 (9.3%) | 0.00     |
| 1 minute Apgar ≤7                            | 66 (1%) | 10 (2.5%)       | 0.553    | 1.26   | 0.59-2.7 | 1 (8%)       | 0.222    | 0.61   | 0.27-1.3 | 5 (2.8%)  | 0.00     |
| 5minute Apgar ≤7                             | 10 (0.1%)| 3 (0.7%)        | 0.508    | 2.04   | 0.25-1.6 | 87 (0.5%)    | 0.014    | 2.65   | 1.95-362 | 0 (NC)   | 1.38     |
| NICU admission                               | 781 (11.3%)| 126 (31.2%)     | 0.018    | 1.47   | 1.07-2.0 | 211 (26.3%)  | 0.005    | 1.40   | 1.11-1.7 | 8 (29.9%) | 0.00     |

Table 2 continued
| Pregnancy and Delivery Outcomes | Controls | Male factor | P value* | aOR | 95%CI | Multiple infertility-related diagnoses | P value* | aOR | 95%CI |
|---------------------------------|----------|-------------|----------|-----|-------|----------------------------------------|----------|-----|-------|
| Gestational Hypertension        | 276 (4%) | 28 (6.9%)   | 0.350    | 1.23 | 0.79, 1.92 | 4 (3.2%) | 0.179 | 0.50 | 0.18, 1.38 |
| Preeclampsia                    | 203 (2.9%) | 25 (6.2%)   | 0.370    | 1.25 | 0.77, 2.05 | 9 (7.1%) | 0.540 | 1.26 | 0.60, 2.64 |
| mild                            | 65 (0.9%)  | 4 (1%)      | 0.566    | 0.73 | 0.25, 2.13 | 2 (1.6%) | 0.908 | 1.09 | 0.26, 4.66 |
| severe                          | 138 (2%)   | 21 (5.2%)   | 0.144    | 1.52 | 0.87, 2.66 | 7 (5.6%) | 0.439 | 1.40 | 0.60, 3.24 |
| GDM                             | 1147 (16.6%) | 87 (21.6%) | 0.252    | 1.32 | 0.82, 2.14 | 37 (29.4%) | 0.001 | 1.97 | 1.32, 2.95 |
| ICP                             | 19 (0.3%)  | 5 (1.2%)    | 0.786    | 1.18 | 0.36, 3.86 | 1 (0.8%) | 0.916 | 0.89 | 0.11, 7.33 |
| Placenta previa                 | 96 (1.4%)  | 14 (3.5%)   | <0.00    | 3.36 | 1.78, 6.35 | 5 (4%) | 0.028 | 3.06 | 1.13, 8.30 |
| complete                        | 49 (0.7%)  | 5 (1.2%)    | 0.080    | 2.60 | 0.89, 7.58 | 3 (2.4%) | 0.114 | 2.94 | 0.77, 11.2 |
| partial                         | 0          | 0           | NC       | NC  | NC   | 0 | NC | NC | NC |
| marginal                        | 47 (0.7%)  | 9 (2.2%)    | 0.002    | 3.57 | 1.62, 7.87 | 0 | NC | NC | NC |
| Placental abruption             | 95 (1.4%)  | 30 (0.7%)   | 0.228    | 0.48 | 0.14, 1.59 | 4 (3.2%) | 0.131 | 2.29 | 0.78, 6.73 |
| pROM                            | 167 (2.4%) | 32 (7.9%)   | 0.068    | 1.72 | 0.96, 3.06 | 6 (4.8%) | 0.362 | 0.60 | 0.20, 1.80 |
| Abnormal placental cord insertion | 200 (2.9%) | 19 (4.7%)   | 0.701    | 1.11 | 0.66, 1.87 | 6 (4.8%) | 0.827 | 1.10 | 0.47, 2.59 |
| Placental adhesion or implantation | 148 (2.1%) | 13 (3.2%)   | 0.142    | 1.59 | 0.86, 2.96 | 4 (3.2%) | 0.511 | 1.42 | 0.50, 4.09 |
| Postpartum haemorrhage          | 597 (8.6%) | 45 (11.2%)  | 0.080    | 1.39 | 0.96, 2 | 12 (9.5%) | 0.470 | 1.27 | 0.67, 2.42 |
| Polyhydramnios                  | 67 (1%)    | 8 (2%)      | 0.149    | 1.84 | 0.80, 4.22 | 1 (0.8%) | 0.634 | 0.61 | 0.08, 4.63 |
| Oligohydramnios                 | 248 (3.6%) | 13 (3.2%)   | 0.787    | 1.08 | 0.60, 1.95 | 2 (1.6%) | 0.310 | 0.48 | 0.12, 1.98 |
| Chorioamnionitis                | 92 (1.3%)  | 3 (0.7%)    | 0.471    | 0.65 | 0.20, 2.10 | 4 (3.2%) | 0.037 | 3.04 | 1.07, 8.64 |
| Neonatal Outcomes               |           |             |          |     |       |                                        |          |     | |
| Preterm birth                   | 409 (5.9%) | 84 (20.8%)  | <0.00    | 4.11 | 2.88, 5.87 | 27 (21.4%) | <0.00 | 5.93 | 3.50, 10.0 |
| Low Birthweight                 | 297 (4.3%) | 86 (21.3%)  | <0.00    | 4.08 | 2.79, 5.97 | 28 (22.2%) | <0.00 | 4.81 | 2.62, 8.83 |
| Small for gestational age Macrosomia | 521 (7.5%) | 20 (5%)     | 0.860    | 1.04 | 0.65, 1.68 | 6 (4.8%) | 0.842 | 1.09 | 0.46, 2.56 |
| 1 minute Apgar≤7                 | 314 (4.5%) | 47 (11.7%)  | <0.00    | 2.29 | 1.62, 3.24 | 19 (15.1%) | <0.00 | 3.42 | 2.03, 5.78 |
| 5 minute Apgar≤7                 | 66 (1%)    | 10 (2.5%)   | 0.240    | 1.58 | 0.74, 3.37 | 6 (4.8%) | 0.021 | 3.03 | 1.18, 7.74 |
| NICU admission                   | 111 (27.5%) | 111 (27.5%) | 0.269    | 1.21 | 0.87, 1.68 | 35 (27.8%) | 0.939 | 0.98 | 0.56, 1.72 |

Note: Analyses were adjusted for maternal age, gravidity, parity, pre-pregnancy BMI, plurality, and previous cesarean delivery. GDM = Gestational diabetes mellitus; ICP = Intrahepatic cholestasis of pregnancy; NICU = neonatal intensive care unit; CI = confidence interval; aOR = adjusted odds ratio; NC = not calculated due to low numbers. *Logistic regression analysis
