

ORIGINAL RESEARCH

Assisted Reproductive Technology and Risk of Congenital Heart Defects in the Offspring: A Systematic Review and Meta-Analysis

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BACKGROUND: To date, >10 million children have been conceived via assisted reproductive technology (ART) globally. However, there are some concerns about potential adverse outcomes associated with ART-conceived pregnancies, including the risk of congenital heart defects (CHDs). This meta-analysis aimed to evaluate the association between ART and the risk of major CHDs as well as their specific subtypes.

METHODS: Major electronic databases were screened for studies comparing the incidence of CHD following ART-conceived pregnancies versus spontaneous conception. The primary end point was study-defined incidence of CHDs. Secondary end points included incidence of tetralogy of Fallot, transposition of the great arteries, aortic coarctation, ventricular septal defect, atrial septal defect, pulmonary valve atresia, tricuspid valve atresia, and hypoplastic left heart. Pairwise meta-analyses were performed using frequentist random-effect models to calculate risk ratios and 95% CIs.

RESULTS: Thirteen studies, encompassing a total of 45916925 subjects (4986 conceived via ART), were included in the quantitative synthesis. ART was significantly associated with a higher risk of major CHD compared with natural pregnancy (risk ratio, 2.35 [95% CI, 1.68–3.28]), with significant heterogeneity across the studies. An increased risk of tetralogy of Fallot, ventricular septal defect, and atrial septal defect following ART-conceived pregnancies was found, while no difference was found on other CHDs. Prespecified sensitivity analyses were in line with the primary findings of the meta-analysis.

CONCLUSIONS: Our meta-analysis shows a potential link between ART and increased risk of major CHDs, particularly on tetralogy of Fallot, ventricular septal defect, and atrial septal defect.

Key Words: assisted reproductive technology ■ congenital heart disease ■ meta-analysis ■ pregnancy outcomes

Congenital heart defects (CHDs) represent the most common group of congenital anomalies, affecting ≈1% to 2% of live births and significantly contributing to perinatal morbidity and death worldwide.^{1–3}

These anomalies encompass a broad clinical spectrum, from minor defects to severe, life-threatening conditions such as tetralogy of Fallot (ToF), transposition of the great arteries (TGA), and hypoplastic left

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CLINICAL PERSPECTIVE

What Is New?

- In this large meta-analysis of >45 million pregnancies, conception via assisted reproductive technology was associated with a higher risk of major congenital heart defects, with the excess risk driven primarily by tetralogy of Fallot and septal defects rather than uniformly across all defect subtypes.

What Are the Clinical Implications?

- Although the absolute risk remains low, these findings support increased clinical awareness and consideration of targeted fetal cardiac evaluation in pregnancies conceived via assisted reproductive technology to facilitate early diagnosis, counseling, and perinatal management of clinically significant congenital heart defects.

Nonstandard Abbreviations and Acronyms

ART	assisted reproductive technology
ICSI	intracytoplasmic sperm injection
TGA	transposition of the great arteries
ToF	tetralogy of Fallot

heart syndrome.^{4,5} Despite major advances in neonatal and pediatric cardiology, CHDs remain a leading cause of death related to congenital abnormalities and impose a considerable burden on health care systems.⁶ Assisted reproductive technology (ART) has revolutionized infertility treatment.⁷ To date, >10 million children have been conceived through ART globally, with ART births accounting for ≈3.0% and 2.3% of all live births in Europe and the United States, respectively.^{8,9} However, concerns persist about potential adverse outcomes in ART-conceived pregnancies, including preterm birth, low birth weight, and congenital anomalies, particularly CHDs.¹⁰

Indeed, the association between ART and CHD risk has been widely investigated but remains controversial.^{11–13} Several large population-based studies have reported a higher prevalence of CHDs among ART-conceived offspring, with estimates suggesting a 30% to 70% excess risk, whereas others have found no meaningful difference after adjustment for major confounders.^{14–17} These discrepancies likely reflect differences in study design, population characteristics, ART techniques, and diagnostic criteria, underscoring

the need for an updated and comprehensive quantitative synthesis. Evidence in singleton pregnancies is particularly inconsistent, as some analyses suggest that the association persists even among singletons, while others attribute it to factors related to multiple gestations.^{14,15,18,19} Moreover, most prior studies have treated CHDs as a single outcome, without differentiating between major defects and specific subtypes. Consequently, it remains unclear whether ART preferentially increases the risk of particular lesions or exerts a uniform effect across categories. Furthermore, uncertainty also persists about the impact of specific ART modalities, as differences in gamete manipulation, fertilization technique, and culture environment have been proposed to influence early embryogenesis, but available evidence is conflicting.^{20,21}

To better characterize the association between ART and CHDs, we conducted a systematic review and meta-analysis. By incorporating recently published, large-scale studies,^{22–25} we aimed to provide more precise estimates of relative risk for major and subtype-specific CHDs, refining current evidence and informing prenatal screening strategies for ART pregnancies.

METHODS

This study was prospectively registered in the International Prospective Register of Systematic Reviews database (CRD420251006295), and no amendments were made after registration. It was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 recommendations (Table S1).^{26,27} Ethical approval was waived due to the nature of the research. All meta-analytic data are available upon reasonable request to the corresponding author. The authors declare that all supporting data are available within the article and its online supplemental files.

Eligibility Criteria, Search Strategy, Data Extraction, and Qualitative Assessment

Studies were included if they met the following criteria: (1) They evaluated the effects of any ART compared with natural pregnancy; and (2) they reported at least 1 end point of interest. Studies that analyzed multiple pregnancies only were excluded. No restrictions were imposed on the basis of patients' age, sex, race and ethnicity, or language of publication.

An electronic search of Medline through PubMed, Web of Science, and Scopus databases was performed from database inception until February 2025. The detailed search strategy for each database is reported in Table S2. Websites of leading cardiology societies, news outlets, and reference lists of eligible studies were also reviewed. Three investigators (C.L.,

A.C., F.M.A.) independently screened articles at the title, abstract, and full-text levels. Disagreements were resolved by consensus, and when consensus could not be achieved, a fourth investigator (K.B.) was consulted. Data on outcomes of interest and population characteristics were independently extracted from each eligible report by 2 coauthors (K.B., C.L.) and entered into dedicated electronic spreadsheets. Any discrepancies were resolved by consensus. Study investigators were not contacted to obtain or confirm unclear data. Before conducting statistical analyses, risk of bias for each included study was evaluated separately by the same 2 coauthors (K.B., C.L.) using the Cochrane's Risk Of Bias In Nonrandomized Studies of Interventions tool, with any disagreements resolved through discussion and consensus.²⁸ Publication bias was assessed visually using contour-enhanced funnel plots and Egger's regression test.²⁹ Moreover, the Grading of Recommendations Assessment, Development, and Evaluation approach was used to assess the certainty of the evidence.³⁰

Study End Points

The prespecified primary end point was study-defined major CHD. Given the heterogeneity in classification across observational studies, we adopted the definition provided by each study. When multiple definitions were reported, priority was given to those aligning with clinically significant CHDs, generally encompassing severe or critical structural defects requiring surgical or catheter-based intervention within the first year of life (eg, conotruncal defects, hypoplastic left heart syndrome, severe valve atresia), whereas isolated minor lesions were generally not included in major CHD definitions. Secondary end points included the individual incidence of ToF, TGA, aortic coarctation, ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary valve atresia, tricuspid valve atresia, and hypoplastic left heart.

Statistical Analysis

To address expected interstudy biological variability and clinical and methodological differences across observational studies, including differences in population characteristics, ART protocols, and outcome definitions, pairwise meta-analyses were performed using frequentist random-effect models to calculate risk ratios (RRs) and 95% CIs for the comparison of ART with natural pregnancy, with treatment-arm continuity correction to account for sparse 2×2 tables and studies with 0-event cells. Statistical heterogeneity was assessed through τ^2 , I^2 , and prediction intervals. For end points with moderate or high heterogeneity, individual trial contributions were examined to identify potential outliers.

Sensitivity analyses were conducted to assess the robustness of the findings. These included analyses restricted to studies not deemed at serious risk of bias, studies conducted within the same country, studies with at least 1000 subjects in the exposed cohort, and analyses limited to studies published after 2010, to account for potential effects of advances in ART techniques and changes in the epidemiology of infertility over the past 2 decades. Moreover, a repeat analysis excluding outlying studies was performed for end points with at least moderate heterogeneity. Finally, a repeated random-effects analysis with Hartung–Knapp adjustment was performed to improve CI calibration, particularly given the limited number of studies contributing to several end points, and a sensitivity analysis using a fixed-effects (study-adjusted) model was conducted with binomial regression, including study as a fixed factor.³¹

To further explore potential sources of between-study heterogeneity for the primary end point, random-effects meta-regression analyses were performed using the study-specific log rate ratio for major CHD as the dependent variable. Covariates included mean maternal age in the ART group, publication year, and the proportion of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) procedures. All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Selection and Baseline Characteristics

The study selection process is illustrated in [Figure 1](#). The potentially eligible studies that were excluded are listed in [Table S3](#). After screening, 13 studies encompassing a total of 45916925 pregnancies were included in the quantitative synthesis.^{12,22–25,32–39} As summarized in [Table 1](#),^{12,22–25,32–39} the included studies were predominantly large, population-based cohorts published between 1997 and 2024, with sample sizes ranging from <1000 to >14 million pregnancies. Across studies, ART exposure most commonly included IVF and ICSI, often in combination with other fertility procedures, and ART-conceived pregnancies were consistently characterized by higher maternal age and a lower prevalence of smoking compared with spontaneous conceptions.

The global and individual risks of bias are presented in [Figure 2](#) and [Figure S1](#), respectively. Six studies were classified as having a serious risk of bias, mainly due to potential confounding and participant selection. Visual inspection of funnel plots and Egger's tests revealed no evidence of significant publication bias ([Figure S2](#)).

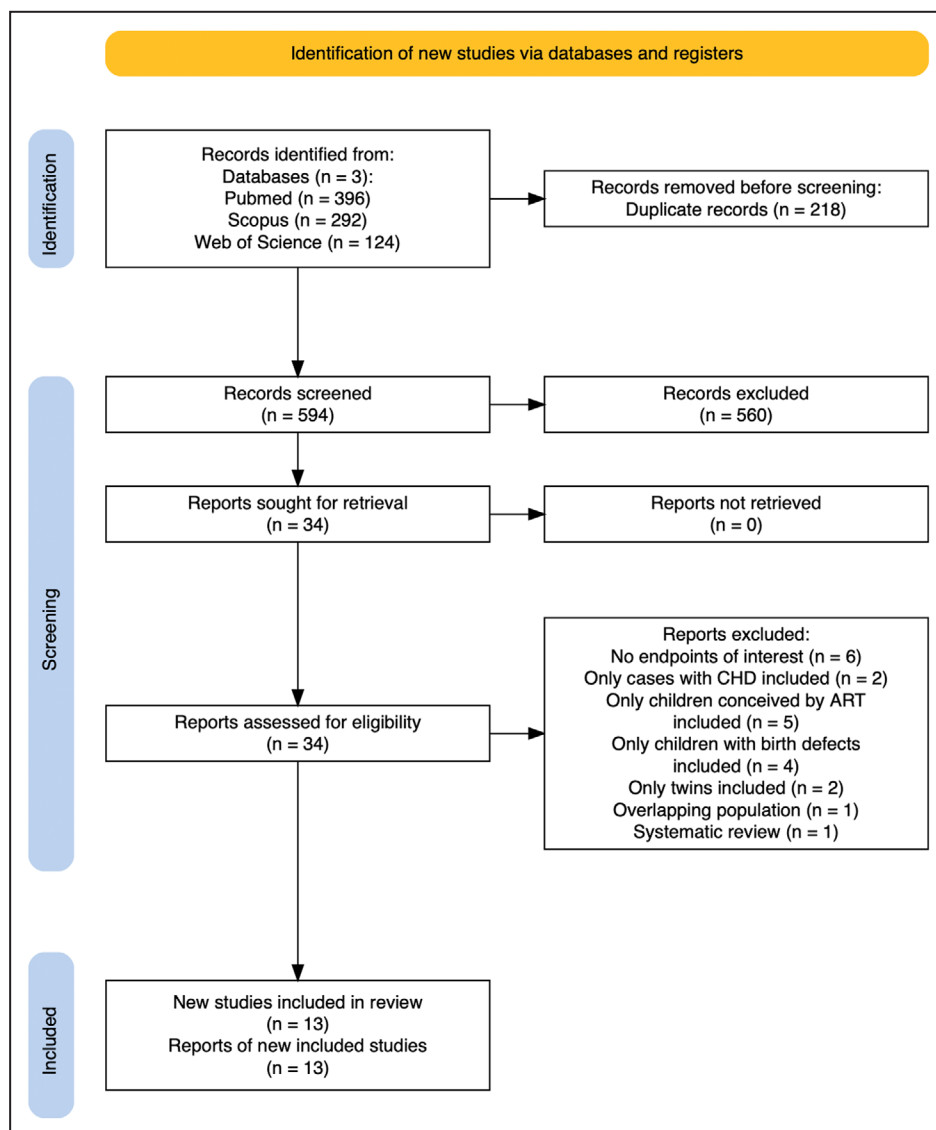


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart. ART indicates assisted reproductive technology; and CHD, congenital heart defect.

Across the pooled population, the weighted mean maternal age was 34.3 years, and 4986 (1.09%) were conceived via ART. Available end points are summarized in Table S4 and study-specific definitions of major CHD in Table S5.

Primary End Point: Association Between ART and Major CHD

ART was significantly associated with a higher risk of major CHD compared with natural pregnancy (RR, 2.35 [95% CI, 1.68–3.28]; Figures 3 and 4^{12,22–25,32–39}). Between-study heterogeneity was substantial ($\tau^2=0.314$; $I^2=98.9\%$; prediction interval, 0.65–8.41), indicating that the strength of the association varied markedly across studies, from no clear effect to a several-fold increase in risk. Eight studies were

identified as the main contributors to this heterogeneity (Figure S3A).^{12,22,25,32,35–38} In the sensitivity analysis after excluding these studies, the association remained significant (RR, 2.21 [95% CI, 1.91–2.56]) with no residual heterogeneity ($\tau^2=0.000$; $I^2=0\%$; prediction interval, 1.80–2.72; Figure S4A).

Secondary End Points: Subtype-Specific Associations

ART was associated with an increased risk of ToF (RR, 1.58 [95% CI, 1.27–1.97]) and septal defects, including VSD (RR, 1.40 [95% CI, 1.20–1.64]), and ASD (RR, 1.40 [95% CI, 1.10–1.78]). No significant differences were observed for TGA, hypoplastic left heart, or valvular atresia with ART compared with natural pregnancies (Figure 3). Complete forest plots and

Table 1. Characteristics of the Included Studies

Author, year	Assisted reproductive technology	Number of children included	Maternal age at conception, y, %	Maternal BMI, %, kg/m ²	Maternal smoking status, %
Sargisian et al 2024 ²⁵	ICSI, IVF, FET	7 747 637	33.4 (I); 29.3 (C)	<18.5: 2.4 (I); 3.5 (C) 18.5–24.9: 63.4 (I); 63.4 (C) 25–29.9: 24.2 (I); 22.4 (C) >30: 10 (I); 10.8 (C)	5.9 (I); 12.3 (C)
Appiah et al 2024 ²⁴	IVF, GIFT, ZIFT, and other infertility treatment (non-ART, AI, IUI, or use of other fertility procedures and fertility-enhancing drugs for initiating pregnancy)	9553676	35.2 (I); 26.9 (C)	26.3 (I); 26.5 (C)	0.9 (I); 6.2 (C)
Rasouli et al 2024 ²³	ICSI, IUI, IVF, OI, and surrogacy	109	31.2 (I); 28.83 (C)	NR	NR
Wei et al 2024 ²²	IVF; ICSI; assisted hatching; embryo biopsy; preimplantation genetic testing; embryo transfer; GIFT; ZIFT; gamete and embryo cryopreservation; semen, oocyte, and embryo donation; and gestational carrier cycles	1 001 593	<30: 18.0 (I); 48 (C) 30–34: 35.3 (I); 33.7 (C) 35–39: 31.3 (I); 15.3 (C) >40: 15.3 (I); 3 (C)	NR	NR
Wen et al 2020 ¹²	ICSI, IVF	507 390	35.8 (I); 30.3 (C)	NR	1.4 (I); 10.2 (C)
Shechter-Maor et al 2018 ³⁷	ART	11 862 780	<25: 1.02 (I); 31.06 (C) 25–29: 11.81 (I); 28.59 (C) 30–34: 33.32 (I); 25.62 (C) 35–39: 32.28 (I); 11.88 (C) 40–44: 16.11 (I); 2.69 (C) >45: 5.46 (I); 0.17 (C)	<18.5: 2.74 (I); 3.88 (C) 18.5–24.9: 55.18 (I); 46.88 (C) 25–29.9: 24.26 (I); 25.45 (C) >30: 17.82 (I); 23.8 (C)	0.53 (I); 7.16 (C)
Shamshirsaz et al 2017 ³⁶	IVF, GIFT, and fertility-enhancing drugs, AI or IUI	14 242 267	<25: 1.06 (I); 30.64 (C) 25–29: 11.67 (I); 28.79 (C) 30–34: 33.62 (I); 25.87 (C) 35–39: 32.26 (I); 11.92 (C) 40–44: 15.95 (I); 2.62 (C) >45: 5.44 (I); 0.15 (C)	<25: 55.65 (I); 48.37 (C) 25–35: 34.11 (I); 37.47 (C) >35: 10.25 (I); 14.16 (C)	0.54 (I); 8.07 (C)
Schofield et al 2017 ³⁸	OI, IUI, IVF, ICSI	818	NR	NR	NR
Iwashima et al. 2017 ³⁹	OI, AI, IVF, ICSI	2746	<20: 0.0 (I); 1.1 (C) 20–24: 0.5 (I); 8.3 (C) 25–29: 10.8 (I); 30.2 (C) 30–34: 33.8 (I); 36.7 (C) 35–39: 42.4 (I); 19.3 (C) >40: 12.5 (I); 4.4 (C)	NR	NR
Heisey et al 2015 ³⁵	IVF, ICSI, GIFT	1 137 172	34.9 (I); 28.7 (C)	NR	3.4 (I); 12.4 (C)
Wen et al 2010 ³⁴	IVF, ICSI	2954	35.1 (I); 33.8 (C)	NR	3.83 (I); 12.09 (C)
Koivurova et al 2002 ³³	IVF	873	NR	NR	NR
Kurinczuk et al 1997 ³²	ICSI	100 874	31.2 (I); 27.9 (C)	NR	NR

AI indicates artificial insemination; ART, assisted reproductive technology; BMI, body mass index; C, control; FET, frozen embryo transfer; GIFT, gamete intrafallopian transfer; I, intervention; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; NR, not reported; OI, ovulation induction; and ZIFT, zygote intrafallopian transfer.

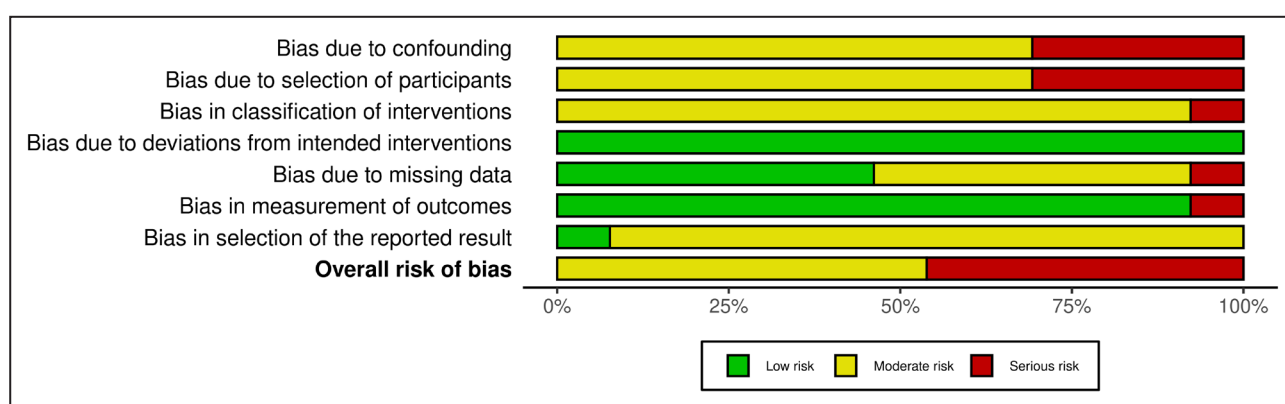


Figure 2. Global risk of bias.

study-specific contributions are shown in Figure S5. Substantial heterogeneity was observed only for TGA ($\tau^2=0.217$; $I^2=63.7\%$; prediction interval, 0.22–8.76), indicating that the observed effects differed meaningfully between studies, which was primarily driven by a single study (Figure S3B). After excluding the trial that contributed mainly to heterogeneity (Figure S3B), the results were consistent (RR, 0.99 [95% CI, 0.74–1.32]; $\tau^2=0.000$; $I^2=0\%$; prediction interval, 0.53–1.88; Figure S4B).

Meta-Regression Analysis: Impact of ART Modality

Meta-regression analyses did not identify maternal age, publication year, or the proportion of intracytoplasmic sperm injection procedures as significant modifiers of the association between ART and major CHD. A borderline positive association was observed with the proportion of IVF procedures, suggesting that studies with greater IVF use tended to report numerically stronger associations with CHD risk, although this did not reach conventional statistical significance ($\beta=0.01$ [95% CI, –0.0003 to 0.03]; $P=0.054$; Table 2).

Sensitivity Analyses

Analyses restricted to studies with low or moderate risk of bias, large sample sizes (>1000 ART-conceived pregnancies), conducted within a single country, limited to studies published after 2010, as well as the sensitivity analyses using Hartung–Knapp adjustment or fixed-effects (study-adjusted) models yielded results consistent with the main analysis (Tables S6–S10, Figure 4, Figure S5).

Certainty of Evidence

The overall quality of evidence was deemed low for major CHD, ToF, and VSD. The remaining outcomes were graded with very low certainty (Table S11).

DISCUSSION

The main findings of this meta-analysis of >45 million pregnancies can be summarized as follows: (1) conception via ART was associated with a significantly increased risk of major CHDs compared with natural conception, with a pooled RR of 2.35; and (2) ART was associated with an increased risk of specific subsets of CHDs, particularly ToF, and septal defects, including ASD and VSD.

Our results are broadly consistent with large, contemporary registry-based cohorts, which have generally reported an increased risk of CHDs among ART-conceived offspring.^{22–25,36,37} Furthermore, our study updates and extends prior meta-analyses. Indeed, an early CHD-specific meta-analysis by Giorgione et al reported an excess risk (pooled odds ratio, 1.45 overall; 1.55 in singleton IVF), consistent with our results but smaller in magnitude, likely due to broader end point definitions, older study periods, and the absence of recent high-quality data sets included in our analysis.¹¹ A recent broad anomaly meta-analysis by Bhat et al⁴⁰ found only a modest increase in overall congenital anomalies after ART; however, that review pooled all congenital anomalies and was not focused on major CHD. Similarly, Gullo et al⁴¹ reported a signal largely for minor CHDs and concluded that evidence for major CHDs was insufficient given the limited size and heterogeneity of available data. Conversely, by including more recent and substantially larger registries, our analysis demonstrates a clear and consistent association with major CHDs that persists after rigorous sensitivity analyses eliminating heterogeneity, thereby strengthening causal inference. Notably, some earlier studies highlighted plurality as the principal mediator of risk, suggesting no significant excess among singletons.^{25,34} However, our meta-analysis specifically excluded cohorts restricted to multiple gestations and still demonstrated a robust association with major CHD, even after removing studies that drove heterogeneity.

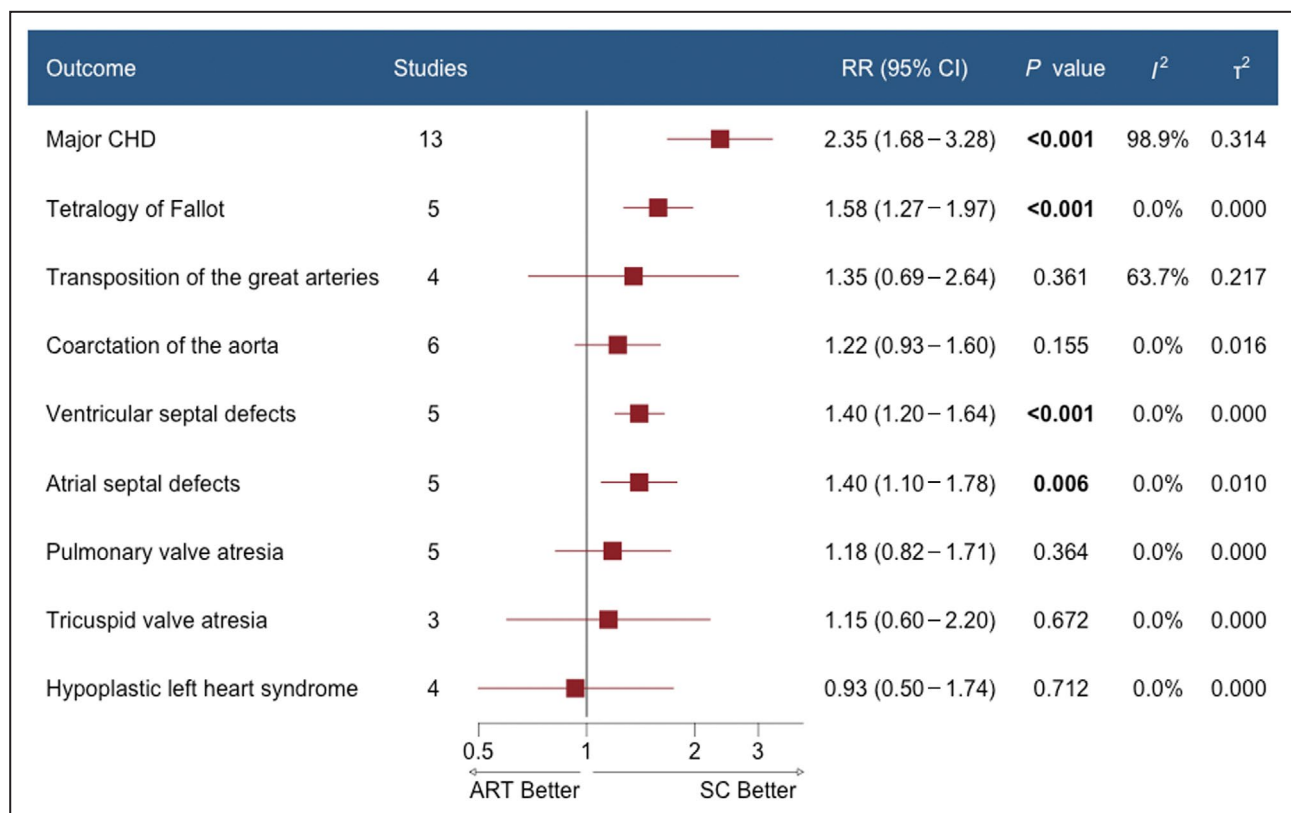


Figure 3. Forest plot presenting a summary of meta-analysis results.

ART indicates assisted reproductive technology; CHD, congenital heart defect; RR, risk ratio; and SC, spontaneous conception.

This indicates that plurality alone does not explain the observed excess, and the consistency of our findings with reports restricted to singleton populations further strengthens this interpretation.^{24,35}

An important novelty of our study is the demonstration that the risk of CHDs associated with ART is not uniform across subtypes. Previous population-based studies often reported an excess of “cyanotic CHD” as a broad category without distinguishing which lesions were driving the signal.^{24,36,37} Our analysis refines this evidence by showing that the excess risk is driven primarily by a 58% increase in ToF and a 40% increase in VSD and ASD, whereas TGA and other severe cyanotic lesions were not significantly increased, even after sensitivity correction. This selective pattern suggests that ART may preferentially affect developmental pathways involved in cardiac septation and conotruncal morphogenesis. In particular, the specific signal for ToF, but not for TGA or hypoplastic left heart, raises the hypothesis that ART-related factors may interfere with endocardial cushion development or neural crest cell migration, rather than broadly disrupting all conotruncal processes.^{42,43} Accordingly, animal and human studies have shown that ART procedures, including ovarian hyperstimulation, in vitro gamete and embryo manipulation, and exposure to culture media, can induce

epigenetic changes affecting imprinted genes and key signaling cascades (eg, Notch, BMP, and Wnt), which are critical for cardiac septation and outflow tract remodeling.^{44–46} However, this remains speculative and further mechanistic studies are needed to clarify these pathways.

Furthermore, evidence about ART modality remains inconclusive. Indeed, our meta-regression showed only a borderline trend with the proportion of IVF procedures ($P=0.054$), and data on laboratory practices (culture media, cryopreservation protocols) were lacking. Early ICSI-era cohorts suggested strong cardiovascular signals, but these findings may not reflect contemporary techniques.³²

The clinical implications of our findings are relevant, especially considering the global rise in ART use. Although the absolute risk of CHDs remains low, the relative increase observed underscores the importance of incorporating this information into counseling, prenatal screening, and postnatal care. Targeted fetal echocardiography may be reasonable in ART pregnancies to enable early detection of CHDs and timely referral to an obstetric specialist for appropriate management. Clinicians should also discuss this modest but significant increase in CHD risk alongside other established ART-related risks, such as prematurity and

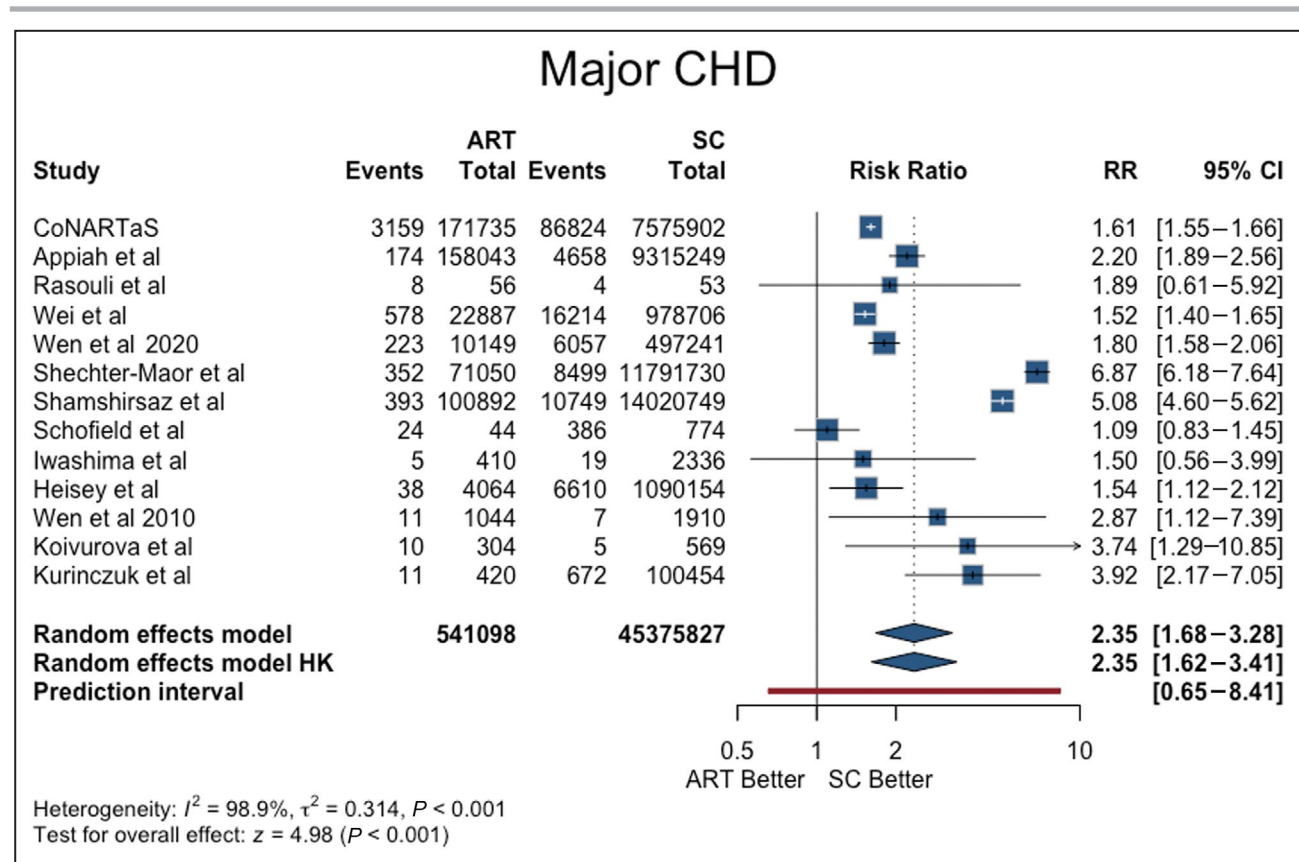


Figure 4. Forest plots presenting the results of the meta-analysis for the primary end point.^{12,22–25,32–39}

ART indicates assisted reproductive technology; CHD, congenital heart defect; HK, Hartung–Knapp adjustment; RR, risk ratio; and SC, spontaneous conception.

low birth weight, to support informed shared decision making.⁴⁷ Notably, while recent evidence confirms that ART does not increase the long-term cardiovascular risk for mothers, our findings highlight a measurable cardiovascular impact on offspring, emphasizing the need for vigilance in fetal and neonatal follow-up.⁴⁸ Future research should aim to clarify the contribution of ART procedures versus underlying parental factors. Large-scale prospective studies with detailed data on ART techniques, gamete source, and embryo handling are required, ideally coupled with genetic and epigenetic profiling to explore biological mechanisms such as altered imprinting, signaling pathways, or placental dysfunction. Finally, long-term follow-up of

ART-conceived individuals is essential to determine whether the increased risk of CHD extends to lifelong cardiovascular morbidity, thereby informing screening strategies beyond the perinatal period.

Limitations

This study has several limitations. First, all included studies were observational, making the findings inherently susceptible to residual confounding. Considering the study-level character of the meta-analysis, adjustment for potentially important factors, such as ethnicity, parental comorbidities, lifestyle factors, infertility pathogenesis, maternal age, and plurality, was not

Table 2. Meta-Regression Analyses for Major CHD

Predictor	β coefficient for log RR (95% CI)	P value	R ² , %	Residual I ² , %
Maternal age, per 1-y increase	0.004 (−0.07 to 0.08)	0.92	0.0	90.0
Publication year, per 1-y increase	−0.03 (−0.07 to 0.02)	0.21	3.85	98.4
ICSI proportion, per 1% increase	0.01 (−0.001 to 0.02)	0.07	49.4	75.2
IVF proportion, per 1% increase	0.01 (−0.0003 to 0.03)	0.054	22.5	49.7

β coefficients indicate the change in log relative risk for major congenital heart defects associated with each 1-unit increase in the corresponding study-level covariate. Positive values indicate a stronger association between assisted reproductive technology and congenital heart defects as the covariate increases. CHD indicates congenital heart defects; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; and RR, risk ratio.

feasible. Similarly, prematurity represents an additional potential confounder that could not be accounted for in the present analysis. As individual studies rarely reported CHD outcomes stratified by or adjusted for those factors, we were unable to assess their potential mediating or confounding roles formally. Second, substantial heterogeneity was observed across studies, reflecting differences in population characteristics, ART protocols (eg, IVF versus ICSI, fresh versus frozen embryo transfer, culture conditions), and diagnostic criteria. Consistent with this, the estimated between-study variance (τ^2) and wide prediction intervals indicate that variation in effect sizes across studies is clinically relevant relative to the pooled estimate. In some analyses, prediction intervals extended beyond the range of observed study effects, highlighting uncertainty in the estimation of between-study heterogeneity given the limited number of studies and warranting cautious interpretation. While sensitivity analyses reduced heterogeneity and confirmed the robustness of our results, variability in ART practices across countries could not be fully accounted for. Third, registry-based data sets may underreport mild or clinically silent CHDs as well as apply nonuniform diagnostic classifications. However, our primary focus on major CHDs likely mitigates the impact of this limitation. Finally, we lacked access to individual patient-level data, which prevented more granular analyses of ART subtypes, gene–environment interactions, or parental infertility factors.

CONCLUSIONS

Assisted reproductive technology is associated with a higher risk of major CHD and some specific CHD, including VSD, ASD defects, and ToF. While absolute risks remain low, the growing global use of ART amplifies the public health relevance of this association. Considering high heterogeneity across included studies and potential residual confounding, further large, prospective studies are needed to confirm those findings. Furthermore, continued research into mechanistic pathways and ART technique refinements will be essential to optimize safety for future generations.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S11

Figures S1–S5

REFERENCES

- Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. *Adv Exp Med Biol*. 2010;686:349–364. doi: [10.1007/978-90-481-9485-8_20](https://doi.org/10.1007/978-90-481-9485-8_20)
- Liu Y, Chen S, Zühke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol*. 2019;48:455–463. doi: [10.1093/IJE/DYZ009](https://doi.org/10.1093/IJE/DYZ009)
- Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163–172. doi: [10.1161/CIRCULATIONAHA.106.627224](https://doi.org/10.1161/CIRCULATIONAHA.106.627224)
- Baumgartner H, de Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Jung B, Kluin J, Lang IM, Meijboom F, et al. 2020 ESC guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42:563–645. doi: [10.1093/EURHEARTJ/EHAA554](https://doi.org/10.1093/EURHEARTJ/EHAA554)
- Egdy Assenza G, Krieger EV, Baumgartner H, Cupido B, Dimopoulos K, Louis C, Lubert AM, Stout KK, Valente AM, Zeppenfeld K, et al. AHA/ACC vs ESC guidelines for Management of Adults with Congenital Heart Disease: JACC guideline comparison. *J Am Coll Cardiol*. 2021;78:1904–1918. doi: [10.1016/J.JACC.2021.09.010](https://doi.org/10.1016/J.JACC.2021.09.010)
- Bouma BJ, Mulder BJM. Changing landscape of congenital heart disease. *Circ Res*. 2017;120:908–922. doi: [10.1161/CIRCRESAHA.116.309302](https://doi.org/10.1161/CIRCRESAHA.116.309302)
- Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, De Mouzon J, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke ID, et al. The international glossary on infertility and fertility care, 2017. *Hum Reprod*. 2017;32:1786–1801. doi: [10.1093/HUMREP/DEX234](https://doi.org/10.1093/HUMREP/DEX234)
- Smeenk J, Wyns C, De Geyter C, Kupka M, Bergh C, Saiz IC, de Neubourg D, Rezabek K, Tandler-Schneider A, Rugescu I, et al. ART in Europe, 2019: results generated from European registries by ESHRE. *Hum Reprod*. 2023;38:2321–2338. doi: [10.1093/HUMREP/DEAD197](https://doi.org/10.1093/HUMREP/DEAD197)
- Graham ME, Jelin A, Hoon AH, Wilms Floet AM, Levey E, Graham EM. Assisted reproductive technology: short- and long-term outcomes. *Dev Med Child Neurol*. 2023;65:38–49. doi: [10.1111/DMCN.15332](https://doi.org/10.1111/DMCN.15332)
- Zhao J, Yan Y, Huang X, Li Y. Do the children born after assisted reproductive technology have an increased risk of birth defects? A systematic review and meta-analysis. *J Matern Fetal Neonatal Med*. 2020;33:322–333. doi: [10.1080/14767058.2018.1488168](https://doi.org/10.1080/14767058.2018.1488168)
- Giorgione V, Parazzini F, Fesslova V, Cipriani S, Candiani M, Inversetti A, Sigismondi C, Tiberio F, Cavoretto P. Congenital heart defects in IVF/ICSI pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2018;51:33–42. doi: [10.1002/UOG.18932](https://doi.org/10.1002/UOG.18932)
- Wen SW, Miao Q, Taljaard M, Loughheed J, Gaudet L, Davies M, Lanes A, Leader A, Corsi DJ, Sprague AE, et al. Associations of assisted reproductive technology and twin pregnancy with risk of congenital heart defects. *JAMA Pediatr*. 2020;174:446–454. doi: [10.1001/JAMAPEDIATRICS.2019.6096](https://doi.org/10.1001/JAMAPEDIATRICS.2019.6096)
- Tararbit K, Lelong N, Thieulin AC, Houyel L, Bonnet D, Goffinet F, Khoshnood B; the EPICARD Study Group. The risk for four specific congenital heart defects associated with assisted reproductive techniques:

- a population-based evaluation. *Hum Reprod*. 2013;28:367–374. doi: [10.1093/HUMREP/DES400](#)
14. Qin JB, Sheng XQ, Wu D, Gao SY, You YP, Yang TB, Wang H. Worldwide prevalence of adverse pregnancy outcomes among singleton pregnancies after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2017;295:285–301. doi: [10.1007/S00404-016-4250-3](#)
 15. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18:485–503. doi: [10.1093/HUMUPD/DMS018](#)
 16. Hansen M, Kurinczuk JJ, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. *Hum Reprod Update*. 2013;19:330–353. doi: [10.1093/HUMUPD/DMT006](#)
 17. Henningsen AKA, Opdahl S, Wennerholm UB, Tiitinen A, Rasmussen S, Romundstad LB, Bergh C, Gissler M, Forman JL, Pinborg A. Risk of congenital malformations in live-born singletons conceived after intracytoplasmic sperm injection: a Nordic study from the CoNARTaS group. *Fertil Steril*. 2023;120:1033–1041. doi: [10.1016/J.FERTNSTERT.2023.07.003](#)
 18. McDonald SD, Han Z, Mulla S, Murphy KE, Beyene J, Ohlsson A. Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2009;146:138–148. doi: [10.1016/J.EJOGRB.2009.05.035](#)
 19. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. *Obstet Gynecol*. 2004;103:551–563. doi: [10.1097/01.AOG.0000114989.84822.51](#)
 20. Talebi T, Mohsen-Pour N, Hesami M, Maleki M, Kalayinia S. The association between in vitro fertilization and intracytoplasmic sperm injection treatment and the risk of congenital heart defects. *J Matern Fetal Neonatal Med*. 2022;35:7471–7485. doi: [10.1080/14767058.2021.1949705](#)
 21. Hoorsan H, Mirmiran P, Chaichian S, Moradi Y, Hoorsan R, Jesmi F. Congenital malformations in infants of mothers undergoing assisted reproductive technologies: a systematic review and meta-analysis study. *J Prev Med Public Health*. 2017;50:347–360. doi: [10.3961/JPMMPH.16.122](#)
 22. Wei SQ, Paradis G, Ayoub A, Lewin A, Auger N. Assisted reproductive technology and cardiovascular outcomes in parents and offspring. *Can J Cardiol*. 2024;40:130–137. doi: [10.1016/J.CJCA.2023.09.013](#)
 23. Rasouli S, Radgoodarzi M, Azarbad R, Ghazvini A, Sotoudeheian M, Taghizadeh M, Dakkali MS. Congenital heart defects in pregnancies conceived by assisted reproductive technology: comparing functional and structural defects. *Cureus*. 2024;16:e54810. doi: [10.7759/CUREUS.54810](#)
 24. Appiah D, Sang J, Olayemi OE, Broni EK, Baykoca-Arslan B, Ebong IA, Kim C. Infertility treatments and cyanotic congenital heart defects among livebirths in the USA: findings from a contemporary cohort. *Hum Reprod*. 2024;39:2115–2123. doi: [10.1093/HUMREP/DEAE161](#)
 25. Sargisian N, Petzold M, Furenäs E, Gissler M, Spangmose AL, Malchau Lauesgaard S, Opdahl S, Pinborg A, Henningsen AKA, Westvik-Johari K, et al. Congenital heart defects in children born after assisted reproductive technology: a CoNARTaS study. *Eur Heart J*. 2024;45:4840–4858. doi: [10.1093/EURHEARTJ/EHAE572](#)
 26. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: [10.1136/BMJ.N71](#)
 27. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Wiley; 2019.
 28. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Online)*. 2016;355:i4919. doi: [10.1136/bmj.i4919](#)
 29. Anzures-Cabrera J, Higgins JPT. Graphical displays for meta-analysis: an overview with suggestions for practice. *Res Synth Methods*. 2010;1:66–80. doi: [10.1002/JRSM.6](#)
 30. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383–394. doi: [10.1016/J.JCLINEPI.2010.04.026](#)
 31. Rice K, Higgins JPT, Lumley T. A re-evaluation of fixed effect(s) meta-analysis. *J R Stat Soc Ser A Stat Soc*. 2018;181:205–227. doi: [10.1111/RSSA.12275](#)
 32. Kurinczuk JJ, Bower C. Birth defects in infants conceived by intracytoplasmic sperm injection: an alternative interpretation. *BMJ*. 1997;315:1260–1266. doi: [10.1136/BMJ.315.7118.1260](#)
 33. Koivurova S, Hartikainen AL, Gissler M, Hemminki E, Sovio U, Järvelin MR. Neonatal outcome and congenital malformations in children born after in-vitro fertilization. *Hum Reprod*. 2002;17:1391–1398. doi: [10.1093/HUMREP/17.5.1391](#)
 34. Wen SW, Leader A, White RR, Léveillé MC, Wilkie V, Zhou J, Walker MC. A comprehensive assessment of outcomes in pregnancies conceived by in vitro fertilization/intracytoplasmic sperm injection. *Eur J Obstet Gynecol Reprod Biol*. 2010;150:160–165. doi: [10.1016/J.EJOGRB.2010.02.028](#)
 35. Heisey AS, Bell EM, Herdt-Losavio ML, Druschel C. Surveillance of congenital malformations in infants conceived through assisted reproductive technology or other fertility treatments. *Birth Defects Res A Clin Mol Teratol*. 2015;103:119–126. doi: [10.1002/BDRA.23355](#)
 36. Shamshirsaz AA, Bateni ZH, Sangi-Haghpeykar H, Arian SE, Erfani H, Shamshirsaz AA, et al. Cyanotic congenital heart disease following fertility treatments in the United States from 2011 to 2014. *Heart*. 2018;104:945–948. doi: [10.1136/HEARTJNL-2017-312015](#)
 37. Shechter-Maor G, Czuzoj-Shulman N, Spence AR, Abenhaim HA. The effect of assisted reproductive technology on the incidence of birth defects among livebirths. *Arch Gynecol Obstet*. 2018;297:1397–1403. doi: [10.1007/S00404-018-4694-8](#)
 38. Schofield SJ, Doughty VL, Van Stiphout N, Franklin RCG, Johnson MR, Daubeney PEF, Cullinan P. Assisted conception and the risk of CHD: a case-control study. *Cardiol Young*. 2017;27:473–479. doi: [10.1017/S104795116000743](#)
 39. Iwashima S, Ishikawa T, Itoh H. Reproductive technologies and the risk of congenital heart defects. *Hum Fertil (Camb)*. 2017;20:14–21. doi: [10.1080/14647273.2016.1254352](#)
 40. Bhat P, Dhyani VS, Lakshmi V, Uppangala S, Adiga SK, Adiga P, Kumar P, Gupta A. Congenital anomalies observed in children conceived through assisted reproductive technology—a systematic review and meta-analysis. *J Assist Reprod Genet*. 2025;42:1547–1565. doi: [10.1007/S10815-025-03454-0](#)
 41. Gullo G, Scaglione M, Laganà AS, Perino A, Andrisani A, Chiantera V, Cuccinella G, Gitas G, Barra F, Riemma G. Assisted reproductive techniques and risk of congenital heart diseases in children: a systematic review and meta-analysis. *Reprod Sci*. 2023;30:2896–2906. doi: [10.1007/S43032-023-01252-6](#)
 42. Keyte A, Hutson MR. The neural crest in cardiac congenital anomalies. *Differentiation*. 2012;84:25–40. doi: [10.1016/J.DIFF.2012.04.005](#)
 43. Li Y, Du J, Deng S, Liu B, Jing X, Yan Y, Liu Y, Wang J, Zhou X, She Q. The molecular mechanisms of cardiac development and related diseases. *Signal Transduct Target Ther*. 2024;9:368. doi: [10.1038/S41392-024-02069-8](#)
 44. Mani S, Ghosh J, Coutifaris C, Sapienza C, Mainigi M. Epigenetic changes and assisted reproductive technologies. *Epigenetics*. 2020;15:12–25. doi: [10.1080/15592294.2019.1646572](#)
 45. Choux C, Binquet C, Carmignac V, Bruno C, Chapusot C, Barberet J, Lamotte M, Sagot P, Bourc'his D, Fauque P. The epigenetic control of transposable elements and imprinted genes in newborns is affected by the mode of conception: ART versus spontaneous conception without underlying infertility. *Hum Reprod*. 2018;33:331–340. doi: [10.1093/HUMREP/DEX366](#)
 46. Oveisi A, Vahdati A, Shahhoseini M, Favaedi R, Maroufizadeh S, Movaghar B. Ovulation induction changes epigenetic Marks of imprinting genes in mice fetus organs. *Cell J*. 2021;23:99–108. doi: [10.22074/CELLJ.2021.6953](#)
 47. De Robertis V, Stampalija T, Abuhamad AZ, Bosco M, Chaoui R, Formigoni C, Moon-Grady AJ, Paladini D, Pilu G, Ramezzana IG, et al. Indications for fetal echocardiography: consensus and controversies among evidence-based national and international guidelines. *Ultrasound Obstet Gynecol*. 2025;65:682–693. doi: [10.1002/UOG.29224](#)
 48. Pivato CA, Inversetti A, Condorelli G, Chieffo A, Levi-Setti PE, Latini AC, Busnelli A, Messa M, Cristodoro M, Bragato RM, et al. Cardiovascular safety of assisted reproductive technology: a meta-analysis. *Eur Heart J*. 2025;46:687–698. doi: [10.1093/EURHEARTJ/EHAE886](#)