Complications and adverse outcomes in pregnancy and childbirth among women who conceived by assisted reproductive technologies: a nationwide birth cohort study of Japan environment and children’s study

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Abstract

Background: Although pregnancies conceived by assisted reproductive technology (ART) have a higher risk of maternal/perinatal complications, the overall risk of adverse outcomes necessitating advanced obstetric care has not been closely examined. The present study aimed to assess and compare the risk of maternal/perinatal complications and adverse outcomes in pregnancy and childbirth conceived by ART with those conceived naturally.

Methods: This study was conducted as a part of the Japan environment and children’s study (JECS), an ongoing nationwide birth cohort study in Japan. The risk of maternal/perinatal complications and adverse outcomes was assessed by mode of conception (natural conception, ovulation induction [OI] without ART, conventional in vitro fertilization and embryo transfer [IVF-ET], or intracytoplasmic sperm injection [ICSI]) using logistic regression and generalized estimating equations controlling for potential confounders.

Results: The final dataset included women who conceived naturally (N = 90,506), by OI without ART (N = 3939), by conventional IVF-ET (N = 1476), and by ICSI (N = 1671). Compared with women who conceived naturally, those who conceived by conventional IVF-ET were at higher risk of placenta previa (adjusted OR 2.90 [95% CI 1.94, 4.34]), morbidly adherent placenta (6.85 [3.88, 12.13]), and pregnancy-induced hypertension (1.40 [1.10, 1.78]) whereas those who conceived by ICSI had a higher risk of placental abruption (2.16 [1.20, 3.88]) as well as placenta previa (2.01 [1.29, 3.13]) and morbidly adherent placenta (7.81 [4.56, 13.38]). Women who conceived by ART had a higher risk of blood transfusion (conventional IVF-ET: 3.85 [2.52, 5.88]; ICSI: 3.76 [2.49, 5.66]) and ICU admission (conventional IVF-ET: 2.58 [1.11, 6.01]; ICSI: 3.45 [1.68, 7.06]) even after controlling for potential confounders. Neonates conceived by ART had a higher risk of preterm birth (conventional IVF-ET: 1.42 [1.13, 1.78]; ICSI: 1.31 [1.05, 1.64]).

(Continued on next page)
Conclusions: Women who conceived by ART had a higher risk of maternal/perinatal complications necessitating advanced obstetric care. Obstetricians should be aware of the increased risk of adverse outcomes among this population.

Keywords: Assisted reproductive technology, ART, In vitro fertilization, IVF, Intracytoplasmic sperm injections, ICSI, Ovulation induction, Placental diseases, Blood transfusion, Intensive care unit

Background
In recent years, a substantial number of children have been conceived using assisted reproductive technology (ART) particularly in high-income countries [1]. Currently the proportion of children conceived by ART in Japan is roughly 5% [2] and is rising [2–5]. However, women who conceive by ART have a higher risk of maternal and perinatal complications, such as pregnancy-induced hypertension (PIH), placenta previa, placental abruption, morbidly adherent placenta (MAP), preterm birth, and low birth weight [6–10]. Numerous studies have investigated the reasons for this higher risk without reaching any definite conclusions. Potential causes include underlying maternal characteristics which necessitated the use of ART as well as the ART itself [10–16].

Although complications related to ART pregnancies have been well studied using large-scale registry and cohort data worldwide, many of these studies have focused on outcomes in fetuses and neonates born after ART [7–9]. Less attention has been paid to adverse maternal outcomes, and only a few studies have assessed the overall risk of life-threatening conditions, such as blood transfusion, peripartum hysterectomy, intensive care unit (ICU) admission, and maternal death in this population [15–20]. In Japan, there is an online registration system which covers more than 90% of ART cycles conducted nationwide and their outcomes. Although this system collects detailed information on ART, data pertaining to maternal/perinatal complications and adverse outcomes are limited [2].

To redress this omission, we conducted the present study as an adjunct to the Japan environment and children’s study (JECS), a nationwide cohort study of environmental impacts on child health. The aim of the present study was to assess and compare the risk of maternal/perinatal complications and adverse outcomes between women who conceived by ART and women who conceived naturally.

Methods
This study was conducted as an adjunct to the JECS, an ongoing nationwide birth cohort study in Japan aiming to determine the impact of environmental factors on child health (data set: jecs-ag-20,160,424). Details of the JECS protocol have been published elsewhere [21]. Briefly, JECS is being conducted in 15 regions covering a variety of regions throughout Japan. Expecting mothers were recruited either at cooperating obstetric facilities or local government offices between January 2011 and March 2014. JECS covers a total of 103,099 pregnancies and includes follow up studies of the children resulting from those pregnancies until they have reached the age of 13.

During pregnancy and at one month postpartum, various data were collected from the participants using a self-administered questionnaire. The collected information included maternal and paternal characteristics, anthropometric measurements, medical history, socio-economic status (e.g., income, occupation, and education), life-style (food consumption, exercise, and sleep), mental health, exposure to chemicals, etc. Furthermore, medical information pertaining to the pregnancy course, delivery, and postpartum condition was collected by extraction of data from the participants’ medical records either by clinicians or trained research coordinators.

JECS was approved by the institutional review board of the Ministry of the Environment and the ethics committees of all the participating institutions and is being conducted in accordance with the Declaration of Helsinki and other relevant regulations in Japan. Written informed consent was obtained from all the participants. As the present study used anonymized data, individual approval from the ethics committee was deemed unnecessary.

Target population, variables of interest, and outcomes
The target population of the present study consisted of all women who participated in JECS and conceived by one of the following methods: 1) naturally; 2) using ovulation induction (OI) without ART; 3) conventional in vitro fertilization and embryo transfer (IVF-ET); or 4) intracytoplasmic sperm injection (ICSI). For the outcomes pertaining to fetuses/neonates, we analyzed only those delivered at 22 weeks or more of gestation. The variables of interest were conventional IVF-ET and ICSI. Women who conceived naturally served as the reference group. We also included women who conceived using OI without ART in order to estimate their risk level in case this might differ from that of natural pregnancies,
given the former group’s history of infertility and the effect of OI [16, 17, 22].

Maternal complications and adverse outcomes included placenta previa, placental abruption, MAP, PIH, gestational diabetes, cesarean section, maternal blood transfusion, maternal admission to the ICU, and maternal death. Stillbirth (≥ 22 weeks of gestation), pre-term birth (< 37 weeks of gestation), and low birth weight (< 2500 g) were considered to be adverse fetal/neonatal outcomes. All of the maternal/perinatal complications and adverse outcomes were diagnosed following the protocol at each participating institution, which was presumably based on the relevant Japanese guidelines. Pregnancy-induced hypertension was defined as “hypertension (systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90 mmHg) observed from the 20th week of gestation to 12 weeks postpartum with or without proteinuria (≥300 mg/day), not just as a continuing pre-existing condition” [23]. Gestational diabetes was defined as a “glucose metabolism disorder occurring or recognized during pregnancy, excluding overt diabetes” [24]. An oral glucose tolerance test with 75 g sugar was used for diagnosis, and the diagnostic criteria were blood glucose values of: 1) ≥92 mg/dL in a fasted state; 2) ≥180 mg/dL after one hour; or 3) ≥153 mg/dL after two hours.

Statistical analysis
First, we described the background characteristics of the participants who were included in the analysis, their pregnancy course, maternal and perinatal complications, and adverse outcomes by group (i.e., natural conception, OI without ART, conventional IVF-ET or ICSI). Next, the effect of each mode of conception on maternal/perinatal complications and adverse outcomes was assessed using logistic regression for maternal outcomes and generalized estimating equations (GEE) for fetal/neonatal outcomes, with women who conceived naturally serving as the reference group. The crude odds ratio (OR) and adjusted odds ratio (aOR) were calculated; adjusted covariates included maternal age, maternal body mass index (BMI) before pregnancy, maternal height, maternal weight before delivery, parity, prior cesarean section, pre-existing condition (e.g., chronic hypertension, hyperthyroidism, hypothyroidism, diabetes mellitus, autoimmune disease, heart disease, kidney disease, hepatitis, cerebral infarction, intracranial hemorrhage, epilepsy, blood disease, malignancy, psychiatric disorder, neurologic disease, thrombosis, and others), multiple pregnancies, fetal presentation, folic acid supplementation, maternal smoking during pregnancy, maternal drinking during pregnancy, maternal educational level, paternal smoking, paternal educational level, and household income. The variables included in the multivariate models as potential confounders were selected based on previous studies, biological plausibility, and their availability in the JECS data set [25–31]. We reported all crude ORs and aORs with the corresponding 95% confidence interval (CI). In order to improve the robustness of the analysis, we also conducted multiple imputation and compared the results with those from the model with case-wise deletion of missing data. The statistical analysis was conducted using the SAS software program (version 9.4; SAS Institute Inc., Cary, NC, USA).

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Fig. 1 Flow chart of participants in the analysis
| Table 1   | Background characteristics of participants by mode of conception |
|----------|---------------------------------------------------------------|
|          | Natural conception | OI without ART | Conventional IVF-ET | ICSI |
|          | N= 90,506          | N= 3939        | N= 1476              | N= 1671 |
|          | Median | IQR    | Median | IQR    | Median | IQR    | Median | IQR    |
| Maternal age (years) | 31 | 8 | 33 | 6 | 36 | 6 | 36 | 6 |
| Maternal height (cm) | 158.0 | 8.0 | 158.0 | 7.5 | 158.7 | 8.0 | 1585 | 7.0 |
| Maternal BMI before pregnancy (kg/m²) | 20.6 | 3.5 | 20.6 | 3.7 | 20.7 | 3.4 | 20.7 | 3.3 |
| Maternal weight before delivery (kg) | 62.3 | 10.6 | 62.1 | 11.1 | 62.4 | 10.6 | 61.8 | 10.5 |
| Parity | 0 | 33,760 | 38.2 | 2290 | 59.9 | 949 | 66.0 | 1089 | 68.1 |
|         | 1 | 34,934 | 39.5 | 1331 | 34.8 | 447 | 31.1 | 469 | 29.3 |
|         | 2 or more | 19,712 | 22.3 | 201 | 5.3 | 42 | 2.9 | 42 | 2.6 |
| Prior cesarean section | No | 82,242 | 90.9 | 3680 | 93.5 | 1346 | 91.2 | 1530 | 91.6 |
|         | Yes | 8200 | 9.1 | 257 | 6.5 | 130 | 8.8 | 141 | 8.4 |
| Marital status | Married | 85,789 | 95.2 | 3919 | 99.6 | 1474 | 100.0 | 1668 | 99.8 |
|          | Single | 4304 | 4.8 | 16 | 0.4 | 0 | 0.0 | 3 | 0.2 |
| Pre-existing maternal condition | No | 74,963 | 85.4 | 3080 | 81.3 | 1087 | 75.3 | 1242 | 77.6 |
|          | Yes | 12,858 | 14.6 | 710 | 18.7 | 357 | 24.7 | 359 | 22.4 |
| Folic acid supplementation | No | 47,803 | 53.0 | 1310 | 33.3 | 470 | 31.9 | 476 | 28.5 |
|          | A few times per month | 4610 | 5.1 | 184 | 4.7 | 38 | 2.6 | 52 | 3.1 |
|          | A few times per week | 14,127 | 15.7 | 735 | 18.7 | 251 | 17.0 | 293 | 17.6 |
|          | Daily | 23,721 | 26.3 | 1706 | 43.4 | 716 | 48.5 | 847 | 50.8 |
| Maternal smoking during pregnancy | No | 85,152 | 94.8 | 3867 | 98.7 | 1453 | 99.0 | 1649 | 99.1 |
|          | Yes | 4659 | 5.2 | 51 | 1.3 | 15 | 1.0 | 15 | 0.9 |
| Maternal drinking during pregnancy | No | 81,033 | 90.0 | 3579 | 91.1 | 1362 | 92.5 | 1525 | 91.4 |
|          | Yes | 9033 | 10.0 | 350 | 8.9 | 111 | 7.5 | 143 | 8.6 |
| Maternal educational level | Junior high/high school | 33,026 | 37.5 | 904 | 23.5 | 335 | 23.3 | 358 | 22.0 |
|          | Vocational school/junior college | 36,499 | 41.5 | 1866 | 48.6 | 673 | 46.8 | 777 | 47.7 |
|          | University/graduate school | 18,469 | 21.0 | 1069 | 27.8 | 430 | 29.9 | 494 | 30.3 |

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Table 1 Background characteristics of participants by mode of conception (Continued)

| Characteristic                        | Natural conception | OI without ART | Conventional IVF-ET | ICSI |
|---------------------------------------|--------------------|----------------|---------------------|------|
|                                       | N = 90,506         | N = 3939       | N = 1476            | N = 1671 |
| Paternal smoking                      |                    |                |                     |      |
| No                                    | 45,916             | 2464           | 977                 | 1145  |
|                                       | 51.8               | 63.3           | 66.9                | 69.5  |
| Yes                                   | 42,688             | 1428           | 484                 | 503   |
|                                       | 48.2               | 36.7           | 33.1                | 30.5  |
| (Missing)                             | 3105               | 105            | 39                  | 45    |
| Paternal educational level            |                    |                |                     |      |
| Junior high/high school               | 39,601             | 1229           | 475                 | 503   |
|                                       | 45.3               | 32.1           | 33.1                | 30.9  |
| Vocational school/junior college      | 19,687             | 902            | 272                 | 351   |
|                                       | 22.5               | 23.5           | 18.9                | 21.6  |
| University/graduate school            | 28,113             | 1703           | 690                 | 772   |
|                                       | 32.2               | 44.4           | 48.0                | 47.5  |
| (Missing)                             | 8435               | 283            | 93                  | 116   |
| Household income (×10,000 Japanese yen) |                  |                |                     |      |
| < 200                                 | 4956               | 73             | 17                  | 20    |
|                                       | 6.0                | 2.0            | 1.2                 | 1.3   |
| ≥ 200, < 400                         | 29,346             | 949            | 279                 | 258   |
|                                       | 35.8               | 26.0           | 20.2                | 16.6  |
| ≥ 400, < 600                         | 26,979             | 1319           | 480                 | 521   |
|                                       | 32.9               | 36.1           | 34.7                | 33.5  |
| ≥ 600, < 800                         | 12,554             | 747            | 318                 | 391   |
|                                       | 15.3               | 20.4           | 23.0                | 25.1  |
| ≥ 800, < 1000                        | 5012               | 328            | 161                 | 204   |
|                                       | 6.1                | 9.0            | 11.6                | 13.1  |
| ≥ 1000                               | 3224               | 240            | 128                 | 161   |
|                                       | 3.9                | 6.6            | 9.3                 | 10.4  |
| (Missing)                             | 8435               | 283            | 93                  | 116   |

ART, assisted reproductive technologies; BMI, body mass index; ICSI, intracytoplasmic sperm injection; IQR, interquartile range; IVF-ET, in vitro fertilization and embryo transfer; OI, ovulation induction.

Proportions were calculated excluding cases with missing data.

Table 2 Pregnancy and fetal/neonatal characteristics by mode of conception

| Characteristic                        | Natural conception | OI without ART | Conventional IVF-ET | ICSI |
|---------------------------------------|--------------------|----------------|---------------------|------|
|                                       | N = 90,506         | N = 3939       | N = 1476            | N = 1671 |
| Pregnancies                           |                    |                |                     |      |
| Singleton pregnancy                   | 88,873             | 3702           | 1407                | 1586  |
|                                       | 99.3               | 95.1           | 95.7                | 96.0  |
| Multiple pregnancies                  | 625                | 189            | 63                  | 66    |
|                                       | 0.7                | 4.9            | 4.3                 | 4.0   |
| (Missing)                             | 1008               | 48             | 6                   | 19    |
| Fetus/Neonate born ≥22 weeks          | N = 89,576         | N = 4067       | N = 1518            | N = 1699 |
|                                       |                    |                |                     |      |
| Number of fetuses                     |                    |                |                     |      |
| Singletons                            | 88,337             | 3682           | 1393                | 1570  |
|                                       | 98.6               | 90.6           | 91.8                | 92.4  |
| Multiples                             | 1209               | 383            | 125                 | 129   |
|                                       | 1.4                | 9.4            | 8.2                 | 7.6   |
| (Missing)                             | 30                 | 2              | 0                   | 0     |
| Fetal presentation                    |                    |                |                     |      |
| Cephalic                              | 85,331             | 3726           | 1345                | 1516  |
|                                       | 96.4               | 93.2           | 90.7                | 90.8  |
| Non-cephalic                          | 3179               | 273            | 138                 | 153   |
|                                       | 3.6                | 6.8            | 9.3                 | 9.2   |
| (Missing)                             | 1066               | 68             | 35                  | 30    |
| Sex of neonate                        |                    |                |                     |      |
| Male                                  | 45,942             | 2062           | 805                 | 850   |
|                                       | 51.3               | 50.7           | 53.0                | 50.0  |
| Female                                | 43,608             | 2003           | 713                 | 849   |
|                                       | 48.7               | 49.3           | 47.0                | 50.0  |
| (Missing)                             | 26                 | 2              | 0                   | 0     |

ART, assisted reproductive technology; ICSI, intracytoplasmic sperm injection; ICU, intensive care unit; IVF-ET, in vitro fertilization and embryo transfer; OI, ovulation induction.

Proportions were calculated excluding cases with missing data.
Table 3 Maternal/perinatal complications and adverse outcomes by mode of conception in all pregnancies, pregnancies with singletons, and pregnancies with multiples

|                        | Natural conception | OI without ART | Conventional IVF-ET | ICSI |
|------------------------|--------------------|----------------|---------------------|------|
|                        | N                  | N%             | N                   | N%   |
| All women and a fetus/neonate born ≥22 weeks |                    |                |                     |      |
| Maternal outcomes      |                    |                |                     |      |
| Placenta previa        | 489                | 0.5            | 22                   | 0.6  |
| Placental abruption    | 382                | 0.4            | 19                   | 0.5  |
| MAP                    | 172                | 0.2            | 9                    | 0.2  |
| Gestational diabetes   | 2304               | 2.6            | 138                  | 3.5  |
| PIH                    | 2632               | 2.9            | 177                  | 4.5  |
| Cesarean section       | 16,433             | 18.5           | 933                  | 24.2 |
| Blood transfusion      | 377                | 0.4            | 20                   | 0.5  |
| ICU admission          | 105                | 0.1            | 8                    | 0.2  |
| Maternal death         | 10                 | 0              | 0                    | 0    |
| Fetal/neonatal outcomes|                    |                |                     |      |
| Stillbirth             | 230                | 0.3            | 17                   | 0.4  |
| Preterm birth < 37 w   | 4768               | 5.3            | 423                  | 10.4 |
| Low birth weight < 2500 g | 7980           | 8.9            | 651                  | 16.0 |
| Women with a singleton pregnancy and singleton born ≥22 weeks |                    |                |                     |      |
| Maternal outcomes      |                    |                |                     |      |
| Placenta previa        | 486                | 0.5            | 20                   | 0.5  |
| Placental abruption    | 380                | 0.4            | 18                   | 0.5  |
| MAP                    | 172                | 0.2            | 8                    | 0.2  |
| Gestational diabetes   | 2271               | 2.6            | 132                  | 3.6  |
| PIH                    | 2573               | 2.9            | 165                  | 4.5  |
| Cesarean section       | 15,912             | 18.0           | 780                  | 21.2 |
| Blood transfusion      | 368                | 0.4            | 16                   | 0.4  |
| ICU admission          | 97                 | 0.1            | 5                    | 0.1  |
| Maternal death         | 10                 | 0              | 0                    | 0    |
| Fetal/neonatal outcomes|                    |                |                     |      |
| Stillbirth             | 216                | 0.2            | 8                    | 0.2  |
| Preterm birth < 37 w   | 4153               | 4.7            | 211                  | 5.7  |
| Low birth weight < 2500 g | 7141           | 8.1            | 373                  | 10.1 |
| Women with multiple pregnancies and multiples born ≥22 weeks |                    |                |                     |      |
| Maternal outcomes      |                    |                |                     |      |
| Placenta previa        | 3                  | 0.5            | 1                    | 0.5  |
| Placental abruption    | 2                  | 0.3            | 1                    | 0.5  |
| MAP                    | 0                  | 0              | 1                    | 0.5  |
| Gestational diabetes   | 31                 | 5.1            | 6                    | 3.2  |
| PIH                    | 57                 | 9.4            | 12                   | 6.5  |
| Cesarean section       | 518                | 85.8           | 151                  | 81.2 |
| Blood transfusion      | 9                  | 1.5            | 3                    | 1.6  |
| ICU admission          | 8                  | 1.3            | 3                    | 1.6  |
| Maternal death         | 0                  | 0              | 0                    | 0    |
Table 3 Maternal/perinatal complications and adverse outcomes by mode of conception in all pregnancies, pregnancies with singletons, and pregnancies with multiples (Continued)

| Fetal/neonatal outcomes | Natural conception N = 1209 | OI without ART N = 383 | Conventional IVF-ET N = 125 | ICSI N = 129 |
|------------------------|-----------------------------|------------------------|-----------------------------|-------------|
| Stillbirth             | 13 1.1                      | 9 2.3                  | 2 1.6                      | 1 0.8       |
| Preterm birth < 2500 g | 613 50.7                    | 212 55.4               | 64 51.2                    | 62 48.1     |
| Low birth weight < 2500 g | 838 69.3                 | 278 72.8               | 84 67.2                    | 86 66.7     |

ART assisted reproductive technologies, ICSI intracytoplasmic sperm injection, ICU intensive care unit, IVF-ET in vitro fertilization and embryo transfer, MAP morbidly adherent placenta, OI ovulation induction, PIH pregnancy-induced hypertension
Proportions were calculated excluding cases with missing data

Results
The final set of participants included in the main analysis consisted of women who conceived naturally (N = 90,506), by OI without ART (N = 3939), by conventional IVF-ET (N = 1476), and by ICSI (N = 1671). These pregnancies resulted in 96,860 fetuses/neonates in total delivered at 22 weeks or more of gestation, including live births and stillbirths, counting singletons and multiples, while excluding miscarriages/abortions before 22 weeks of gestation and cases with missing data on gestational age at birth. 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.

Table 1 summarizes the background characteristics of the women who were included in the main analysis. Women who conceived by ART were more likely to be older, nulliparous, have a pre-existing condition, taking daily folic acid supplementation, non-smokers, have a higher education, and come from a wealthier household in contrast to women who conceived naturally. Table 2 shows the pregnancy and fetal/neonatal characteristics by mode of conception. Women who conceived by OI without ART had the highest proportion of multiple births among the four groups (4.9%). Table 3 shows the maternal/perinatal complications and adverse outcomes by mode of conception in all pregnancies, pregnancies with singletons, and pregnancies with multiples.

The association between each mode of conception and maternal/perinatal complications and adverse outcomes was assessed using a logistic regression and GEE analysis, with women who conceived naturally serving as a reference (Table 4). Pregnancies resulting from OI without ART did not have an increased risk of maternal/perinatal complications or adverse outcomes. Maternal death and stillbirth were not assessed because the number of cases was insufficient to calculate the aORs.

Women who conceived by conventional IVF-ET were at higher risk of placenta previa (aOR 2.90 [95% CI 1.94, 4.34]), MAP (aOR 6.85 [95% CI 3.88, 12.13]), and PIH (aOR 1.40 [95% CI 1.10, 1.78]) than those who conceived naturally. Women who conceived by ICSI had a higher risk of placental abruption (aOR 2.16 [95% CI 1.20, 3.88]) as well as placenta previa (aOR 2.01 [95% CI 1.29, 3.13]), MAP (aOR 7.81 [95% CI 4.56, 13.38]), and marginally significant PIH (aOR 1.25 [95% CI 0.98, 1.60]). Furthermore, women who conceived by ART were more likely to have a cesarean section and had a significantly higher risk of blood transfusion (conventional IVF-ET: aOR 3.85 [95% CI 2.52, 5.88]; ICSI: aOR 3.76 [95% CI 2.49, 5.66]) and ICU admission (conventional IVF-ET: aOR 2.58 [95% CI 1.11, 6.01]; ICSI: aOR 3.45 [95% CI 1.68, 7.06]) even after controlling for potential confounders. Neonates born after ART were at higher risk of preterm birth (conventional IVF-ET: aOR 1.42 [95% CI 1.13, 1.78]; ICSI: aOR 1.31 [95% CI 1.05, 1.64]) compared to those conceived naturally.

We also performed multiple imputation and compared the results with those from the logistic regression model with case-wise deletion of missing data (Table 4). The estimated effects of the variables of interest were similar in terms of their direction and magnitude.

Discussion
Compared with women who conceived naturally, those who conceived by conventional IVF-ET were at higher risk of placenta previa, MAP, and PIH whereas those who conceived by ICSI had a higher risk of placental abruption in addition to the above. Women who conceived by ART had a significantly higher risk of blood transfusion and ICU admission even after controlling for maternal age, pre-existing condition, and other potential confounders. Neonates conceived by ART were at higher risk of preterm birth.

The increased risk of maternal and perinatal complications observed in the present study were largely consistent with the findings of previous studies [6–10, 14–16]. Among these complications, the risk of MAP was conspicuous, with an aOR of 6.85 for conventional IVF-ET and 7.81 for ICSI. More than 1% of women who conceived by ART had MAP; however, this figure should be interpreted with caution as the diagnoses were made clinically irrespective of pathological examination in JECS. The relationship between IVF pregnancies and MAP was first reported by Esh-Broder, et al. in 2011 [10]. MAP is one of
| Table 4 Effect of mode of conception on maternal/perinatal complications and adverse outcomes |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                  | Logistic regression with case-wise deletion of missing data | Multiple imputation |
|                                  | Crude OR 95% CI aOR 95% CI | aOR 95% CI | aOR 95% CI |
| OI without ART                  |                                  |                                  |                                  |
| Maternal outcomes a             |                                  |                                  |                                  |
| Placenta previa                 | 0.76 0.43 1.31 0.62 0.35 1.09   | 0.85 0.55 1.32 |
| Placental abruption             | 1.33 0.82 2.18 1.33 0.80 2.19   | 1.13 0.71 1.81 |
| MAP                            | 1.46 0.74 2.86 1.46 0.73 2.91   | 1.23 0.62 2.45 |
| Gestational diabetes            | 1.40 1.16 1.69 0.97 0.80 1.19   | 0.98 0.81 1.18 |
| PIH                            | 1.55 1.30 1.84 1.10 0.91 1.32   | 1.11 0.94 1.31 |
| Cesarean section                | 1.41 1.29 1.53 1.12 0.99 1.26   | 1.08 0.97 1.21 |
| Blood transfusion               | 1.35 0.83 2.21 1.03 0.62 1.71   | 0.94 0.59 1.5  |
| ICU admission                   | 2.16 1.04 4.46 1.29 0.60 2.79   | 1.07 0.49 2.3  |
| Fetal/neonatal outcomes b       |                                  |                                  |                                  |
| Preterm birth                   | 1.93 1.71 2.18 1.05 0.09 1.24   | 1.01 0.86 1.18 |
| Low birth weight                | 1.88 1.70 2.07 1.04 0.93 1.19   | 1.04 0.93 1.17 |
| Conventional IVF-ET             |                                  |                                  |                                  |
| Maternal outcomes a             |                                  |                                  |                                  |
| Placenta previa                 | 4.68 3.22 6.82 2.90 1.94 4.34   | 2.86 1.99 4.12 |
| Placental abruption             | 1.03 0.43 2.50 0.91 0.37 2.26   | 1.08 0.53 2.22 |
| MAP                            | 6.88 4.09 11.58 6.85 3.88 12.13 | 5.74 2.93 11.2 |
| Gestational diabetes            | 1.88 1.45 2.45 0.99 0.75 1.31   | 1.13 0.88 1.45 |
| PIH                            | 2.43 1.94 3.05 1.40 1.10 1.78   | 1.41 1.13 1.76 |
| Cesarean section                | 2.69 2.39 3.02 1.85 1.58 2.17   | 1.9 1.64 2.19 |
| Blood transfusion               | 6.18 4.20 9.09 3.85 2.52 5.88   | 3.57 2.45 5.21 |
| ICU admission                   | 4.98 2.30 10.80 2.58 1.11 6.01   | 2.04 0.89 4.66 |
| Fetal/neonatal outcomes b       |                                  |                                  |                                  |
| Preterm birth                   | 2.59 2.18 3.08 1.42 1.13 1.78   | 1.36 1.11 1.66 |
| Low birth weight                | 1.90 1.63 2.22 0.94 0.76 1.15   | 1.01 0.85 1.2  |
| ICSI                           |                                  |                                  |                                  |
| Maternal outcomes a             |                                  |                                  |                                  |
| Placenta previa                 | 3.37 2.22 5.11 2.01 1.29 3.13   | 2.02 1.36 3.01 |
| Placental abruption             | 2.44 1.40 4.26 2.16 1.20 3.88   | 2.35 1.44 3.82 |
| MAP                            | 7.41 4.57 12.00 7.81 4.56 13.38 | 7.86 4.56 13.5 |
| Gestational diabetes            | 1.85 1.43 2.38 0.97 0.74 1.27   | 1.06 0.83 1.35 |
| PIH                            | 2.16 1.73 2.71 1.25 0.98 1.60   | 1.34 1.07 1.67 |
| Cesarean section                | 2.75 2.46 3.07 1.89 1.62 2.19   | 1.82 1.59 2.09 |
| Blood transfusion               | 5.98 4.11 8.69 3.76 2.49 5.66   | 3.43 2.37 4.96 |
| ICU admission                   | 7.11 3.78 13.36 3.45 1.68 7.06   | 3.87 2.07 7.24 |
| Fetal/neonatal outcomes b       |                                  |                                  |                                  |
| Preterm birth                   | 2.33 1.96 2.77 1.31 1.05 1.64   | 1.21 0.99 1.47 |
| Low birth weight                | 1.78 1.53 2.07 0.87 0.72 1.06   | 0.89 0.74 1.06 |

aOR adjusted odds ratio, ART assisted reproductive technologies, CI confidence intervals, ICSI intracytoplasmic sperm injection, ICU intensive care unit, IVF-ET in vitro fertilization and embryo transfer, MAP morbidly adherent placenta, OI ovulation induction, OR odds ratio, PIH pregnancy-induced hypertension

Women who conceived naturally served as the reference group

Adjusted odds ratios were calculated by controlling for maternal age, maternal body mass index (BMI) before pregnancy, maternal height, maternal weight before delivery, parity, prior cesarean section, pre-existing maternal conditions, multiple pregnancies, fetal presentation, folic acid supplementation, maternal smoking during pregnancy, maternal drinking during pregnancy, maternal educational level, paternal smoking, paternal educational level, and household income

"logistic regression; °generalized estimating equations (GEE)"
the major causes of catastrophic outcomes in obstetrics, and placenta previa and previous cesarean section are known risk factors of MAP [32, 33]. Prenatal diagnosis is crucial for appropriate management, and ultrasound examination and magnetic resonance imaging are used especially for women with risk factors [34, 35]. However, prenatal diagnosis is not always possible. Given the observed relationship between ART and MAP, obstetricians should consider women who conceived by ART as a high risk group for MAP regardless of their prenatal diagnosis. In addition to the incidence of MAP, the observed incidence of placenta previa was also high among ART pregnancies (2.4% for conventional IVF, 1.8% for ICSI).

With regard to life-threatening maternal conditions, studies such as the one by Belanoff et al. have reported a higher risk of severe maternal morbidity in women who conceived using ART [17–19]. Cromi et al. reported on the risk of a peripartum hysterectomy in pregnancies resulting from ART in 2016, arguing that such pregnancies should be managed as “high risk” [20]. In our study, more than 2% of women who conceived by ART received a blood transfusion. We realize that the incidence of these complications may be overestimated (or underestimated) depending upon the participants’ characteristics, given that JECS is not completely population-based. However, according to the profile paper of JECS, characteristics of the women and children who participated in JECS appeared to be comparable to those reported in Japan’s Vital Statistics Survey [36]. Hence, the observed higher risk of blood transfusion (conventional IVF-ET: aOR 3.85, ICSI: aOR 3.76) and ICU admission (conventional IVF-ET: aOR 2.58, ICSI: aOR 3.45) in ART pregnancies is deemed to be reliable.

In the present study, we estimated the risk levels of women who conceived using OI without ART separately from those of women who conceived naturally, considering the possibility that they might differ given the former’s history of infertility and the effect of OI. Although univariate analysis demonstrated an increased risk for some of the maternal/perinatal complications and adverse outcomes, none reached statistical significance after controlling for potential confounders.

The present study has several strengths. First and foremost, JECS is the largest birth cohort in the country and collects wide-ranging, in-depth information from participants and their medical records. This enabled us to control for various potential confounders including participants’ socio-economic status. In addition, the present study included blood transfusion and ICU admission as maternal adverse outcomes, unlike previous studies.

Nonetheless, the present study has several limitations. First, JECS was not designed to cover all expecting mothers during the recruitment period or apply complete random sampling (JECS aimed to cover 50% of the births in each study area [21].) Therefore, bias may have entered into the selection of the participants, thus leading to overestimation or underestimation of the incidence of maternal/perinatal complications and adverse outcomes. As mentioned above, however, the JECS profile paper suggested that the characteristics of the study participants were comparable to those collected in the national survey [36]. Second, the data pertaining to each woman’s mode of conception were self-reported, potentially jeopardizing their reliability. Furthermore, detailed data on the drugs and techniques used for OI or ART (e.g., fresh or frozen embryo transfer, blastocyst or cleavage stage embryo transfer) were not assessed. Third, data on some of the adverse outcomes, such as hysterectomy, were not collected in JECS. The number of maternal deaths and stillbirths was limited; hence, these figures were not included in the main analysis. Last, the diagnoses of maternal and perinatal complications were made at each participating facility, and subsequent interventions (e.g., blood transfusion and ICU admission) were conducted based on institutional protocols; hence, there may have been some variation in the diagnostic criteria and/or management strategies.

Conclusions
Women who conceived by ART were at higher risk of maternal and perinatal complications necessitating advanced/emergency obstetric care, such as a blood transfusion or ICU admission. Obstetricians should be aware of the increased risk of adverse maternal outcomes among women who conceived by ART.

Abbreviations
aOR: Adjusted odds ratio; ART: Assisted reproductive technology; BMI: Body mass index; CI: Confidence interval; ICSI: Intracytoplasmic sperm injection; ICU: Intensive care unit; IQR: Interquartile range; IVF-ET: In vitro fertilization and embryo transfer; JECS: Japan Environment and Children’s Study; MAP: Morbidly adherent placenta; NA: Not available; OI: Ovulation induction; OR: Odds ratio; PIH: Pregnancy-induced hypertension

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Availability of data and materials
The JECS data are not publicly available due to ethical restrictions and the legal framework of Japan. All inquiries about access to the data should be sent to the JECS Programme Office, National Institute for Environmental Studies (jeecs-enries.go.jp).

Authors’ contributions
JECS was initiated by the Japan Environment & Children’s Study Group, and the data were collected at 15 participating regional centers. The final data set was prepared and provided by the JECS Programme Office. CN and HS conceived the present study. LY conducted the statistical analyses. CN drafted the manuscript and agreed to be accountable for their own contributions and to ensure that questions regarding the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate
JECS was approved by the institutional review board on epidemiological studies of the Ministry of the Environment and the ethics committees of all the participating institutions (i.e., NIES, NCCHD, Hokkaido University, Sapporo Medical University, Ashikawa Medical College, Japanese Red Cross Hokkaido College of Nursing, Tohoku University, Fukushima Medical University, Chiba University, Yokohama City University, University of Yamanashi, Shinshu University, University of Toyama, Nagoya City University, Kyoto University, Doshisha University, Osaka University, Osaka Medical Center and Research Institute for Maternal and Child Health, Hyogo College of Medicine, Tottori University, Kochi University, University of Occupational and Environmental Health, Kyushu University, Kumamoto University, University of Miyazaki, and University of the Ryukyus). JECS is being conducted in accordance with the Declaration of Helsinki and other relevant regulations in the country. Written informed consent was obtained from all participants. The present study was conducted as a part of JECS and used anonymized data; hence, additional approval from the ethics committee was not required.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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