Congenital heart disease in a singleton pregnancy conceived through assisted reproductive technology

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Objective: To evaluate the risk of congenital heart disease (CHD) in offspring of singleton primiparous pregnancies conceived via assisted reproductive technology (ART).
Design: Retrospective, nationwide cohort study.
Subjects: Patients with singleton pregnancies who delivered between 2017 and 2021.
Exposure: Singleton pregnancies conceived by natural conception, intrauterine insemination, fresh embryo transfer, and frozen embryo transfer were compared.
Main Outcome Measures: The primary outcome was the rate of CHDs among offspring. Secondary outcomes included CHD subtype distribution, sex differences, and perinatal outcomes.
Results: Among 651,964 mother–child pairs, 6.19% were diagnosed with CHD, with the higher incidence in frozen embryo transfer (10.4%). Frozen embryo transfer, fresh embryo transfer and intrauterine insemination (IUI) exhibited 54.5%, 29.6%, and 21.5% increased risk of CHD compared with natural conception. Frozen embryo transfer was associated with an increased risk of right outflow malformations after adjusting for confounding factors. Septal defects and patent ductus arteriosus were increased in both the IUI and embryo transfer groups, with the highest prevalence observed in the frozen embryo transfer group. Findings within each sex subgroup were consistent with the overall trends. In natural conceptions, male fetuses showed a significantly higher risk of conotruncal defects and left ventricular outflow tract anomalies, but a lower risk of patent ductus arteriosus, compared with female fetuses. However, in IUI and embryo transfer pregnancies, no significant sex-specific differences were observed across the types of CHDs.
Conclusion: Singleton pregnancies achieved through IUI and ART, especially frozen embryo transfer, are associated with a higher incidence of CHD in offspring in this population-based study. Sex difference no longer had an impact on the CHD risk in IUI or ART. The findings should be communicated to patients undergoing pre-ART counseling. Because our outcome definition was based on claims data including mild lesions and early neonatal diagnoses, the absolute prevalence of CHD may appear higher than registry-based estimates. (Fertil Steril® 2026;126:67–74. ©2026 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Congenital heart disease, assisted reproductive technology, embryo transfer, singleton pregnancy, intrauterine insemination

Pregnancies achieved via assisted reproductive technology (ART) carry a higher likelihood of adverse outcomes, such as congenital malformation, preterm birth, growth restriction or overgrowth, cesarean section, hypertensive disorders, and postpartum hemorrhage (1–3). The risk of congenital malformation has been reported to be 30–70% higher than that in natural conception (4). Therefore, concerns regarding the safety issues related to pregnancy outcomes are increasing.

Assisted reproductive technology, including in vitro fertilization and embryo transfer (IVF-ET)—fresh or frozen cycles—and intracytoplasmic sperm injection, is widely utilized to achieve pregnancy. Numerous studies have investigated how these methods affect offspring. However, a debate is still

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ongoing, with some studies suggesting an increased risk, and others demonstrating no significant association (5). The majority of the studies included both singleton and multiple pregnancies. Notably, multiple pregnancies are associated with an elevated risk of fetal malformations.

However, with the introduction of single-ET (SET), the incidence of singleton pregnancies has increased steadily. Meta-analyses and large observational studies have reported an increased risk of obstetric complications (6). This is believed to be influenced by the unique environmental factors associated with ART. Despite the improvement in ART technology, the factors such as medications for ovulation induction or pregnancy support, the composition of the culture media, duration of in vitro culture, conditions for freezing and thawing, hormonal supplementation during implantation, handling of gametes and embryos, the degree of procedural invasiveness, as well as the underlying cause and nature of infertility are plausible causes of pregnancy complications (4, 7, 8).

Congenital heart disease (CHD) is the most frequent type of birth defect, accounting for approximately 50% of all cases. Approximately 1–2% of children in the general population are born with CHD, although these rates cannot account for cases resulting in termination or stillbirth. A recent meta-analysis of 41 studies reported a 45% increased risk of CHD in children conceived via ART (9). Similarly, other studies have confirmed this association, identifying twinning as a major contributing factor (10, 11). Additionally, analyses of the specific classification of CHD have been inconsistent and limited.

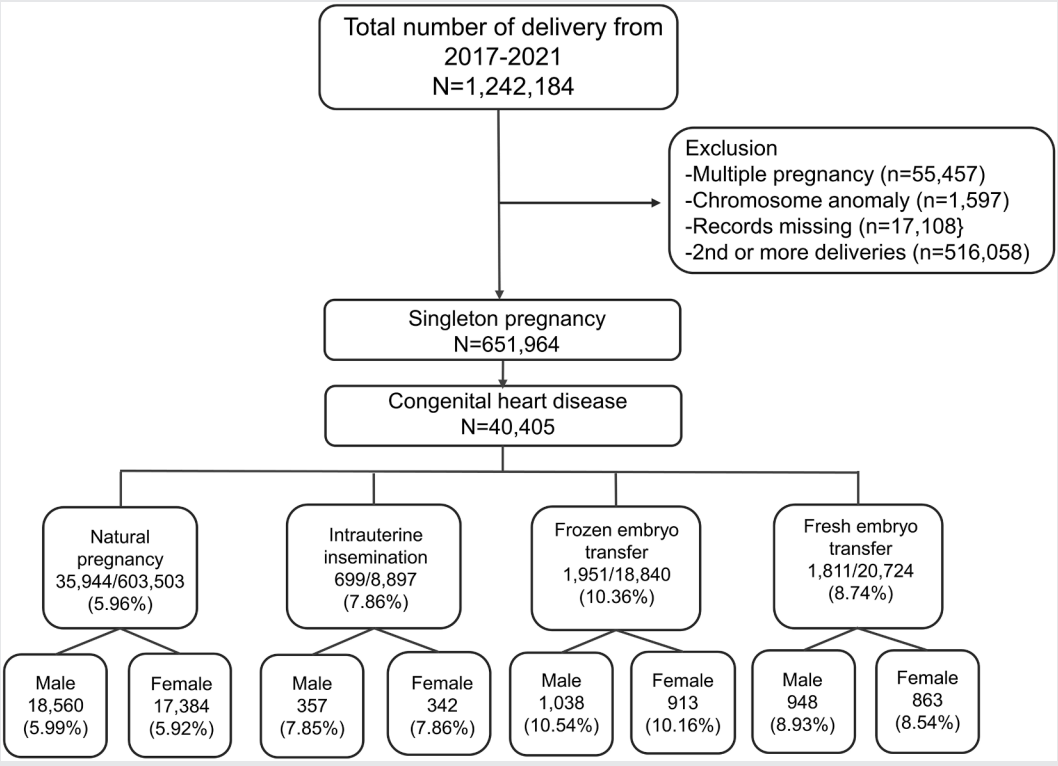
Cohort studies consistently report that male sex is associated with higher incidence of outflow-tract and other severe CHD subtypes such as conotruncal defects, whereas female sex more often correlates with milder lesions such as septal defects or patent ductus arteriosus. Recent genomic investigations further support a genetic basis for this sex bias and beyond genetics, biological sex differences in cardiac development, gene expression, and hormone-mediated signaling, as well as divergent responses to in utero environmental exposures, are hypothesized to contribute to sex-specific vulnerability (12–15).

Herein, we assessed various classifications of CHDs in children conceived through IUI and different ART methods in singleton pregnancies and examined the influence of sex differences.

MATERIALS AND METHODS

The study utilized the Korea National Health Insurance (KNHI) claims database to identify all patients who delivered singletons for the first time between January 1, 2017, and

FIGURE 1



Flowchart of the enrollment of study participants.

Kim. Risk of congenital heart disease in singleton. Fertil Steril 2026.

December 31, 2021, along with their child pairs (n = 651,964). Figure 1 demonstrates the flowchart of study population. Children with CHDs were defined as those diagnosed within the first year of life. The exclusion criteria were multiple pregnancies, chromosomal anomalies, and the absence of records. Delivery week and birth status were verified using the National Health Screening Program for Infants and Children (NHSP-IC) database. However, information on termination or stillbirth owing to birth defects was unavailable. This study followed the Stretching the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. The study was approved by the Institutional Review Board (2025GR0070), which waived the requirement for informed consent.

ART was defined according to the criteria established in a previous report (16). The main predictive variable was ART exposure, including IUI, fresh ET, and frozen ET.

Study outcomes

The primary outcome of CHD was assessed based on the principal or secondary diagnosis according to the International Classification of Diseases, 10th Revision (ICD-10) (Supplemental Table 1, available online). The secondary outcomes included severe and nonsevere CHDs. Severe CHDs were defined according to a previous study and sex differences in various types of CHDs were also examined. The study categorized various CHDs, including conotruncal (Q200, Q201, Q203, Q213, Q214), atrioventricular septal defect (AVSD) (AVSD: Q212), anomalous pulmonary venous return(APVR) (APVR: Q262, Q263, Q264), left ventricular outflow tract (LVOT) (LVOT; Q230, Q231, Q232, Q233, Q234, Q238, Q244, Q251, Q252, Q253), and right ventricular outflow tract (RVOT) (RVOT: Q220, Q221, Q222, Q223, Q224, Q225, Q226, Q228, Q229, Q243, Q255, Q256) malformation. Ventricular defects (Q210), atrial defects (Q211), and patent ductus arteriosus (PDA) (Q250) were not considered severe. The other classifications, which were ambiguous or could not be categorized were defined as "Others 1 and Others 2" (Others 1: Q202, Q204, Q205, Q206, Q208, Q218, Q240, Q241, Q242, Q245, Q246, Q248, Q254, Q257, Q258, Q260, Q261, Q268) (Others 2: Q209, Q219, Q239, Q249, Q259, Q269).

Covariates

Maternal and neonatal characteristics were collected, including parity, pregnancy-induced hypertension(HTN), chronic HTN before pregnancy, diabetes mellitus(DM) before pregnancy, DM during pregnacy, preterm birth, gestational age at delivery, delivery mode, sex of baby, birthweight, low birthweight, macrosomia, and polycystic ovarian syndrome.

Statistical analysis

Continuous variables are reported as means ± SD, whereas categorical variables are presented as percentages. Group comparisons for continuous data employed t-tests or analysis of variance, meanwhile, categorical data were analyzed using a χ^2 test. Modified Poisson regression was applied to estimate the adjusted relative risks (aRRs) and 95% confidence intervals (CIs) for various types of CHD risks among the natural conception, IUI, frozen ET, and fresh ET groups. Variables adjusted were maternal age, parity, HTN before pregnancy, DM before pregnancy, sex of baby, and polycystic ovarian syndrome. All statistical tests were two-sided, with significance set at $P < .05$. Statistical analyses were performed using SAS software for Windows (version 9.4; SAS Inc., Cary, NC, USA).

RESULTS

The prevalence of CHD in this claims-based cohort was 6.19%, 619 per 10,000, higher than registry-based cohort, likely reflecting broader diagnostic capture including mild defects and increased surveillance. Maternal age and the rates of primiparity, cesarean section, HTN before and during pregnancy, diabetes before and during pregnancy, low birthweight, and polycystic ovarian syndrome were significantly elevated in the IUI and ART group (Table 1). The incidence rate of hypertension during pregnancy was high in the IUI and ART group, particularly in the frozen ET group. The rate of low birthweight was highest in IUI group followed by fresh ET and frozen ET. The fresh ET group had a high incidence of preterm births, whereas the frozen ET group was more likely to deliver macrosomia babies.

Stratification of the different CHD types was based on a previous report (17). The overall prevalence of CHD was significantly higher in the IUI and ART group compared with the prevalence in the natural conception group, with the highest rates observed in the frozen ET group, followed by the fresh ET and IUI groups (Table 1). Conotruncal and RVOT defects were most common in the frozen ET group, followed by the fresh ET and IUI groups. The AVSD rate was higher in the ET group. The prevalence of LVOT defects was highest in the frozen ET group, followed by the IUI and fresh ET groups. Minor CHD, including septal defects and PDA, had the highest prevalence in the frozen ET group, followed by the fresh ET and IUI groups. No significant differences in the rate of APVR were observed among groups.

Modified Poisson regression analysis

After adjustment for maternal age, parity, hypertension, and DM before pregnancy, sex of baby and polycystic ovary syndrome, frozen ET was associated with a significant risk of overall CHD (adjusted risk ratio [aRR], 1.55 (95% CI, 1.47–1.62)) followed by fresh ET and IUI compared with natural conception. Frozen ET was solely associated with an increased risk of RVOT (aRR 1.82, 95% CI, 1.41–2.32). Septal defects and PDA were all significantly increased in IUI and ET compared with natural conception, whereas the highest risk was observed in frozen ET (Table 2). A similar pattern was observed across IUI and the different types of embryo transfer even when the analysis was restricted to major CHDs with a lower potential for detection bias, excluding PDA, septal defects and others (Supplemental Table 2).

TABLE 1

Characteristics and demographics of study population by IUI and fresh and frozen ET in singleton pregnancies.

	Natural conception n = 603,503 (%)	IUI(n=8,897)	Frozen ET n = 18,840 (%)	Fresh ET n = 20,724 (%)	*P*-value
Maternal age	31.8 ± 4.1	34.1 ± 3.3	35.5 ± 3.6	36.0 ± 3.6	<.0001
Cesarean section	320,731 (53.1)	5,374 (60.4)	14,455 (76.7)	13,878 (67.0)	<.0001
Hypertension before conception	4,544 (0.75)	111 (1.25)	339 (1.80)	359 (1.73)	<.0001
Diabetes before conception	8,776 (1.5)	273 (3.1)	588 (3.1)	692 (3.3)	<.0001
Hypertension during pregnancy	32,011 (5.3)	605 (6.8)	1,465 (7.8)	1,383 (6.7)	<.0001
Diabetes during pregnancy	58,351 (9.7)	1,376 (15.5)	2,999 (15.9)	3,445 (16.6)	<.0001
Polycystic ovarian syndrome	21,086 (3.5)	2,014 (22.6)	3,767 (20.0)	3,079 (14.9)	<.0001
Preterm birth	16,812 (2.8)	394 (4.4)	947 (5.0)	1,056 (5.1)	<.0001
Gestational age at delivery	39.6 ± 1.5	39.3 ± 1.6	39.2 ± 1.7	39.1 ± 1.6	<.0001
Male sex	309,778 (51.3)	4,547 (51.1)	9,851 (52.3)	10,620 (51.2)	0.293
Birthweight	3.2 ± 0.4	3.1 ± 0.5	3.2 ± 0.5	3.1 ± 0.5	<.0001
Low birthweight	22,053 (3.7)	602 (6.8)	950 (5.0)	1,379 (6.7)	<.0001
Macrosomia	19,828 (3.3)	202 (2.3)	811 (4.3)	520 (2.5)	0.045
CHDs	35,944 (6.0)	699 (7.9)	1,951 (10.4)	1,811 (8.7)	<.0001
Major CHDs	17,138 (2.84)	335 (3.77)	884 (4.69)	801 (3.87)	<.0001
Conotruncal anomaly	508 (0.1)	7 (0.1)	26 (0.1)	24 (0.1)	0.013
AVSD	120 (0.02)	1 (0.01)	7 (0.04)	8 (0.04)	0.025
APVR	85 (0.01)	1 (0.01)	4 (0.02)	3 (0.01)	0.679
LVOT	367 (0.06)	7 (0.08)	20 (0.11)	12 (0.06)	0.223
RVOT	1,139 (0)	18 (0.2)	71 (0.4)	47 (0.2)	<.0001
Septal defect	17,074 (2.8)	341 (3.8)	993 (5.3)	913 (4.4)	<.0001
PDA	4,733 (0.8)	95 (1.1)	252 (1.3)	257 (1.2)	<.0001
Others	493 (0.1)	9 (0.1)	30 (0.2)	29 (0.1)	<.0001
Others 2	1,111 (0.2)	23 (0.3)	58 (0.3)	42 (0.2)	<.0001

Notes: Major CHDs; conotruncal, AVSD, LVOT and RVOT malformation.
Table 1 shows perinatal characteristics and different types of CHDs among study population. The prevalence of CHD was significantly higher in the IUI and ART group than the prevalence in the natural conception group, with the highest rates observed in the frozen ET group, followed by the fresh ET and IUI groups.
Abbreviations: IUI = intrauterine insemination, ET = embryo transfer, CHD = congenital heart disease, AVSD = atrioventricular septal defect, APVR = anomalous pulmonary venous return, LVOT = left ventricular outflow tract anomaly, RVOT = right ventricular outflow tract anomaly, PDA = patent ductus arteriosus.

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Sex differences in the risk of CHD

When analyzed separately for males and females, overall CHD risk increased in both IUI and ET, with the highest risk observed in frozen ET (Supplemental Table 3 and 4). By defect subtype, RVOT defects showed a significant increase only in the frozen ET group for both sexes. Septal defects and PDA were increased in males following both IUI and ET, with the greatest increase observed in frozen ET; a similar pattern of septal defects was also noted in females. PDA in females showed the highest increase seen in frozen ET followed by IUI and fresh ET. In females, the risk of defects categorized in the "Others 2" group was also increased in the frozen ET group.

When stratified by sex, only in natural pregnancies were male infants found to have a higher risk of conotruncal anomalies and LVOT defects compared with females, whereas the risk of PDA was lower in males. However, no significant sex differences were observed in IUI, frozen ET, or fresh ET pregnancies (Table 3).

DISCUSSION

The etiology of CHD is known to be <15% and includes genetic factors, syndromes, environmental factors, maternal factors, and infection. The use of ART has become a prominent factor, gaining attention due to the increasing prevalence of infertility. Concerns regarding the health of children raise doubts and require further exploration. This population-based study highlighted the influence of IUI and fresh and frozen ET on the risk of CHDs in singleton pregnancies. One of the main strengths of the study is the stratification of various types of ART methods and sex differences in CHD, aiding in understanding the effects of ART on children's hearts. Conflicting results have been reported regarding the incidence of CHDs after ART (9, 18–21). A recent meta-analysis concluded that the risk of CHD after ART remains inconclusive (22). Most of these studies did not differentiate between singleton and multiple pregnancies and different types of ET. Additionally, the studies did not compare natural conception, IUI, or fresh or frozen ET and their influence on various subtypes of CHD. One large cohort study identified an increased risk of major CHDs in singleton and multiple pregnancies conceived by ART, but observed no differences in CHD among ICSI, fresh, and frozen IVF-ET compared with natural conception in singleton pregnancies (3). This study has a limitation in that IUI was included in the natural conception group, potentially diluting the effect of ART on CHD risk.

Few studies have investigated the risk of congenital malformations in fresh vs. frozen ET. A previous meta-analysis of neonatal outcomes in singleton pregnancies demonstrated no differences in congenital malformations (23); however, the sample size was too small for a meaningful comparison. Notably, the evaluation of CHDs remains limited. Evidence

TABLE 2

Risk of congenital heart defects in a singleton liveborn infant conceived by IUI, frozen ET and fresh ET vs. natural conception.

	CHDs		Conotruncal anomaly		RVOT		Septal		PDA		Others 2	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
IUI	1.319 (1.223–1.42)	1.215 (1.126–1.309)	0.935 (0.4–1.819)	0.893 (0.381–1.748)	1.072 (0.648–1.653)	0.999 (0.602–1.547)	1.355 (1.215–1.505)	1.229 (1.101–1.367)	1.362 (1.104–1.657)	1.293 (1.046–1.577)	1.404 (0.902–2.069)	1.332 (0.852–1.972)
frozen ET	1.739 (1.661–1.819)	1.545 (1.474–1.619)	1.64 (1.078–2.379)	1.5 (0.976–2.206)	1.997 (1.557–2.517)	1.822 (1.409–2.32)	1.863 (1.746–1.985)	1.616 (1.512–1.726)	1.706 (1.499–1.931)	1.567 (1.371–1.782)	1.672 (1.27–2.156)	1.575 (1.187-2.05)
fresh ET	1.467 (1.399–1.538)	1.296 (1.234–1.36)	1.376 (0.889–2.023)	1.246 (0.797–1.854)	1.202 (0.885–1.589)	1.097 (0.803–1.462)	1.557 (1.456–1.663)	1.34 (1.25–1.434)	1.581 (1.391–1.789)	1.435 (1.258–1.63)	1.101 (0.797–1.477)	1.044 (0.75–1.411)

Notes: Adjusted for maternal age, primiparity, hypertension, and diabetes before and during pregnancy, baby sex, polycystic ovary syndrome.
The frozen ET was associated with a significant risk of overall CHD followed by fresh ET and IUI compared with natural conception. Frozen ET was associated with an increased risk of RVOT, septal defects, PDA and others 2 while babies born following fresh ET demonstrated no significant increased risks in specific types of CHD such as conotruncal and RVOT.
Abbreviations: IUI intrauterine insemination, ET embryo transfer, CHD congenital heart disease, AVSD atrioventricular septal defect, APVR anomalous pulmonary venous return, LVOT = left ventricular outflow tract anomaly, RVOT = right ventricular outflow tract anomaly, PDA = patent ductus arteriosus.

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TABLE 3

Risk of congenital heart defects by sex stratified by assisted reproductive technology method.

	Natural pregnancy					IUI					Frozen ET					Fresh ET				
	Male n (%)	Female (reference %)	*P*-value	Unadjusted RR	Adjusted RR	Male n (%)	Female (reference %)	*P*-value	Unadjusted RR	Adjusted RR	Male n (%)	Female (reference)	*P*-value	Unadjusted RR	Adjusted RR	Male n (%)	Female (reference)	*P*-value	Unadjusted RR	Adjusted RR
Total CHD	18560 (5.99)	17384 (5.92)	.231	1.012 (0.992–1.034)	1.012 (0.992–1.034)	357 (7.85)	342 (7.86)	0.985	0.999 (0.861–1.158)	0.999 (0.861–1.158)	1038 (10.54)	913 (10.16)	0.392	1.037 (0.949–1.134)	1.042 (0.953–1.139)	948 (8.93)	863 (8.54)	0.326	1.045 (0.953–1.146)	1.047 (0.955–1.148)
Conotruncal	305 (0.1)	203 (0.07)	< .001	1.425 (1.193–1.701)	1.425 (1.193–1.701)	6 (0.13)	1 (0.02)	0.067	5.74 (0.6911–47.678)	5.808 (0.699–48.254)	17 (0.17)	9 (0.1)	0.181	1.724 (0.768–3.867)	1.736 (0.774–3.895)	13 (0.12)	11 (0.11)	0.775	1.124 (0.504–2.51)	1.121 (0.502–2.501)
AVSD	59 (0.02)	61 (0.02)	.635	0.917 (0.641–1.312)	0.917 (0.641–1.312)	0 (0)	1 (0.02)	0.307	-	-	4 (0.04)	3 (0.03)	0.797			6 (0.06)	2 (0.02)	0.179		
APVR	52 (0.02)	33 (0.01)	0.069	1.494 (0.966–2.311)	1.494 (0.966–2.312)	0 (0)	1 (0.02)	0.307	-	-	2 (0.02)	2 (0.02)	0.927			2 (0.02)	1 (0.01)	0.593		
LVOT	211 (0.07)	156 (0.05)	0.018	1.283 (1.043–1.577)	1.282 (1.043–1.577)	3 (0.07)	4 (0.09)	0.662			11 (0.1)	9 (0.1)	0.808			7 (0.07)	5 (0.05)	0.623		
RVOT	574 (0.19)	565 (0.19)	0.528	0.963 (0.858–1.082)	0.963 (0.858–1.082)	8 (0.18)	10 (0.23)	0.571	0.765 (0.302–1.939)	0.775 (0.306–1.964)	35 (0.36)	36 (0.4)	0.613	0.887 (0.557–1.413)	0.887 (0.557–1.413)	24 (0.23)	23 (0.23)	0.980	0.993 (0.56–1.759)	0.99 (0.559–1.754)
Septal defect	8940 (2.89)	8134 (2.77)	0.006	1.042 (1.011–1.074)	1.042 (1.011–1.074)	177 (3.89)	164 (3.77)	0.763	1.033 (0.835–1.277)	1.031 (0.834–1.275)	543 (5.51)	450 (5.01)	0.121	1.101 (0.972–1.248)	1.108 (0.98–1.256)	487 (4.59)	426 (4.22)	0.195	1.088 (0.955–1.239)	1.093 (0.959–1.244)
PDA	2315 (0.75)	2418 (0.82)	0.001	0.908 (0.858–0.961)	0.908 (0.858–0.961)	41 (0.9)	54 (1.24)	0.119	0.726 (0.48–1.090)	0.726 (0.484–1.090)	132 (1.34)	120 (1.33)	0.976	1.004 (0.784–1.285)	1.013 (0.791–1.297)	133 (1.25)	124 (1.23)	0.870	1.021 (0.799–1.303)	1.019 (0.798–1.302)
Others	281 (0.09)	212 (0.07)	0.012	1.257 (1.0515–1.502)	1.257 (1.0515–1.502)	2 (0.04)	7 (0.16)	0.083	0.273 (0.0568–1.316)	0.273 (0.0567–1.315)	16 (0.16)	14 (0.16)	0.909	1.043 (0.509–2.137)	1.050 (0.513–2.152)	19 (0.1)	10 (0.1)	0.124	1.808 (0.841–3.888)	1.829 (0.850–3.935)
Others 2	568 (0.18)	543 (0.18)	0.891	0.992 (0.882–1.116)	0.992 (0.882–1.116)	15 (0.33)	8 (0.18)	0.175	1.794 (0.761–4.231)	1.792 (0.760–4.228)	31 (0.27)	37 (0.36)	0.273	0.767 (0.476–1.236)	0.768 (0.476–1.238)	23 (0.22)	19 (0.19)	0.648	1.152 (0.627–2.115)	1.149 (0.626–2.109)

Notes: Adjusted for maternal age, hypertension, and diabetes before and during pregnancy, polycystic ovary syndrome.
When stratified by sex, only in natural pregnancies were male infants found to have a higher risk of conotruncal anomalies, LVOT defects, and others compared with females, whereas the risks of PDA were lower in males. However, no significant sex differences were observed in IUI, frozen ET, or fresh ET pregnancies.
Abbreviations: IUI = intrauterine insemination, ET = embryo transfer, CHD = congenital heart disease, AVSD = atrioventricular septal defect, APVR = anomalous pulmonary venous return, LVOT = left ventricular outflow tract anomaly, RVOT = right ventricular outflow tract anomaly, PDA = patent ductus arteriosus.

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that frozen ET pregnancies are associated with a higher risk of preeclampsia and large-for-gestational-age babies compared with fresh ET pregnancies (24). The increased risk of preeclampsia may partially explain the elevated incidence of CHDs as preeclampsia is a recognized risk factor for such defects. Consistent with previous findings, the prevalence of hypertension during pregnancy and macrosomia in our study was highest in the frozen ET group compared with the other groups. Further research is warranted to investigate the potential link between frozen ET pregnancies and the heightened risk of CHDs.

Compared with fresh ET, frozen ET requires endometrial preparation with hormone therapy and thawing. The process associated with the preparation for frozen ET may negatively impact the abnormal placentation and fetal heart development. Recent data suggest fetal cardiovascular remodeling, in which right heart changes are predominant in singletons and twins. This remodeling includes enlargement of the atria, right ventricular changes with both systolic and diastolic dysfunction, and a more globular and hypertrophic ventricle response to pressure overload on the right side (25). One hypothesis is that epigenetic dysregulation, such as DNA methylation and histone modification associated with ART, may influence cardiac-regulating genes. This effect could be particularly pronounced due to the freezing and thawing methods in frozen ET (26, 27).

Early placental dysfunction is another hypothesis that leads to fetal CHD (28, 29). Low pregnancy-associated plasma protein A levels and high free beta-human chorionic gonadotropin levels in the first trimester have been observed in ART pregnancies (30). Another study suggested that placental vascular resistance, which affects fetal circulation and heart development, may contribute to CHDs, as evidenced by small placentas with vascular abnormalities in affected children (31, 32). To the best of our knowledge, the underlying pathophysiology of this condition has not been elucidated. Our results may help generate hypotheses regarding the association between ART and nonchromosomal CHDs, as well as the impact of sex differences on CHDs.

Sex disparities have been extensively reported in various fields, and one of the biological causes of these differences may be endothelial and smooth cell dysfunction (33). The sex distribution of adult CHD is similar to that of CHD at birth, with inflow tract malformations, including septal defects, being more common in females, whereas outflow tract malformations are more prevalent in males. In adult studies, differences exist in the subtypes of CHD; septal defects, pulmonary stenosis and atresia, AVSD, Ebstein's anomaly, and PDA are more common in females than in males (34). A Taiwanese national data study reported that simple or minor CHDs were more common in females and severe CHD, including transposition of the great arteries, tetralogy of Fallot, and aortic stenosis, were more prevalent in males (35). Variations in susceptibility to CHD between sexes may be attributed to differing vulnerabilities to specific pathogenic mechanisms.

Several biological and clinical mechanisms have been proposed to explain why the sex differences in CHD risk that are typically observed in natural pregnancies, appear to diminish following ART. First, the effect of ART manipulation or underlying maternal conditions, such as old age, unfavorable uterine environment or early placentation stress outweigh the natural sex different embryogenesis therefore it may exert developmental stress on cardiac development (26). Second, the overall elevation in risk after ART pregnancies may obscure sex-specific susceptibility. Third, ART is known to induce epigenetic modifications—such as altered DNA methylation and imprinting disturbances—during very early development, before sex-specific hormonal pathways fully diverge. These epigenetic changes may affect both sexes similarly. Finally, embryo selection inherent in ART may reduce natural variation in developmental vulnerability, potentially equalizing the baseline risk between male and female embryos. Understanding the differences and vulnerabilities associated with ART is crucial for tailoring therapeutic approaches to better address sex-specific risks in CHD.

This study is the first large-scale investigation focused on an East Asian population and adds significance to the literature. Considering the minimal differences between ICSI and IVF, we specifically examined the outcomes of fresh and frozen ET in IVF-ET. A key strength of this study lies in its detailed analysis of CHD types stratified by the child's sex.

One limitation was that the classification criteria varied, making it difficult to determine whether cyanosis was present in certain cases. In the case of septal defects, the classification does not differentiate whether intervention is required. Second, pregnancy termination, mortality, and loss to follow-up were not considered in this study. Third, the use of donor oocytes or embryo stage at transfer, number of embryos transferred, causes of infertility, subfertility, and different endometrial preparations in frozen ET were not considered. Fourth, the overall CHD prevalence was very high in this study compared with international estimates because of broader diagnostic capture and surveillance in ART pregnancy. This was probably due to claims database characteristics, making it impossible to validate each patient. However, the sensitivity analysis excluding milder lesions likely mitigates concerns regarding potential overestimation. Lastly, possible confounding factors such as vitamin or mineral intake, socioeconomic status, and paternal factors were not adjusted for.

CONCLUSION

Congenital heart disease is associated with long-term morbidity and mortality in children; therefore, a life-course care plan should be established. Although ART is a safe and essential method for achieving pregnancy, we observed an increased risk of CHD, particularly in pregnancies conceived through frozen embryo transfer. These findings suggest that even with single-embryo transfer, the risk of fetal cardiac defects may rise, underscoring the need for appropriate counseling of patients and families as well as careful evaluation through detailed fetal cardiac assessment. Furthermore, although additional research is needed, our findings highlight that sex-related differences in CHD risk may also be altered in ART pregnancies, a point that should not be overlooked.

CRediT Authorship Contribution Statement

Ho Yeon Kim: Writing – original draft, Methodology, Data curation, Conceptualization. **Ki Hoon Ahn:** Writing – review & editing, Formal analysis. **Soon-Cheol Hong:** Writing – review & editing, Formal analysis. **Min-Jeong Oh:** Writing – review & editing, Supervision, Data curation. **Geum Joon Cho:** Validation, Formal analysis, Conceptualization.

Declaration of Interests

H.Y.K. has nothing to disclose. K.H.A. has nothing to disclose. S-C.H. has nothing to disclose. M-J. O. has nothing to disclose. G.J.C. has nothing to disclose.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be found online at https://doi.org/10.1016/j.fertnstert.2026.03.034.

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Cardiopatía congénita en embarazo único concebido mediante tecnología de reproducción asistida.

Objetivo: Evaluar el riesgo de cardiopatía congénita (CC) en la descendencia de primigestas con embarazos únicos concebidos mediante tecnología de reproducción asistida (TRA).

Diseño: Estudio de cohorte retrospectivo a nivel nacional.

Sujetos: Pacientes con embarazos únicos que culminaron en parto entre 2017 y 2021.

Exposición: Se compararon embarazos únicos concebidos mediante concepción natural, inseminación intrauterina, transferencia de embrión fresco y transferencia de embrión congelado.

Medidas Principales de Resultado: El resultado principal fue la tasa de cardiopatías congénitas en la descendencia. Los resultados secundarios incluyeron la distribución de subtipos de cardiopatía congénita, diferencias según el sexo y desenlaces perinatales.

Resultados: Entre 651,964 pares madre-hijo, 6.19% fueron diagnosticados con cardiopatía congénita, con la incidencia más alta observada en el grupo de transferencia de embrión congelado (10.4%). La transferencia de embrión congelado, la transferencia de embrión fresco y la inseminación intrauterina presentaron un incremento en el riesgo de cardiopatía congénita de 54.5%, 29.6% y 21.5%, respectivamente, en comparación con la concepción natural. La transferencia de embrión congelado se asoció con un mayor riesgo de malformaciones del tracto de salida derecho después del ajuste por factores de confusión. Los defectos septales y el conducto arterioso persistente aumentaron tanto en los grupos de inseminación intrauterina como de transferencia embrionaria, con la mayor prevalencia observada en el grupo de transferencia de embrión congelado. Los hallazgos dentro de cada subgrupo por sexo fueron consistentes con las tendencias generales. En las concepciones naturales, los fetos masculinos mostraron un riesgo significativamente mayor de defectos conotruncales y anomalías del tracto de salida del ventrículo izquierdo, pero un menor riesgo de conducto arterioso persistente, en comparación con los fetos femeninos. Sin embargo, en los embarazos logrados mediante inseminación intrauterina y transferencia embrionaria, no se observaron diferencias significativas según el sexo entre los distintos tipos de cardiopatía congénita.

Conclusión: Los embarazos únicos logrados mediante inseminación intrauterina y TRA, especialmente mediante transferencia de embrión congelado, se asociaron con una mayor incidencia de cardiopatía congénita en la descendencia en este estudio poblacional. Las diferencias por sexo dejaron de influir en el riesgo de cardiopatía congénita en embarazos logrados mediante inseminación intrauterina o TRA. Estos hallazgos deben comunicarse a los pacientes durante la asesoría previa a TRA. Debido a que la definición de desenlaces se basó en datos administrativos que incluyeron lesiones leves y diagnósticos neonatales tempranos, la prevalencia absoluta de cardiopatía congénita puede parecer mayor que la estimada en registros clínicos.