Association of infertility cause with perinatal outcomes in a freeze-all policy: an analysis including 10,151 singleton newborns

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BACKGROUND: In vitro fertilization-conceived babies, even singletons, are at a higher risk of poor birth outcomes such as low birthweight and preterm birth than naturally conceived counterparts. It remains unclear as to what extent these adverse outcomes are attributed to the underlying causes of infertility. Evidence on this topic is scarce and has mainly focused on fresh embryo transfer cycles.

OBJECTIVE: This study aimed to investigate the effect of infertility cause on perinatal outcomes when a freeze-all strategy is applied.

STUDY DESIGN: We conducted a retrospective cohort study involving singleton live births born to women who had undergone frozen-thawed embryo transfer during the period from January 2014 to December 2019 at a single center. Subjects were categorized into 7 groups as follows according to the sole cause of infertility: tubal disorder, polycystic ovary syndrome, diminished ovarian reserve, uterine factor infertility, endometriosis, male factor, and unexplained infertility. The perinatal outcomes evaluated were as follows: birthweight, newborn gender, gestational age, preterm birth, low birthweight, small for gestational age, large for gestational age, and macrosomia. Multivariable regression analyses were introduced to control for several important confounders, with unexplained infertility as a reference group.

RESULTS: A total of 10,151 women were included for the final analysis. The most common maternal infertility diagnosis of the entire cohort was tubal disorder (42.5%), followed by diminished ovarian reserve (9.5%), endometriosis (9.4%), polycystic ovary syndrome (5.7%), and uterine factor infertility (1.6%). Male factor infertility was present in 19.8% of cycles, and infertility was diagnosed as unexplained in 11.4% of cycles. In the unadjusted analyses, the prevalence of low birthweight (odds ratio, 2.05; 95% confidence interval, 1.24−3.38) and preterm birth (odds ratio, 1.97; 95% confidence interval, 1.33−2.92) was higher among singletons in the polycystic ovary syndrome group than in those from the unexplained infertility group. However, these differences were no longer significant after correction for parental characteristics, treatment variables, and pregnancy complications (adjusted odds ratio, 1.50; 95% confidence interval, 0.98−2.28 for preterm birth; adjusted odds ratio, 1.70; 95% confidence interval, 0.99−2.91 for low birthweight). The risks of preterm birth (adjusted odds ratio, 2.66; 95% confidence interval, 1.53−4.63) and low birthweight (adjusted odds ratio, 3.51; 95% confidence interval, 1.79−6.90) with uterine factor infertility were significantly increased vs the reference group in both unadjusted and adjusted analyses. In addition, the perinatal outcomes in women with other infertility causes were comparable with unexplained infertility in terms of the rates of preterm birth, low birthweight, small for gestational age, large for gestational age, and macrosomia.

CONCLUSION: With the exception of uterine factor infertility, other infertility causes do not seem to compromise perinatal outcomes when compared with unexplained infertility in a freeze-all approach. With the ever-increasing use of frozen-thawed embryo transfer globally, our data hold relevant clinical implications, as they can guide physicians in patient counseling.

Key words: ART, frozen-thawed embryo transfer, infertility cause, in vitro fertilization, perinatal outcome

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**Why was this study conducted?**
Emerging evidence has demonstrated that in vitro fertilization-conceived babies were more likely to have a higher risk of adverse perinatal outcomes than naturally conceived peers. It remains unclear as to what extent this excess risk is attributed to the underlying causes of infertility, particularly in women undergoing frozen embryo transfer (FET).

**Key findings**
The cause of infertility, with the exception of uterine factor infertility, does not seem to have a negative impact on perinatal outcomes when compared with unexplained infertility in FET cycles.

**What does this add to what is known?**
In the context of the increasing use of FET globally, our work holds relevant clinical implications, as it can guide physicians in patient counseling.

**Introduction**
From the time the first pregnancy and live birth conceived by in vitro fertilization (IVF) was reported in 1978,1 >8 million babies have been born as a result of this technology.2 In 2016, the total number of infants born through IVF in China exceeded 300,000, representing 1.69% of the total national birth cohort.3 In some European countries, the percentage of children born subsequent to IVF is substantially higher; for instance in Spain, it is estimated that approximately 8% of children born originate from IVF treatment.4 Safety monitoring of IVF offspring is of utmost importance to the future generations.5 In general, most IVF babies are healthy. However, evidence from epidemiologic studies indicates that IVF pregnancies, even those limited to singletons, are associated with an increased risk of adverse perinatal outcomes than naturally conceived peers.6–9 Although the exact mechanism behind this difference remains obscure, infertility itself or parental characteristics are believed to be an important contributor to the poor perinatal outcomes in IVF singletons.8,9 In addition, it has been well documented that the specific IVF process (including controlled ovarian stimulation [COS]), fertilization method, and embryo cryopreservation may also play a role.10–12 Furthermore, laboratory parameters such as the type of embryo culture media and incubator systems could also be involved.13,14

An unresolved question in research into adverse outcomes following IVF is how much of this excess risk is reproductive technology-related, and how much of it is the result of the biology of infertile couples?11 Separating the contribution of these 2 key elements from outcomes is difficult, as selecting an appropriate control group for children born after IVF remains a major challenge for fertility specialists.8 In fact, most of the literature available in this area compared IVF pregnancies with those of fertile women rather than with those of infertile cohorts who did not undergo IVF.11,15–17 Thereafter, the pure influence of underlying infertility disorder on the birth outcomes is still not well understood.

Few studies have been designed to specially look at the relationship between the perinatal outcomes following IVF and the causes of infertility.18–21 Of note, most of these studies were established on data obtained from national registers and therefore may be biased by the inconsistent IVF practices and different laboratory conditions between clinics. Moreover, existing literature has mainly focused on fresh transfer cycles without eliminating the possibility of adverse fetal growth caused by a hyperestrogenic milieu.10,22 As opposed to fresh cycles, frozen-thawed embryo transfer (FET) appears to provide a better and more physiological uterine environment for early implantation and fetal development.23,24 In the context of the increasing adoption of FET globally, additional data would be more than welcome to explore whether the type of infertility cause may have any significant influence on birth outcomes resulting from FET cycles. The objective of this study was therefore to investigate the effect of infertility cause on perinatal outcomes when a freeze-all strategy was applied from a single center.

**Materials and Methods**

**Study design and population**
A retrospective study was carried out at the Center for Reproductive Medicine of the Ninth People’s Hospital of Shanghai Jiao Tong University School of Medicine. FET cycles performed during the period from January 2014 to December 2019 and resulting in a singleton live birth were screened for potential inclusion. Women with the following criteria were excluded: (1) preexisting medical conditions (eg, hypertension, diabetes mellitus, and thyroid dysfunction); (2) donor cycles; (3) more than 1 infertility cause; (4) smoking history; and (5) vanishing twin syndrome. Couples with chromosomal abnormalities were also excluded. If more than 1 delivery for the same women was in the database, only the first pregnancy was retained. Notably, preimplantation genetic diagnosis is not available in our center, and none of the women included in the present study used this technology. Furthermore, a nonelective freeze-all policy has been adopted in our center as a routine practice, and the reason for employing this strategy has been discussed in detail in our previous statement.25–27 The vitrification and thawing procedures have been previously described by Kuwayama et al.28 A maximum of 2 embryos were allowed to be transferred in compliance with the national regulations of China.29

Patients were grouped into 7 groups based on a single infertility cause, namely, tubal disorder, polycystic ovary syndrome (PCOS), endometriosis, male factor, diminished ovarian reserve (DOR), uterine factor, and unexplained. The cause of infertility was diagnosed by medical history or assessed by a
baseline fertility work-up, and unexplained infertility was defined in case no cause could be found.

**Data source**

Data for couples who initiated IVF treatments were captured from the database of our fertility center, which contains comprehensive information on parental demographics, detailed medical history, indication for fertility treatment, cycle-specific treatment parameters, and pregnancy and delivery outcomes. On accessing the database via a unique identification number allocated to each couple, highly trained staff collected and updated the treatment data continuously along with the IVF procedures until embryo transfer. The follow-up programs have been extensively discussed in our previous publications. Any adverse outcomes were adjudicated by a dedicated research nurse.

**Outcome measures and definitions**

Live birth was defined as the delivery of a viable infant at ≥22 weeks’ gestation.²² The gestational age (GA) for FET was calculated by the number of culture days and the date of embryo transfer, defined as day 17 of the cycle for cleavage-stage embryo and day 19 for the blastocyst transfer. Occurrence of live birth at <37 weeks’ GA was defined as a preterm birth (PTB) and a birthweight <2500 g was classified as low birthweight (LBW). Small for gestational age (SGA) was considered as neonatal birthweight below the 10th percentile, whereas large for gestational-age (LGA) was considered as having a birthweight above the 90th percentile, after being adjusted for the GA and gender, according to the updated nationwide neonatal birthweight curve in China.³³

**Statistical analyses**

Data were analyzed by SPSS software, version 26.0 (IBM Corp, Armonk, NY). Continuous variables were expressed as mean±standard deviation, whereas categorical variables were described as the number of cases (n) with percentage (%). The maternal and treatment characteristics and perinatal outcomes were compared between groups by one-way analysis of variance for continuous data and Pearson chi-square test or Fisher exact test for categorical data as appropriate.

To detect the relationship between the infertility cause and the main perinatal outcomes, univariable and multivariable regression analyses were introduced. The following potential confounders were entered in the multivariable models: parental age and body mass index (BMI), parity, infertility duration, educational level, FET cycle rank, type of infertility, insemination method, embryonic stage at transfer, number of embryos transferred, year of treatment, and pregnancy complications including gestational diabetes and hypertensive disorders of pregnancy. Unexplained infertility was considered as a reference group in the multivariable models in accordance with previous studies.¹⁸,³⁴

Of note, 4 additional sensitivity analyses were undertaken to check the robustness of the main findings. The first was based on the number of embryos transferred. Given that previous labor and delivery might affect subsequent perinatal outcomes, subgroup analysis restricted to nulliparous women was carried out. Moreover, considering that performing IVF or intracytoplasmic sperm injection (ICSI) might affect early embryonic development, placentation and consequently the birth outcome, the perinatal outcomes were separately presented according to the insemination method. Finally, the cohort was subdivided according to the developmental stage of embryos transferred.

**Results**

A total of 10,151 women who met the inclusion criteria and delivered a live-born singleton were included for final analysis. The most common maternal infertility diagnosis of the entire cohort was tubal disorder (42.5%), followed by DOR (9.5%), endometriosis (9.4%), PCOS (5.7%), and uterine factor infertility (1.6%). Male factor infertility was present in 19.8% of cycles, and infertility was diagnosed as unexplained in 11.4% of cycles.

**Demographics**

Parental demographics and main cycle characteristics stratified by the infertility cause are depicted in Table 1. As expected, women and men in the DOR group were older (35.27±4.56 years for mothers and 36.85±5.63 years for fathers) compared with their counterparts in other groups. In addition, the youngest parents were in the PCOS (30.49±3.29 years for mothers and 32.19±3.92 years for fathers) group, and women with PCOS were more likely to have a greater BMI (24.04±4.19 kg/m²) than groups with other infertility diagnoses. Most of our study population (90.6%) was nulliparous. IVF was the common insemination method in the cohorts apart from male factor causes that predominantly had ICSI. Notably, 2 day-3 embryos were transferred in most of the patients, except that a single embryo transfer was performed in a higher proportion of women with uterine factor infertility (58.4%). Pregnancy-related complications such as gestational diabetes mellitus and hypertensive disorders of pregnancy occurred more frequently in women with PCOS.

**Perinatal outcomes**

The perinatal outcomes are summarized in Table 2. Apart from the singletons born to women with uterine-related infertility (mean birthweight of 3006.77±542.14 g), mean birthweight in the other 6 groups averaged >3300 g. Specifically, singletons from the unexplained infertility group had the highest birthweight (3409.07±457.73 g), whereas those from the PCOS group had the lowest birthweight (3315.91±563.33 g). The GA across groups exceeded 37 weeks. However, babies resulting from the uterine infertility group had a 0.6–1.1 weeks shorter GA than those resulting from other groups. The proportion of PTB across cohorts was the highest among singletons from uterine factor infertility at 14.3%, followed by 8.9% of singletons derived from women with PCOS. The incidence
| Characteristic                        | Tubal factor (n=4313) | Polycystic ovary syndrome (n=583) | Endometriosis (n=963) | Diminished ovarian reserve (n=964) | Uterine factor (n=161) | Male factor (n=2005) | Unexplained (n=1162) | P value |
|--------------------------------------|----------------------|-----------------------------------|-----------------------|-----------------------------------|------------------------|-----------------------|-----------------------|---------|
| Maternal age (y)                    | 31.88±4.06           | 30.49±3.29                        | 32.07±3.84           | 35.27±4.56                       | 31.63±3.88             | 31.71±4.32           | 32.38±3.58           | <.001   |
| Maternal BMI (kg/m²)                | 21.64±2.93           | 24.04±4.19                        | 21.10±2.86           | 21.76±2.77                       | 21.89±3.09             | 21.63±2.97           | 21.44±2.99           | <.001   |
| Maternal education level, university| 1690 (39.2)          | 279 (47.9)                        | 553 (57.4)           | 525 (54.5)                       | 80 (49.7)              | 1009 (50.3)          | 652 (56.1)           | <.001   |
| Paternal age (y)                    | 33.55±5.04           | 32.19±3.92                        | 33.59±4.94           | 36.85±5.63                       | 33.20±5.24             | 34.03±5.78           | 34.08±4.70           | <.001   |
| Paternal BMI (kg/m²)                | 24.22±3.45           | 24.55±3.44                        | 24.16±3.36           | 24.36±3.32                       | 24.16±3.04             | 24.14±3.44           | 24.32±3.29           | .164    |
| Paternal education level, university| 1804 (41.8)          | 274 (47.0)                        | 545 (56.6)           | 561 (58.2)                       | 89 (55.3)              | 1026 (51.2)          | 653 (56.2)           | <.001   |
| Infertility duration (y)            | 2.81±2.67            | 3.50±2.71                         | 3.03±2.43            | 3.37±3.19                        | 2.66±2.07              | 3.36±2.79            | 3.30±2.60            | <.001   |
| Parity                              |                      |                                   |                      |                                   |                       |                      |                       | <.001   |
| First                               | 3815 (88.5)          | 558 (95.7)                        | 910 (94.5)           | 829 (86.0)                       | 150 (93.2)             | 1860 (92.8)          | 1071 (92.2)          |         |
| High order                          | 498 (11.5)           | 25 (4.3)                          | 53 (5.5)             | 135 (14.0)                       | 11 (6.8)               | 145 (7.2)            | 91 (7.8)             |         |
| Frozen-thawed embryo transfer cycle rank |                   |                                   |                      |                                   |                       |                      |                       | .004    |
| First                               | 2544 (59.0)          | 378 (64.8)                        | 592 (61.5)           | 579 (60.1)                       | 78 (48.4)              | 1228 (61.2)          | 709 (61.0)           |         |
| High order                          | 1769 (41.0)          | 205 (35.2)                        | 371 (38.5)           | 385 (39.9)                       | 83 (51.6)              | 777 (38.8)           | 453 (39.0)           |         |
| Insemination method                 |                      |                                   |                      |                                   |                       |                      |                       | <.001   |
| IVF                                 | 3681 (85.3)          | 307 (52.7)                        | 752 (78.1)           | 724 (75.1)                       | 118 (73.3)             | 193 (9.6)            | 584 (50.3)           |         |
| ICSI                                | 408 (9.5)            | 59 (10.1)                         | 133 (13.8)           | 193 (20.0)                       | 23 (14.3)              | 1602 (79.9)          | 165 (14.2)           |         |
| IVF+ICSI                            | 224 (5.2)            | 217 (37.2)                        | 78 (8.1)             | 47 (4.9)                         | 20 (12.4)              | 210 (10.5)           | 413 (35.5)           |         |
| Number of embryos transferred       |                      |                                   |                      |                                   |                       |                      |                       | <.001   |
| 1                                   | 941 (21.8)           | 146 (25.0)                        | 226 (23.5)           | 326 (33.8)                       | 94 (58.4)              | 457 (22.8)           | 262 (22.5)           |         |
| 2                                   | 3372 (78.2)          | 437 (75.0)                        | 737 (76.5)           | 638 (66.2)                       | 67 (41.6)              | 1548 (77.2)          | 901 (77.5)           |         |
| Developmental stage                 |                      |                                   |                      |                                   |                       |                      |                       | <.001   |
| Day 3                               | 3478 (80.6)          | 488 (83.7)                        | 803 (83.4)           | 820 (85.1)                       | 118 (73.3)             | 1674 (83.5)          | 931 (80.1)           |         |
| Day 5 or 6                          | 835 (19.4)           | 95 (16.3)                         | 160 (16.6)           | 144 (14.9)                       | 43 (26.7)              | 331 (16.5)           | 231 (19.9)           |         |

(continued)
of LBW ranged between 2.7% and 9.9%, with the DOR and unexplained infertility groups having the lowest rates (2.7% and 2.8%, respectively), whereas the PCOS and uterine factor groups had the highest rates (5.5% and 9.9%, respectively). In contrast, fewer babies in the uterine factor group were born as LGA and with macrosomia than their peers from other groups.

In the crude analyses (Table 3), the prevalence of PTB was 3 times higher (odds ratio [OR], 3.36; 95% confidence interval [CI], 2.00–5.63), and that of LBW was 3.9 times higher (OR, 3.90; 95% CI, 2.09–7.28) in singletons from the uterine factor infertility group than in those from the unexplained infertility group. These differences remained statistically significant in multivariable analyses (adjusted OR [aOR], 2.66; 95% CI, 1.53–4.63 for PTB; aOR, 3.51; 95% CI, 1.79–6.90 for LBW). In addition, infants in the uterine factor group were at a lower risk of being LGA and being with macrosomia, and no significant difference was observed with regard to the incidence of SGA between the uterine factor and the reference groups.

The odds of PTB (OR, 1.97; 95% CI, 1.33–2.92) and LBW (OR, 2.05; 95% CI, 1.24–3.38) were elevated among neonates born to women with PCOS in the unadjusted analysis. Of note was that this association disappeared after adjustment for parental demographics, treatment characteristics, and pregnancy complications (aOR, 1.50; 95% CI, 0.98–2.28 for PTB; aOR, 1.70; 95% CI, 0.99–2.91 for LBW). The other perinatal parameters such as macrosomia, LGA, and SGA were similar between the PCOS and reference groups. Most importantly, there was no increased risk of adverse birth outcomes in singletons born to women diagnosed with tubal disorder, endometriosis, DOR, or male factor infertility vs those resulting from the reference group.

Of note, all the sensitivity analyses yielded similar results to those of the main findings (Supplementary Tables 1–14), except for when analyses were restricted to women who received the ICSI procedure and those who

| TABLE 1 | Overall demographics and baseline in vitro fertilization characteristics by infertility causes (continued) |
|-----------|----------------------------------------------------------------------------------|
| Characteristic | Tubal factor | Polycystic ovary syndrome | Endometriosis | Diminished ovarian reserve | Male factor | Uterine factor |
| | (n=4313) | (n=583) | (n=963) | (n=964) | (n=2005) | (n=161) |
| Year of treatment | | | | | | |
| 2014–2015 | 1491 (34.6) | 121 (20.8) | 121 (20.8) | 121 (20.8) | 121 (20.8) | 121 (20.8) |
| 2016–2017 | 1699 (39.4) | 250 (42.9) | 250 (42.9) | 250 (42.9) | 250 (42.9) | 250 (42.9) |
| 2018–2019 | 1123 (26.0) | 212 (36.4) | 212 (36.4) | 212 (36.4) | 212 (36.4) | 212 (36.4) |
| Gestational diabetes mellitus | 389 (8.0) | 81 (13.9) | 81 (13.9) | 81 (13.9) | 81 (13.9) | 81 (13.9) |
| Hypertensive disorders of pregnancy | 120 (2.8) | 24 (2.5) | 24 (2.5) | 24 (2.5) | 24 (2.5) | 24 (2.5) |
| Data are mean±standard deviation or number (percentage). All P values were assessed with the use of the Pearson chi-square test or one-way analysis of variance (ANOVA). BMI, body mass index; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization.
TABLE 2
Perinatal outcomes in singleton live births based on infertility causes

| Outcome                     | Tubal factor (n=4313) | Polycystic ovary syndrome (n=583) | Endometriosis (n=963) | Diminished ovarian reserve (n=964) | Uterine factor (n=161) | Male factor (n=2005) | Unexplained (n=1162) | P value |
|-----------------------------|-----------------------|-----------------------------------|-----------------------|-----------------------------------|-----------------------|----------------------|----------------------|---------|
| Gestational age (wk)        | 38.63±1.52            | 38.25±1.89                        | 38.66±1.52            | 38.60±1.49                        | 37.63±2.25            | 38.64±1.54          | 38.76±1.37          | <.001   |
| Newborn gender              |                       |                                   |                       |                                   |                       |                      |                      | .102    |
| Female                      | 2019 (46.8)           | 275 (47.2)                        | 461 (47.9)            | 478 (49.6)                        | 84 (52.2)             | 982 (49.0)          | 514 (44.2)          |         |
| Male                        | 2294 (53.2)           | 308 (52.8)                        | 502 (52.1)            | 486 (50.4)                        | 77 (47.8)             | 1023 (51.0)         | 648 (55.8)          |         |
| Preterm birth (<37 wk)      | 251 (5.8)             | 52 (8.9)                          | 54 (5.6)              | 42 (4.4)                          | 23 (14.3)             | 97 (4.8)            | 55 (4.7)            | <.001   |
| Birthweight                 | 3381.33±496.30        | 3315.93±565.33                    | 3359.89±470.68        | 3378.20±458.50                    | 3006.77±542.14        | 3367.45±490.88      | 3409.07±457.73      | <.001   |
| Low birthweight (<2500g)    | 149 (3.5)             | 32(5.5)                           | 34(3.5)               | 26(2.7)                           | 16(9.9)               | 66(3.3)             | 32(2.8)             | <.001   |
| Macrosomia (≥4000g)         | 431 (10.0)            | 57 (9.8)                          | 75 (7.8)              | 81 (8.4)                          | 1 (0.6)               | 183 (9.1)           | 96 (8.3)            | .001    |
| Small for gestational age (<10th percentile) | 192 (4.5)       | 23 (3.9)                          | 42 (4.4)              | 44 (4.6)                          | 11 (6.8)              | 90 (4.5)            | 45 (3.9)            | .751    |
| Large for gestational age (>90th percentile) | 1046 (24.3) | 147 (25.2)                        | 210 (21.8)            | 221 (22.9)                        | 17 (10.6)             | 444 (22.1)          | 258 (22.2)          | .002    |

Data are means±standard deviation or number (percentage). All P values were assessed with the use of Pearson chi-square test or one-way analysis of variance (ANOVA).

Results in the context of what is known

A whole analysis restricted to IVF babies evaluating the perinatal outcomes stratified by the diagnosis of infertility was scarce. Wang and colleagues reported that the probability of PTB and LBW in both IVF singleton and twin pregnancies was significantly increased for female factor infertility compared with male factor infertility. Nonetheless, caution should be taken as the authors grouped all types of female infertility into 1 category in the multivariate analyses. An analysis of national data from the United Kingdom showed that when compared with unexplained infertility, a modest but considerably increased likelihood of PTB (aOR, 1.22; 95% CI, 1.06–1.41) with tubal factor infertility 1.68 (95% CI, 1.04–2.72) and male factor infertility 1.54 (95% CI, 1.08–2.19) was observed. However, these results should be treated with caution due to potential biases, such as the higher likelihood of receiving ICSI and single embryo transfer in patients with unexplained infertility.

Principle findings

Over the past 4 decades, there has been an ongoing debate regarding whether the poor birth outcomes following IVF are attributed to the reproductive technology per se, to factors related to inherent infertility, or both. This study, isolating one of the many contributing factors, namely causes of infertility, independently explored its potential relationship with perinatal outcomes within an IVF population. Our findings demonstrated that except for the uterine factor infertility, the other causes of infertility, including tubal disorder, PCOS, endometriosis, DOR, and male factor cause, did not seem to have a negative impact on perinatal outcomes following IVF when a freeze-only policy was applied. This observation was largely owing to the limited number of cases in these 2 subcategories, with merely 23 and 94 women with uterine factor infertility receiving ICSI and single embryo transfer, respectively.

Comment

The likelihood of PTB among women with uterine factor infertility undergoing single embryo transfer, in which though the odds of PTB and LBW were higher among women with uterine factor infertility vs those with unexplained infertility, the difference was not statistically significant. This observation was largely owing to the limited number of cases in these 2 subcategories, with merely 23 and 94 women with uterine factor infertility receiving ICSI and single embryo transfer, respectively.
### TABLE 3

Unadjusted and adjusted odds ratios of preterm birth, low birthweight, macrosomia, small for gestational age, large for gestational age

| Characteristic  | Tubal factor | Polycystic ovary syndrome | Endometriosis | Diminished ovarian reserve | Uterine factor | Male factor | Unexplained |
|----------------|--------------|----------------------------|---------------|---------------------------|---------------|-------------|-------------|
| **PTB (<37 wk)** |              |                            |               |                           |               |             |             |
| OR (95% CI)     | 1.24 (0.92−1.68) | 1.97 (1.33−2.92)        | 1.20 (0.81−1.76) | 0.92 (0.61−1.38) | 3.36 (2.00−5.63) | 1.02 (0.73−1.44) | Reference |
| aOR (95% CI)    | 1.01 (0.73−1.38) | 1.50 (0.98−2.28)        | 1.07 (0.72−1.60) | 0.76 (0.49−1.17) | 2.66 (1.53−4.63) | 1.01 (0.68−1.49) | Reference |
| **LBW (<2500 g)** |              |                            |               |                           |               |             |             |
| OR (95% CI)     | 1.26 (0.86−1.86) | 2.05 (1.24−3.38)        | 1.29 (0.79−2.11) | 0.98 (0.58−1.65) | 3.90 (2.09−7.28) | 1.20 (0.78−1.85) | Reference |
| aOR (95% CI)    | 1.11 (0.73−1.68) | 1.70 (0.99−2.91)        | 1.18 (0.70−1.97) | 0.79 (0.45−1.38) | 3.51 (1.79−6.90) | 1.18 (0.72−1.93) | Reference |
| **Macrosomia (≥4000 g)** |              |                            |               |                           |               |             |             |
| OR (95% CI)     | 1.23 (0.98−1.55) | 1.20 (0.85−1.70)        | 0.94 (0.68−1.29) | 1.02 (0.75−1.39) | 0.07 (0.01−0.50) | 1.12 (0.86−1.44) | Reference |
| aOR (95% CI)    | 1.18 (0.92−1.52) | 0.88 (0.62−1.26)        | 1.01 (0.73−1.39) | 1.12 (0.81−1.55) | 0.07 (0.01−0.51) | 1.02 (0.76−1.37) | Reference |
| **SGA (<10th percentile)** |              |                            |               |                           |               |             |             |
| OR (95% CI)     | 1.16 (0.83−1.61) | 1.02 (0.61−1.70)        | 1.13 (0.74−1.74) | 1.19 (0.78−1.82) | 1.82 (0.92−3.60) | 1.17 (0.81−1.68) | Reference |
| aOR (95% CI)    | 1.22 (0.86−1.74) | 1.14 (0.68−1.93)        | 1.12 (0.72−1.74) | 1.23 (0.79−1.91) | 1.85 (0.92−3.72) | 1.06 (0.70−1.60) | Reference |
| **LGA (>90th percentile)** |              |                            |               |                           |               |             |             |
| OR (95% CI)     | 1.12 (0.96−1.31) | 1.18 (0.94−1.49)        | 0.98 (0.80−1.20) | 1.04 (0.85−1.28) | 0.41 (0.25−0.70) | 0.99 (0.84−1.19) | Reference |
| aOR (95% CI)    | 1.07 (0.91−1.27) | 0.93 (0.73−1.18)        | 1.03 (0.83−1.28) | 1.05 (0.84−1.30) | 0.40 (0.24−0.68) | 1.02 (0.84−1.25) | Reference |

Analyses were adjusted for maternal age, maternal BMI, maternal education level, paternal age, paternal BMI, paternal education level, infertility duration, parity, frozen-thawed embryo transfer cycle rank, insemination method, number of embryos transferred, embryo developmental stage, year of treatment, gestational diabetes, hypertensive disorders of pregnancy.

BMI, body mass index; CI, confidence interval; LBW, low birthweight; LGA, large for gestational age; OR, odds ratio; PTB, preterm birth; SGA, small for gestational age.
do so, as the registry dataset was unable to discern the particular type of ovulation dysfunction. Further, as pointed out by authors as a weakness, Sunkara et al.xx were unable to control for key confounders such as BMI, previous medical history, and pregnancy complications, which might have affected their results. In line with our findings, data from a single fertility center reported an increased risk of PTB with PCOS relative to control subjects in the crude analysis. Nevertheless, this difference was not longer significant once additionally adjusting for the pregnancy complications in a separate multivariable analysis.37

Regarding tubal factor infertility, attention has been shifted to its potential role in the later development of future birth outcomes. The prevalence of PTB and LBW following IVF was reported to be significantly higher in neonates born to women with tubal disorder compared with either male factor38 or unexplained infertility.39 It has been suggested, though speculatively, that a chronic inflammatory state may predispose women with tubal disorder to the onset of specific fetal complications.40,41 The same mechanism may also apply to women with endometriosis,42 who showed an increased risk of poor obstetrical and neonatal outcomes such as PTB and cesarean delivery, compared with controls without this disease.43 Nonetheless, such differences were not seen in our work. It may be informative to investigate whether the freeze-thaw process may have a protective effect against PTB and LBW.44

Not surprisingly, our results identified that the presence of uterine factor infertility was associated with a range of adverse perinatal outcomes. In the present study, uterine factor infertility referred to any congenital uterine abnormality, and its negative impact on pregnancy and child outcomes has been well documented in a number of studies.45,46 Yet, careful interpretation of our findings is needed, owing to the small number of cases in this subgroup. In addition, this study only included women with congenital uterine malformation. Hence, our results may not be applicable to other causes of uterine factor infertility. Future research on a wider range of patients with uterine factor infertility involving large cohorts is warranted. It is worth mentioning that the diagnosis of DOR was also included in our study, though not all published studies on this topic have consistently done so. Concurring with previous studies,22,47,48 our data suggested that once pregnancy was achieved, no detrimental effect on gestation duration and fetal weight was found among women with DOR in IVF pregnancies.

To investigate the impact of infertility cause on perinatal outcomes in an IVF setting, the selection of the control group is always a challenge. Some researchers chose male factor infertility as a control19,49, whereas others selected unexplained infertility as a reference group18,34, and a quite recent study adopted women with previous tubal ligation as their control group.50 The decision regarding the choice of unexplained infertility as a control group in the present study was not just based on previous literature but also on the studies showing that the overall perinatal outcomes among couples with unexplained infertility treated by IVF were good and with similar outcomes compared with spontaneous pregnancies.51

Strengths and limitations
The primary weakness of this study is its retrospective design, and potential bias cannot be neglected. Another limitation of this study was the lack of a non-IVF control group. Nonetheless, by restricting the analysis to women undergoing IVF, we were able to isolate the relationship between infertility diagnosis and perinatal outcomes, which is a crucial strength of our research. In addition, most current patients receive day 3 embryo transfers, as transfer of cleavage-stage embryos is still a dominant strategy in most clinics in China.52 However, recently, the practice has moved toward a single blastocyst transfer policy, particularly in women aged <38 years. It is also important to mention that the main cause of infertility varied considerably between countries. In China, the most common indication for IVF is tubal factor infertility.53 Thus, the distribution of diagnosis for infertility in the present study was skewed with a higher percentage of tubal disease and with relatively lower percentages of other common diagnoses, particularly uterine factors, which may raise concerns regarding the potential generalizability to other patient populations. However, in light of the increasing use of FET globally, our findings are still of clinical relevance, as this is the largest study in the literature to date looking at the perinatal outcomes in relation to infertility causes based on a freeze-all policy. We also need to point out that the BMI of the included women with PCOS was relatively lower than the counterparts of other ethnic groups. Thus, caution should be made when extrapolating our results to obese PCOS patients, in whom certain complication rates may be increased even further.

The major strength of the present study is the large sample size, the inclusion of only FET cycles, and the contemporary time period. Moreover, this was a single-center study where differences in IVF protocols and laboratory conditions were eliminated as opposed to those studies relying on a national register-based database. Finally, we also accounted for several outcome-related confounding variables, which might have biased the findings.

Conclusions and clinical implications
In summary, the present large single-center study provided valuable information that the cause of infertility, with the exception of uterine factor infertility, does not seem to have a negative impact on perinatal outcomes compared with unexplained infertility in freeze-all cycles. FET is becoming a widely adopted technology in modern IVF, and our findings are clinically useful not only to guide patient counseling before treatment but also to guide appropriate antenatal care and surveillance.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2022.100098.
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