

BMJ Open Birth defects surveillance after assisted reproductive technology in Beijing: a whole of population-based cohort study

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ABSTRACT

Objectives To compare the differences in the prevalence of birth defects among offspring conceived by assisted reproductive technology (ART) and conceived spontaneously (non-ART), and assess the contribution of ART to birth defects.

Design A population-based retrospective cohort study.
Setting Beijing.

Participants Pregnant women whose expected date of childbirth was verified as occurring between October 2014 and September 2015, and were registered on the Beijing Maternal and Child Health Information Network System, were the recorded pregnancy outcomes. 2699 ART offspring and 191 368 non-ART offspring (live births, stillbirths and medical terminations) were included in our study.

Interventions None.

Outcome measures Risk ratios (RR) for birth defects were calculated among ART conceptions and non-ART conceptions with confounding factors by using logistic regression models.

Results 194 067 offspring were included in the present study, and 2699 (1.4%) were conceived using ART. Among all the births, the prevalence of any birth defect in the ART offspring (5.5%) was significantly higher than in the non-ART offspring (3.8%) (crude RR, 1.49, 95% CI 1.26 to 1.76). After adjusting for confounding factors, ART use was still associated with an increased risk of any birth defect (5.4% vs 3.5% in ART and non-ART group, adjusted RR (aRR), 1.43, 95% CI 1.08 to 1.90), especially for chromosomal abnormalities (0.5% vs 0.2% in ART and non-ART group, aRR, 3.11, 95% CI 1.28 to 7.58), in singleton births to mothers <35 years. Circulatory system malformations and musculoskeletal system malformations were observed to have a non-significant increase in offspring conceived by ART. However, the associations between ART and birth defects were not detected in multiple births or mothers ≥35 years.

Conclusions This study confirmed a small but significant association between ART and birth defects. However, the risk tends to be non-significant under the conditions of advanced maternal age or multiple pregnancies.

INTRODUCTION

In 1978, the world's first infant conceived with assisted reproductive technology (ART) was born in the UK.^{1,2} According to published reports, almost 1.5 million cycles of in vitro

Strengths and limitations of this study

- We used a whole of population-based surveillance data between 2014 and 2016 in Beijing to analyse the relationship between assisted reproductive technology (ART) and birth defects.
- Rich demographic and clinical information collected by the Beijing Maternal and Child Health Information Network System allowed a thorough adjustment for confounding, assessment of mediation and subgroup analysis.
- The ART information was self-reported by the pregnant women, and the under-reporting of ART experience maybe exist.
- The specific classification of ART at an individual level such as intrauterine insemination, in vitro fertilisation, intracytoplasmic sperm injection or preimplantation genetic testing was not available.

fertilisation (IVF) are performed annually, resulting in 350 000 offspring worldwide.^{3,4} Mainland China's first successful ART-IVF conception occurred in Beijing in 1988.⁵ Fertility treatments including intrauterine insemination (IUI) and all the procedures for ART—IVF, intracytoplasmic sperm injection (ICSI), fresh embryo transfer, frozen embryo transfer (FET), in vitro maturation, elective single embryo transfer, blastocyst embryo transfer, egg donation and preimplantation genetic testing (PGT)—are all permitted by the Chinese National Health Commission and are available to patients.⁶ Between 2013 and 2015, over 25 000 IUI cycles, 65 000 (IVF-ICSI) oocyte aspirations, and 76 000 embryo transfers were reported from the IVF centres in Beijing.⁶

Although ART has been successful in solving infertility problems, there have always been concerns about whether the process—involving superovulation, in vitro culture, fresh or frozen-thawed transfers use of cleavage stage embryos or blastocysts, heterologous IVF with oocyte donation, PGT and other micromanipulations—would interfere with the cell proliferation,



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differentiation and growth of the embryos.^{7–10} Initial cohort studies with small sample sizes showed that ART-conceived infants seemed to be healthy.¹¹ However, subsequent case–control studies and meta-analysis suggested that ART-based conceptions had increased risks for birth defects compared with non-ART conceptions, particularly among singleton pregnancies.^{12–17} A potential increase in cardiovascular, musculoskeletal, urogenital and gastrointestinal system malformations^{18–20} was observed in offspring conceived using ART.

With the expanded use of ART in China, some large-sample studies using data from IVF centres only, or limited-linked resources, were performed in recent years.^{6 21–26} However, the accuracy of the results and the consequent application of the conclusions drawn were restricted by the limited study population.²⁷ In the present study, for the first time, we used a whole of population-based surveillance data between 2014 and 2016 from the Beijing Maternal and Child Health Information Network System (BMCHINS) to assess the prevalence of birth defects among ART-conceived offspring, compared with non-ART conceptions. Thus, we examined the potential risk of birth defects associated with ART in Beijing, China.

MATERIALS AND METHODS

Study design and data sources

We performed a population-based retrospective cohort study using surveillance data from 2014 to 2016, from the BMCHINS, which was officially established to collect information regarding all pregnant women and their offspring, from all the community health service centres, midwifery agencies and children's hospitals in Beijing. Data quality assurance is carried out every year with reports being presented to the ministry of government administration.

The information regarding ART and basic maternal information—including maternal age, prepregnancy body mass index (BMI), residence, ethnicity, education, medical and reproductive history—were collected at a pregnant woman's first visit (usually before 13 weeks gestation) to the community health service centre. The health status, medical complications, examination and treatment received during the pregnancy, fetal screening and diagnoses were recorded and updated at every patient visit to the midwifery agencies. Pregnancy outcomes, including live birth, miscarriage (not included in our study population), stillbirth (after 20 gestational weeks) and medical termination of pregnancy, were also recorded on their electronic medical records at the end of pregnancy.

Congenital abnormalities (birth defects) detected in pregnancy (after 13 gestational weeks) or during the infancy period (within 1 year after birth) were reported by obstetricians or paediatricians to the birth defects unit on BMCHINS with the use of a standardised congenital abnormality form. The diagnoses of birth defects were confirmed by cross-referencing of medical records and

coded according to the modification of the International Classification of Diseases, 10th revision (ICD-10), including structural abnormalities, biochemical abnormalities and chromosomal or otherwise genetic abnormalities.

Statistical analysis

We used the statistical software SPSS V.18.0 (SPSS) for Windows for all analyses. The proportional distributions of sociodemographic characteristics between ART and non-ART offspring were compared using the Pearson χ^2 tests (two tailed, significance level=0.05). The variables included plurality, sex of the offspring, maternal age, residence, ethnicity, education, parity, prepregnancy BMI (categorised as per the WHO guideline for Asian populations²⁸), history of adverse pregnancy outcomes, history of infertility, medical complications in pregnancy (preexisting hypertension, pregnancy-induced hypertension, preexisting diabetes, gestational diabetes, anaemia), maternal folic acid supplementation, first visit to a doctor, and visits to the doctor during pregnancy. Risk ratios were calculated with 95% CIs and Pearson χ^2 analysis, by comparing the incidences of birth defects and the subcategories of birth defects between the two groups. The adjusted analysis used a logistic regression equation, including a priori confounding factors of maternal age (categorised in 5-year groups, in most subcategory analyses of birth defects), parity (first, and second or above), prepregnancy BMI (underweight or normal, overweight and obesity), maternal residence (Beijing and other places), diabetes, hypertension, anaemia and folic acid supplementation (not taking, not regular and regular; only in the model for nervous system malformations analysis). For all comparisons, any birth defect, chromosomal abnormality and Down's syndrome were analysed with stratification into maternal age <35 years and \geq 35 years. We also conducted a subgroup analysis for singleton and multiple births. Multiple pregnancies included twins and triplets in our study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination of our study.

RESULTS

A total of 206 079 pregnant women whose expected date of childbirth was verified to be between October 2014 and September 2015 were registered on BMCHINS. Among them, 2131 ART-conceived pregnant women and 193 271 non-ART pregnant women had recorded pregnancy outcomes (live births, stillbirths, miscarriage and termination of pregnancy). Ultimately, except for those miscarriages, 2699 (1.4%) ART offspring and 191 368 non-ART offspring were included in our retrospective cohort study (figure 1).

Sociodemographic characteristics

The descriptive statistics of the 194 067 offspring by mode of conception are shown in table 1. Compared with the

non-ART group, offspring conceived using ART had higher frequencies of multiple births. The ART mothers had higher frequencies of advanced age, native residence, primipara delivery, being overweight or obese, a history of adverse pregnancy outcomes or infertility and medical complications in pregnancy. They were more willing to follow the doctor's advice, including taking folic acid as recommended (400 µg folic acid per day, beginning 3 months before becoming pregnant and through the first 12 weeks of the pregnancy), and initiating and maintaining earlier and regular visits to the doctor. However, there was no difference in the distributions of sex of the offspring, maternal ethnicity, and maternal education between the two groups.

Risk of birth defects associated with ART

Among all births, the prevalence of birth defects in the ART offspring (5.5%, n=149) was significantly higher than that in non-ART offspring (3.8%, n=7233) (crude RR (cRR), 1.49; 95% CI 1.26 to 1.76). In the stratified analysis based on maternal age, ART was associated with an increased risk of any birth defect in births to mothers <35 years (5.3% vs 3.6% in ART and non-ART group, adjusted risk ratio (aRR), 1.39; 95% CI 1.12 to 1.71), but

not to mothers aged ≥35 years (6.1% vs 5.4% in ART and non-ART group, aRR, 0.98; 95% CI 0.73 to 1.33). When we stratified by plurality (singletons vs multiples), the multivariate analysis showed that the risk was still significantly different between ART use and non-ART to mothers <35 years in singleton births (5.4% vs 3.5% in ART and non-ART group, aRR 1.43; 95% CI, 1.08 to 1.90), but not in multiple births (5.1% vs 6.3% in ART and non-ART group, aRR, 0.79; 95% CI 0.56 to 1.10) (table 2).

On analysis of the subcategories of birth defects among all the births, the results showed an increased risk for circulatory system malformations (2.0% vs 1.4% in ART and non-ART group, cRR, 1.40; 95% CI 1.06 to 1.84), musculoskeletal system malformations and deformations (0.9% vs 0.6% in ART and non-ART group, cRR, 1.59; 95% CI 1.06 to 2.38), multiple defects (0.9% vs 0.5% in ART and non-ART group, cRR, 1.63; 95% CI 1.08 to 2.47) and other malformations (0.7% vs 0.4% in ART and non-ART group, cRR, 1.82; 95% CI 1.14 to 2.90) in the ART-use group. However, these associations were not significant after adjusting for confounding factors. For singleton births, the prevalence of circulatory system malformations (2.3% vs 1.4% in ART and

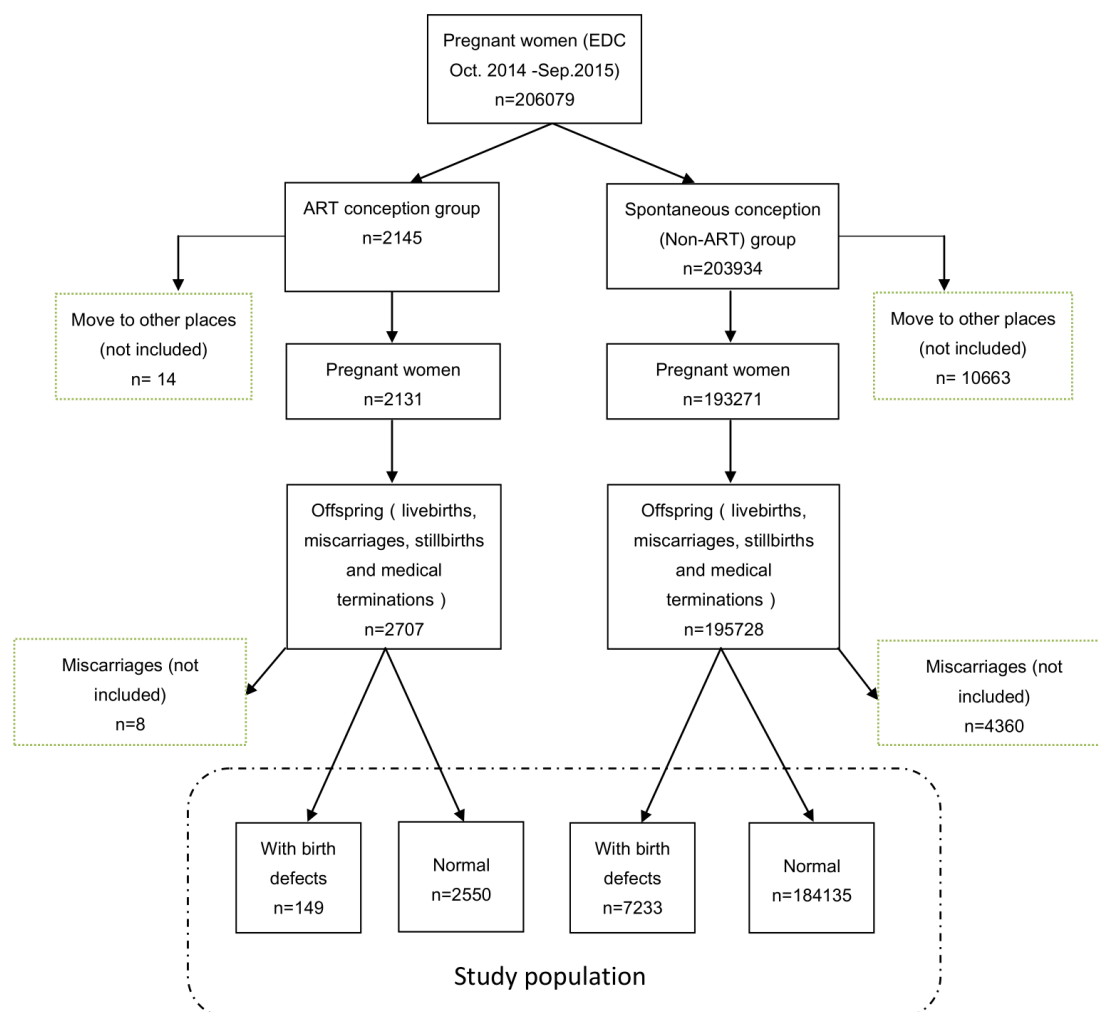


Figure 1 Study population. ART, assisted reproductive technology; EDC, expected date of childbirth.

Table 1 Characteristics of offspring, by mode of conception

Characteristic	No (%)		P value
	ART (n=2699)	Non-ART (n=191 368)	
Plurality			<0.001
Singleton	1546 (57.3)	186 491 (97.5)	
Twins	1141 (42.3)	4832 (2.5)	
Triplets	12 (0.4)	45 (0.0)	
Offspring sex			0.418
Male	1375 (50.9)	99 126 (51.8)	
Female	1314 (48.7)	91 794 (48.0)	
Unknown	10 (0.4)	448 (0.2)	
Maternal age, years *†			<0.001
<25	35 (1.3)	22 160 (11.6)	
25~	491 (18.2)	80 395 (42.0)	
30~	1335 (49.4)	67 187 (35.1)	
35~	701 (26.0)	19 057 (10.0)	
≥40	137 (5.1)	2569 (1.3)	
Maternal residence *†			<0.001
Beijing	1989 (73.7)	125 575 (65.6)	
Others	710 (26.3)	65 793 (34.4)	
Maternal ethnicity			0.547
Han	2551 (94.5)	180 293 (94.2)	
Minority	145 (5.4)	10 792 (5.7)	
Missing	3 (0.1)	283 (0.1)	
Maternal education			0.573
Primary school and illiteracy	21 (0.8)	1699 (0.9)	
Junior middle	423 (15.7)	31 085 (16.2)	
Senior middle	778 (28.8)	53 312 (27.9)	
College and above	1369 (50.7)	94 428 (49.3)	
Missing	108 (4.0)	10 844 (5.7)	
Maternal parity*†			<0.001
First	2124 (78.7)	112 985 (59.1)	
Second	535 (19.9)	67 770 (35.4)	
Third and above	39 (1.4)	10 545 (5.5)	
Missing	1 (0.0)	68 (0.0)	
Maternal prepregnancy BMI*†			<0.001
Underweight (<18.5)	184 (6.8)	24 122 (12.6)	
Normal (18.5–22.9)	1324 (49.1)	106 130 (55.5)	
Overweight (23.0–27.4)	866 (32.1)	45 267 (23.7)	
Obesity (≥27.5)	298 (11.0)	11 764 (6.1)	
Missing	27 (1.0)	4085 (2.1)	
Maternal history of adverse pregnancy outcome (yes) *†	110 (4.1)	5233 (2.7)	<0.001
Maternal history of infertility (yes) *†	301 (11.2)	448 (0.2)	<0.001
Maternal medical complications in pregnancy			
Any diabetes (yes) *†	383 (14.2)	15 688 (8.2)	<0.001
Any hypertension (yes) *†	179 (6.6)	3880 (2.0)	<0.001

Continued

Table 1 Continued

Characteristic	No (%)		P value
	ART (n=2699)	Non-ART (n=191 368)	
Anaemia (yes)†	169 (6.3)	10 175 (5.3)	0.030
Maternal folic acid supplementation as recommended*†			<0.001
No	82 (3.0)	15 083 (7.9)	
Yes but not regularly	290 (10.7)	41 217 (21.5)	
Yes and regularly	2322 (86.1)	134 433 (70.3)	
Missing	5 (0.2)	635 (0.3)	
Maternal first visit to a doctor*†			<0.001
First trimester	2357 (87.3)	135 786 (71.0)	
Second trimester	275 (10.2)	41 741 (21.8)	
Third trimester	64 (2.4)	13 691 (7.1)	
Missing	3 (0.1)	150 (0.1)	
Maternal visits to a doctor in pregnancy *†			<0.001
>4 times	2529 (93.7)	168 912 (88.3)	
0–4 times	53 (2.0)	8316 (4.3)	
Missing	117 (4.3)	14 140 (7.4)	

P value calculated without the condition of unknown data.

*P<0.05 in single offspring when comparing ART group and non-ART group;.

†P<0.05 in multiple offspring when comparing ART group and non-ART group;.

ART, assisted reproductive technology; BMI, body mass index.

non-ART group, cRR, 1.65; 95% CI 1.18 to 2.31) and chromosomal abnormalities (0.5% vs 0.2% in mothers <35 years ART and non-ART group, cRR, 2.96; 95% CI 1.22 to 7.19) (1.7% vs 0.8% in mothers ≥35 years ART and non-ART group, cRR, 2.05; 95% CI 1.04 to 4.03) in ART births were significantly higher than in non-ART births. Nevertheless, the prevalence of Down's syndrome was not higher in the ART births (0.1% vs 0.1% in mothers <35 years ART and non-ART group; cRR, 1.31; 95% CI 0.18 to 9.39) (0.6% vs 0.4% in mothers ≥35 years ART and non-ART group; cRR, 1.40; 95% CI 0.44 to 4.43). After adjusting for confounding factors, only the risk of chromosomal abnormalities was still statistically significant in births to mothers<35 years in the ART group (0.5% vs 0.2% in ART and non-ART group, aRR 3.11; 95% CI 1.28 to 7.58). When the study population was restricted to multiple births, no significant associations were detected (table 2).

DISCUSSION

In this population-based cohort study, ART contributed to approximately 1.4% of the total births in Beijing. This proportion was close to the estimated ART-associated births in China by some researchers (1%–2%),²⁹ but is lower than the percentage reported in a hospital-based cohort study from Shanghai by Min Yang (2.22%),²³ with no more published data being available for further reference. In contrast to the other countries, the proportion is similar to the United States (1.4%–1.8%),^{19 30–32} but is lower than

in Australia (2.0%),¹⁸ Italy (2.5%)³³ and Japan (3.6%).³⁴ In accordance with previous studies and meta-analyses,^{18 19 35–39} including several Chinese big-data studies,^{23 24} ART mothers tended to be older, overweight or obese, were more likely to have a history of adverse pregnancy outcomes, and had a greater incidence of multiple conceptions and chronic conditions during the pregnancy.

Risk of birth defects associated with ART

Our study confirms the results of previous studies, with about a 30%–40% increase in the frequency of birth defects among offspring born after ART. However, the association tends to be non-significant in patients with advanced maternal age, or multiple conceptions.

For all births, the incidence of birth defects in our study was 3.8%, which is close to the reported prevalence of birth defects in China (4%–6%).^{40 41} In the stratified analysis for singleton births, the risk of birth defects in the ART group (5.9%) was significantly higher than in the non-ART group (3.7%). This result was compatible with previous findings.^{18 19 35–39} In the stratified analysis for multiple births, however, the risk of birth defects in the ART group (5.0%) did not seem to be higher than in the non-ART group (6.3%), in fact it was lower, with no statistical difference being found in the values. This association, as previous studies confirmed, might be partly due to more dizygotic twins (owing to insertion of multiple embryos) in ART conceptions than in the non-ART conceptions. Research on twin pregnancies shows that dizygotic twins are at a lower risk of birth defects

Table 2 Prevalence and risk ratios for selected birth defects by mode of conception and plurality

Birth defect category	All births			
	ART n (%)	Non-ART n (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)*
Any defect	149 (5.5)	7233 (3.8)	1.49 (1.26 to 1.76)	1.40 (1.18 to 1.66)†
Any defect (<35 years)	98 (5.3)	6073 (3.6)	1.50 (1.22 to 1.84)	1.39 (1.12 to 1.71)†
Any defect (≥35 years)	51 (6.1)	1160 (5.4)	1.14 (0.86 to 1.53)	0.98 (0.73 to 1.33)†
Multiple defects	23 (0.9)	1005 (0.5)	1.63 (1.08 to 2.47)	1.15 (0.74 to 1.78)
Nervous system malformations: ICD-10 codes Q00–Q07	3 (0.1)	225 (0.1)	0.95 (0.30 to 2.96)	0.87 (0.28 to 2.74)
Eye, ear, face and neck malformations: ICD-10 codes Q10–Q18	23 (0.9)	1201 (0.6)	1.36 (0.90 to 2.06)	1.12 (0.73 to 1.72)
Circulatory system malformations: ICD-10 codes Q20–Q28	53 (2.0)	2706 (1.4)	1.40 (1.06 to 1.84)	1.03 (0.77 to 1.38)
Respiratory system malformations: ICD-10 codes Q30–Q34	0 (0.0)	93 (0.0)	/	/
Cleft lip/palate: ICD-10 codes Q35–Q37	8 (0.3)	342 (0.2)	1.66 (0.82 to 3.35)	1.37 (0.67 to 2.80)
Digestive system malformations: ICD-10 codes Q38–Q45	3 (0.1)	375 (0.2)	0.57 (0.18 to 1.77)	0.51 (0.16 to 1.60)
Genital organs malformations: ICD-10 codes Q50–Q56	10 (0.4)	447 (0.2)	1.59 (0.85 to 2.98)	1.09 (0.56 to 2.13)
Urinary system malformations: ICD-10 codes Q60–Q64	12 (0.4)	512 (0.3)	1.67 (0.94 to 2.95)	1.41 (0.79 to 2.53)
Musculoskeletal system malformations and deformations: ICD-10 codes Q65–Q79	24 (0.9)	1077 (0.6)	1.59 (1.06 to 2.38)	1.36 (0.90 to 2.06)
Chromosomal abnormalities, not elsewhere classified: ICD-10 codes Q90–Q99 (<35 years)	6 (0.3)	284 (0.2)	1.93 (0.86 to 4.34)	2.05 (0.91 to 4.62)†
Down syndrome: Q90 (<35 years)	1 (0.1)	125 (0.1)	0.73 (0.10 to 5.22)	0.79 (0.11 to 5.65)†
Chromosomal abnormalities, not elsewhere classified: ICD-10 codes Q90–Q99 (≥35 years)	10 (1.2)	178 (0.8)	1.46 (0.77 to 2.76)	1.21 (0.63 to 2.33)†
Down syndrome: Q90 (≥35 years)	3 (0.4)	87 (0.4)	0.89 (0.28 to 2.82)	0.69 (0.22 to 2.22)†
Metabolic abnormalities	0 (0.0)	29 (0.0)	/	/
Haematological abnormalities	1 (0.0)	140 (0.1)	0.51 (0.07 to 3.62)	0.41 (0.06 to 2.94)
Other malformations	18 (0.7)	705 (0.4)	1.82 (1.14 to 2.90)	1.58 (0.98 to 2.54)
Singleton births				
ART n (%)	NON-ART n (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)*	ART n (%)
91 (5.9)	6925 (3.7)	1.62 (1.31 to 2.01)	1.51 (1.21 to 1.88)†	58 (5.0)
55 (5.4)	5817 (3.5)	1.57 (1.19 to 2.06)	1.43 (1.08 to 1.90)†	43 (5.1)
36 (6.8)	1108 (5.3)	1.31 (0.93 to 1.84)	1.12 (0.79 to 1.59)†	15 (4.8)
13 (0.8)	935 (0.5)	1.68 (0.97 to 2.92)	1.17 (0.66 to 2.09)	10 (0.9)
2 (0.1)	217 (0.1)	1.11 (0.28 to 4.48)	1.01 (0.25 to 4.09)	1 (0.1)
13 (0.8)	1163 (0.6)	1.35 (0.78 to 2.34)	1.16 (0.67 to 2.02)	10 (0.9)
35 (2.3)	2584 (1.4)	1.65 (1.18 to 2.31)	1.15 (0.80 to 1.65)	18 (1.6)
0 (0.0)	85 (0.0)	/	/	0 (0.0)
3 (0.2)	326 (0.2)	1.11 (0.36 to 3.46)	0.88 (0.28 to 2.75)	5 (0.4)
2 (0.1)	356 (0.2)	0.68 (0.17 to 2.72)	0.61 (0.15 to 2.44)	1 (0.1)
6 (0.4)	421 (0.2)	1.72 (0.77 to 3.86)	1.07 (0.44 to 2.60)	4 (0.3)
Multiple births				
ART n (%)	NON-ART n (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	ART n (%)
58 (5.0)	308 (6.3)	0.79 (0.59 to 1.05)	0.77 (0.57 to 1.03)†	308 (6.3)
43 (5.1)	256 (6.3)	0.80 (0.57 to 1.11)	0.79 (0.56 to 1.10)†	256 (6.3)
15 (4.8)	52 (6.2)	0.77 (0.43 to 1.39)	0.67 (0.36 to 1.24)†	52 (6.2)
10 (0.9)	70 (1.4)	0.60 (0.31 to 1.17)	0.60 (0.30 to 1.19)	70 (1.4)
1 (0.1)	8 (0.2)	0.53 (0.07 to 4.23)	0.61 (0.07 to 5.12)	8 (0.2)
38 (0.8)	38 (0.8)	1.11 (0.55 to 2.24)	0.94 (0.46 to 1.93)	38 (0.8)
122 (2.5)	122 (2.5)	0.62 (0.38 to 1.02)	0.60 (0.36 to 1.00)	122 (2.5)
8 (0.2)	8 (0.2)	/	/	8 (0.2)
16 (0.3)	16 (0.3)	1.32 (0.48 to 3.62)	1.69 (0.60 to 4.79)	16 (0.3)
19 (0.4)	19 (0.4)	0.22 (0.03 to 1.66)	0.21 (0.03 to 1.61)	19 (0.4)
26 (0.5)	26 (0.5)	0.65 (0.23 to 1.87)	0.71 (0.24 to 2.10)	26 (0.5)

Continued

Table 2 Continued

		Multiple births					
Singleton births		ART n (%)		Non-ART n (%)		Non-ART n (%)	
ART n (%)	NON-ART n (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)*	ART n (%)	Non-ART n (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)†
6 (0.4)	494 (0.3)	1.47 (0.66 to 3.29)	1.24 (0.55 to 2.81)	6 (0.5)	18 (0.4)	1.41 (0.56 to 3.57)	1.20 (0.46 to 3.16)
14 (0.9)	1028 (0.6)	1.65 (0.97 to 2.80)	1.40 (0.82 to 2.40)	10 (0.9)	49 (1.0)	0.86 (0.44 to 1.71)	0.87 (0.43 to 1.76)
5 (0.5)	275 (0.2)	2.96 (1.22 to 7.19)	3.11 (1.28 to 7.58)‡	1 (0.1)	9 (0.2)	0.53 (0.07 to 4.21)	/
1 (0.1)	124 (0.1)	1.31 (0.18 to 9.39)	1.43 (0.20 to 10.24)†	0 (0.0)	1 (0.0)	/	/
9 (1.7)	175 (0.8)	2.05 (1.04 to 4.03)	1.72 (0.86 to 3.42)†	1 (0.3)	3 (0.4)	0.90 (0.09 to 8.70)	/
3 (0.6)	85 (0.4)	1.40 (0.44 to 4.43)	1.12 (0.35 to 3.62)†	0 (0.0)	2 (0.2)	/	/
0 (0.0)	27 (0.0)	/	/	0 (0.0)	2 (0.0)	/	/
0 (0.0)	128 (0.1)	/	/	1 (0.1)	12 (0.2)	0.35 (0.05 to 2.71)	0.25 (0.03 to 1.98)
10 (0.6)	651 (0.3)	1.86 (0.99 to 3.48)	1.63 (0.86 to 3.06)	8 (0.7)	54 (1.1)	0.63 (0.30 to 1.32)	0.62 (0.29 to 1.32)

All models were calculated excluding cases with missing categories.

*Adjusted for maternal age, parity, prepregnancy BMI, maternal residence, diabetes, hypertension, anaemia, folic acid supplementation (only in the model for analysis of nervous system malformations).

†Maternal age was not included in the regression model.

‡Adjusted for maternal age, parity, maternal residence, diabetes, hypertension, anaemia, folic acid supplementation (only in the model for analysis of nervous system malformations).

ART, assisted reproductive technology; BMI, body mass index; ICD-10, International Classification of Diseases, 10th revision; RR, risk ratio.

than monozygotic twins,^{42 43} this being attributed to potential errors in the zygotic division or vascular interchange of monozygotic twins.^{44 45}

When stratified by maternal age, the risk of birth defects in the ART group was significantly higher than in the non-ART group only in mothers aged <35 years, but not in mothers aged ≥35 years. The potential explanation for the non-significant association between ART and birth defects among mothers aged ≥35 years, may be due to the broadly lower fertility of older mothers.⁴⁶ As widely accepted, maternal age is an independent risk factor for women's fecundity and their pregnancy outcomes, including birth defects. The lower fertility and higher incidence of birth defects occurred among older mothers not only in ART conceptions but also in non-ART conceptions. Thus, although the prevalence of birth defects in ART conceptions was higher than in non-ART conceptions, the difference tended to be non-significant among mothers aged ≥35 years (the stronger risk factor for birth defects). However, this non-statistical association between ART and birth defects among older mothers was not obtained in previous studies.^{12–17 23 24} The possible reason may be attributed to the differing study populations or differing fertility and health status. Several studies by IVF centres have shown that Chinese patients had more secondary infertility than reported in other countries,⁶ which possibly means fewer embryo problems in the Chinese ART population, and a non-significant difference in the fertility status between the ART and non-ART populations. Further research and data are needed to elucidate the causal mechanisms.

Notably, the subgroup analysis of birth defects in our study documented a significantly increased prevalence of chromosomal abnormalities among singleton ART births to mothers <35 years of age. The result might be explained by the more serious underlying health issues and the poor-quality embryos in young women undergoing ART (the critical reason for ART), although this positive result was not obtained in other studies.^{19 24 33} Another explanation may be due to the good compliance of ART mothers with their doctors. They appeared to be more concerned about their own health and that of their offspring, visiting doctors early and more often, and receiving more prenatal screening. Thus, birth defects in the ART group might be more frequently detected than in the non-ART group, for example, microdeletion or microduplication syndromes, etc.

Additionally, we found that the prevalence of circulatory system malformations, musculoskeletal system malformations, and multiple defects increased in the ART group, although it tended to be statistically non-significant after considering potential confounding factors. The results were compatible with previous findings of the high incidence of these abnormalities among ART births.^{18–20 33 47 48} Previous study showed that increased risk of circulatory system malformations may be a consequence of early placental dysfunction with lower pregnancy-associated plasma protein A, lower placenta growth factors and higher free β-human chorionic gonadotropin concentrations in the

first trimester among IVF/ICSI pregnancies.^{20 49–51} More data were needed for further research and confirmation on the mechanism of increased musculoskeletal system malformations, and multiple defects among ART births.

Strengths and limitations

Our study had several strengths. First, we used a whole of population based surveillance data to analyse the relationship between ART and birth defects in Beijing. The study sample was based on the entire population of Beijing city. Since we had a 100% capture for hospital and home births in Beijing, our study was free from any bias caused by selective inclusion of births. Second, birth defects in our study were detected from 13 weeks of pregnancy up to a child's first birthday, and defined as per the ICD-10 code, so that the birth defect data could be efficiently captured, and were less likely to be under-reported or misclassified. Third, the data quality of BMCHINS has been under strict control and is considered to be high. Rich demographic and clinical information collected by the BMCHINS allowed a thorough adjustment for confounding, assessment of mediation and subgroup analysis, such as the maternal prepregnancy BMI, adverse pregnancy outcome history, and infertility history.

However, there are several limitations in our study as well. First, the ART information was self-reported by the pregnant women. Although ART mothers are generally thought to be willing to announce their ART information to the doctors for better medical care, the under-reporting of ART experience maybe still exist. There might be misclassification within the data such that some ART-conceived offspring are labelled as unexposed. By comparing ART births to 'non-ART' births (ART mixed), effect estimates are likely biased to the null. Second, the specific classification of ART at an individual level such as IUI, IVF, ICSI, fresh or FET and PGT was not available. Studies showed that uterine perfusion and early fetal growth were improved in IVF or ICSI pregnancies conceived after FET as compared with fresh embryo transfer, and this may be highly relevant for organogenesis and embryonic development.^{7 8} PGT aims at avoiding transfer of 'abnormal' embryos to improve the probability of conceiving a viable pregnancy theoretically, but there is still a possibility that the embryo biopsy procedure itself may negatively affect the viability of the embryo and lower the probability of pregnancy. Nevertheless, the differences in the incidence of birth defects between IVF and ICSI, fresh and FET, IVF with PGT and IVF without PGT, were not significantly different in most studies.^{6 9 10 16 19 21 26 52} Finally, paternal information as a confounding factor was not included in our study, although it was usually thought to have little impact on the occurrence of birth defects.^{53 54}

CONCLUSIONS

This study confirmed a small but significant association between ART and birth defects. However, the risks tended

to be non-significant with advanced maternal age and multiple pregnancies. Our result indicated that the underlying subfertility and/or the high proportion of multiple births among ART pregnancies seemed to contribute critical roles in the higher prevalence of birth defects than ART procedures. As previous study confirmed, subfertility and multiple births affect the associations between ART and several birth defects, with subfertility explaining a substantial portion and multiple births explaining about 30% of the relative effect of ART on some birth defects.^{55 56} Hence, couples experiencing problems with infertility or other health issues should be fully assessed and counselled, during the conception period and while pursuing ART.

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