Conception by assisted reproductive technology in infants with critical congenital heart disease in Japan

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Abbreviations:

AIH, artificial insemination

ASD, atrial septal defect

ART, assisted reproductive technology

BVH, biventricular heart defect

CC, clomiphene citrate

CHD, congenital heart disease

CCHD, critical congenital heart disease

f-SV, functional single ventricle

HLHS, hypoplastic left heart syndrome

IVF-ET, in-vitro fertilization-embryo transfer

ICSI, intracytoplasmic sperm injection

PDA, patent ductus arteriosus

TOF, tetralogy of Fallot

UVH, univentricular heart defect

VSD, ventricular septal defect

Abstract

Research Question: Although assisted reproductive technology (ART) increases the risk of congenital heart disease (CHD), the relationship between ART and critical CHD (CCHD) that requires early intervention in neonates is unclear. The objective of this study was to investigate the proportion of ART across different types of neonatal CCHD in a Japanese population.

Design: This study is a retrospective analysis of 418 consecutive infants with CCHDs that required catheter treatment or surgery within the first 28 days of life or ductal-dependent lesions, in two paediatric centres in Japan, between January 2014 and December 2019. The proportion of ART in infants with each type of CCHD was evaluated. We also evaluated the proportion of ART in infants with univentricular heart defect (UVH) compared with those with biventricular heart defect (BVH).

Results: The study group included 229 boys and 189 girls, with a gestational age of 38±2 weeks. Overall, 61 infants (14.5%) were conceived by fertility treatment with 46 (11.0%) conceived by ART. UVH and BVH were identified in 111 infants (26.6%) and 307 infants (73.4%), respectively. The proportion of infants conceived by ART was significantly higher in UVH (16.2%) than in BVH (9.1%), regardless of maternal age and maternal history of miscarriage.

Conclusions: The proportion of ART in infants with CCHD, especially UVH, was high. These findings may be an important basis to consider the rationale for performing fetal echocardiography in fetuses conceived by ART.

Key words: Assisted reproductive technology, critical congenital heart disease, parental age

Introduction

In-vitro fertilization-embryo transfer (IVF-ET) was introduced in 1980s (Hirahara, 2013). Subsequently, assisted reproductive technology (ART), defined as fertility treatments, such as IVF and intracytoplasmic sperm injection (ICSI), where eggs or embryos are handled in the laboratory to establish pregnancy, has increasingly been adopted globally. Japan has one of the highest ART rates in the world (Adamson et al., 2011). Based on the current Japanese ART registry, there were 454,893 ART cycles resulting in 56,979 live births in Japan in 2018, accounting for one in 16.1 neonates born in Japan that year (Ishihara et al., 2020).

Preimplantation genetic testing for aneuploidy conducted by the Japanese Society of Obstetrics and Gynaecology in a research context reported that 70% of preimplantation fertilized eggs prepared by ART had chromosomal abnormalities. There is also accumulating evidence that infants conceived by ART have a high rate of congenital anomalies, and have 3 times higher risk of congenital heart disease (CHD) than those conceived naturally, and also have a 1.5 times higher risk of CHD than those that are conceived by low-technology assisted reproduction (defined as the use of fertility drugs that induce or enhance ovulation in women, and are performed with timed intercourse or intrauterine insemination but without the intention of performing ART)

(Hirahara, 2013; Shanshirsaz et al., 2018; Tararbit et al., 2011; Wen et al., 2010). Thus, although ART is a useful technology, it is associated with some risks, such as chromosomal abnormalities and congenital anomalies that must be considered.

About 7–8 out of 1000 Japanese infants have CHD, the most common form of congenital disorders, and among them, 1.2–1.5 births per 1000 live births have critical CHD (CCHD) that requires early fetal diagnosis and intervention (Chang et al., 2018; Linde et al., 2011; Lytzem et al., 2018). Prenatal diagnosis of CHD can improve infant mortality rate and the prognostic outcome of CHD (Colaco et al., 2017; Eckersley et al., 2016). However, there is no consensus in current practice guidelines on whether ART conception is an indication for performing detailed fetal echocardiography among countries. Three American guidelines (American heart association 2014, American Institute of Ultrasound in Medicine 2019, and American Society of Echocardiography 2004) include ART among maternal indications for fetal echocardiography (American Institute of Ultrasound in Medicine, 2020; Donofrio et al., 2014; Rychik et al., 2004). By contrast, conception by ART is not included in high-risk pregnancies for detailed fetal echocardiography in Japanese and European guidelines (Allan et al., 2004; Carvalho et al., 2013; Japanese Society of Pediatric Cardiology and Cardiac Surgery. 2021; Wood et al., 2009). A

comprehensive meta-analysis investigating the risk of CHD in pregnancies conceived using ART analyzed the relationship between ART and all subgroups of CHD (Giorgione et al., 2018). Not all studies included in the meta-analysis, presented clearly all subgroups of CHD. Therefore, a suspicion was raised that the increased risk was due to a higher proportion of minor CHD or mild symptomatic CHD, such as patent ductus arteriosus (PDA), ventricular septal defect (VSD) and atrial septal defect (ASD), rather than CCHD. However, this could not be determined from the data available. Hence, the relationship between ART and CCHD is unclear. In addition, there are few reports that evaluates the relationship between ART and univentricular heart defect (UVH). Because prenatal diagnosis of UVH have more beneficial impact on prognosis than other CHD, fetal echocardiography for ART conception might be meaningful if there exists a relationship between ART conception and increased risk of UVH.

In this study, in order to verify whether there is merit in detailed fetal echocardiography for ART conceptions, we investigated the proportion of ART in infants identified with CCHD and evaluated the association between each type of CCHD and ART in a sample of Japanese infants with CCHD.

Patients and Methods

Patients

We performed a retrospective review of 418 consecutive infants diagnosed with CCHD (lesions requiring catheter treatment or surgery within 28 days of life, or ductal-dependent lesions) at two paediatric heart centres in Aichi prefecture, Japan (Aichi Children's Health and Medical Centre and Chukyo Children Heart Centre) from January 2014 to December 2019 (Figure 1). Excluded were patients with asymptomatic minor CHD (such as PDA, small VSD and ASD) and patients with mild symptomatic CHD (such as large VSD and mild tetralogy of Fallot [TOF]) who required catheter treatment or surgery after 28 days of life. Characteristics were examined at the level of the parents (maternal age, paternal age, maternal medical history, maternal history of alcohol consumption, maternal smoking history), the level of the pregnancy (conception method, maternal miscarriage history), and the level of infant (sex, gestational age, birth weight, presence of prenatal diagnosis of CCHD, genetic disorder). Preterm birth was defined as any birth before 37 weeks and small-for-gestational age (SGA) was defined as birth weight of less than the 10th percentile for gestational age and sex.

This study was approved by the institutional ethics committee of Aichi Children's Health and Medical Centre (No.2019014), and the requirement to obtain informed consent was waived because of the retrospective nature of the study. All study protocols were performed in accordance with the principles of the Declaration of Helsinki. All authors have full access to and take responsibility for the integrity of the data.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and as proportions for categorical variables. Comparisons of differences among groups were performed by Student's t-test or Mann–Whitney U test for continuous variables and chi-squared test for categorical variables as appropriate. Multivariable logistic regression analysis was performed based on the variables with p-values of < 0.05 in univariate logistic regression analysis. Analyses were performed using JMP 13 Pro software (SAS Institute, Cary, North Carolina, USA). All p-values of < 0.05 were considered statistically significant.

Results

Patients' characteristics

Demographic characteristics of patients with CCHD, are shown in Table 1. In total, 418 consecutive infants (229 boys and 189 girls) were included in this study. The gestational age of all patients was 38 ± 2 weeks and 55 patients were preterm infants (13.2%). The birth weight of all patients was 2736 ± 457 g and 127 patients were SGA infants (30.4%). Seventy-eight patients (18.7%) had a genetic disorder, including: trisomy-21 (Down syndrome) (n=40, 9.6%); 22q11.2 deletion syndrome (n=11, 2.6%); and CHARGE syndrome (n=5, 1.2%). Out of the 418 infants, 220 patients had a prenatal diagnosis of CHD (52.3%). The maternal age in our study group was 32 ± 5 years, with a paternal age of 34 ± 6 years. Seventy-seven mothers (18.4%) had a history of miscarriage. Thirty-nine mothers (9.3%) had a significant past medical history including: thyroid disease (n=7, 1.7%); four of these mothers had a diagnosis of Graves' disease; three had chronic thyroiditis; and five (1.2%) had diabetes. Twenty-seven mothers (6.5%) had a history of cigarette smoking and 7 mothers (1.7%) had a history of alcohol consumption.

Natural conception and conception through fertility treatment

Demographic characteristics of infants conceived by natural conception and those conceived by fertility treatment are reported in Table 1. Sixty-one infants (14.6%) were conceived by fertility treatment. Among these infants, 15 (3.6%) were conceived by low-technology assisted reproduction, such as clomiphene citrate (CC; n=6) and artificial insemination (AIH; n=9), and 46 (11.0%) were conceived by ART (IVF, n=40 and ICSI, n=6).

There was no difference in the sex distribution of infants between the natural conception and the fertility treatment groups. However, parents were older in the fertility treatment group (maternal age, 36 ± 4 years; paternal age, 37±5 years) than in the natural conception group (maternal age, 31 ± 5 years; paternal age, 33±6 years; $p < 0.001$). The proportion of infants with genetic disorders was not different between the fertility treatment group and the natural conception group.

The diagnosis and number of each type of CCHD

The diagnosis and number of each type of CCHD and the patient number of each CCHD classified by the type of ventricle are shown in Figure 2 and Supplemental Table 1, respectively.

Seventy-two patients had TOF (17.2%), 70 patients had aortic coarctation or aortic arch interruption (16.8%), and 48 patients had transposition of the great arteries (11.5%). In addition, 111 patients (26.6%) had a UVH; including: a functional single ventricle (f-SV) associated with heterotaxy syndrome (n=31, 7.4%); f-SV without heterotaxy syndrome (n=29, 6.9%); and hypoplastic left heart syndrome (HLHS, n=23, 5.5%).

Comparing infants with UVH to those with BVH

Demographic characteristics of infants with UVH compared to those with biventricular heart defect (BVH) are summarized in Table 2. Maternal age of infants with UVH was 31 ± 5 years and paternal age of infants with UVH was 33 ± 6 years. In addition, maternal age of infants with BVH was 32 ± 5 years, and paternal age of infants with BVH was 34 ± 6 years. The proportion of prenatal diagnosis in infants with BVH was 43.0% (132/307) while that in infants with UVH was 79.2% (88/111) ($p < 0.001$) (Supplemental Figure1).

Association between CCHD and fertility treatment

Figure 3A shows the proportion of fertility treatment classified by the type of ventricle. The proportion of ART in infants with UVH was 16.2% (18/111), while that in infants with BVH was 9.1% (28/307) (p = 0.041). In addition, the proportion of all fertility treatments, including CC, AIH, IVF, and ICSI, in infants with UVH was 21.6% (24/111), while the proportion of all fertility treatments in infants with BVH was 12.1% (37/307) (p = 0.014). Figure 3B shows the proportion of fertility treatment in each type of CCHD. Notably, the proportion of ART was higher in infants with HLHS (6/23, 26.1%) and those with pulmonary atresia with intact ventricular septum (PA/IVS; 5/19, 26.3%) than other CCHDs. Consistently, the proportion of all fertility treatment was also higher in infants with HLHS (8/23, 34.8%) and PA/IVS (6/19, 31.6%) than in those with other CCHDs.

On multivariable logistic regression analysis, the proportion of ART in infants with UVH was higher than those with BVH, regardless of maternal age and maternal history of miscarriage (p = 0.025) (Table 3).

Parental age in patients with CCHD

Parents of infants with atrioventricular septal defect (AVSD) (maternal age, 35±6 years, and paternal age, 37±6 years) were older than those of infants with other CCHDs ($p < 0.01$). In addition, fathers of infants with total anomalous pulmonary venous connection (TAPVC; 37±6 years) were older than those of infants with other CCHDs ($p = 0.018$).

Discussion

The main findings of our study were: 1) The proportion of ART in patients with CCHD (n=46, 11.0%) was high; 2) The proportion of ART and all fertility treatments in infants with UVH was higher than that of infants with BVH. Notably, the proportion of ART and all fertility treatments in infants with HLHS and PA/IVS was much higher than other CCHDs; and 3) The proportion of ART in infants with UVH was higher than those with BVH, regardless of maternal age and maternal history of miscarriage.

Association between CCHD and fertility treatment

Based on the current Japanese ART registry, ART yields 53,000 live births, accounting for one in 18.2 neonates born in Japan between 2014 and 2018 (Ishihara et al., 2020). Namely, the total

proportion of ART-conceived births in Japan was 5.5%, while the proportion of infants with CCHD who were conceived by ART in our study (11.0%) was high (Ishihara et al., 2020). In addition, our study showed that the proportion of ART and all fertility treatment in infants with UVH was 1.7-fold higher than in infants with BVH.

Women of older age show a significant tendency to have conceived through ART (Kohei et al., 2017) and infertile women have a greater risk of miscarriage (Rosemarie et al., 1995). In addition, aside from advanced maternal age, a maternal miscarriage history has also been reported to increase the risk of CHD in the offspring (Jenkins et al., 2007; Snijders et al., 1999, Yu et al., 2015). However, multivariable logistic regression analysis in our study confirmed that the proportion of ART in infants with UVH was higher than those with BVH, regardless of maternal age and maternal history of miscarriage.

Previous studies have investigated the rate of ART by type of CHD; however, a few studies examined this relationship in detail (Schofield et al., 2017; Tararbit et al., 2011; Votava-Smith et al., 2014). These studies identified that ART was associated with a higher proportion of malformation of the outflow tracts and ventriculoarterial connections, as well as anomalies of the great arteries, and ventricular septal defects; however, there was no association between

ART and UVH. In contrast, in our study, we identified there was higher proportion of ART conception in UVH than BVH, especially HLHS and PA/IVS which were characterized by malformations of the outflow tracts. The discrepancy between our results and those of previous studies may be explained by the fact that PDA, VSD and ASD were the major CHD among previous studies, with the proportion of rare CHD, such as UVH, being lower than in our studies. Additionally, we need to consider that maternal age at conception and the incidence on ART in Japan is higher than in the countries studied previously.

Association between CCHD and parental age

Because the risk of CHD is higher among the offspring of older women, we examined the association between maternal and paternal age with CCHD in our study (Jenkins et al., 2007; Snijders et al., 1999). However, the average parental age of infants with CCHD was comparable to the average parental age of all births in Japan (Japanese Ministry of Health, Labour and Welfare. Vital Statistics, 2020). In addition, we noted that parents of infants with UVH were younger than the average parental age of infants with BVH and all births in Japan. By contrast, the average parental age tends to be higher for infants with AVSD, and this tends to be

associated with trisomy 21. Younger maternal age in infants with UVH is likely related to AVSD in BVH, strongly associated with advanced maternal age. We also noted that higher paternal age was associated with TAPVC.

The higher the maternal and paternal age, the higher the possibility of infertility. When compared to individuals in the natural conception group, parents in the ART/low-technology assisted reproduction group were older. However, it has been reported in previous meta-analysis that ART conception is a risk factor for CHD, independent of maternal and paternal age (Giorgione et al., 2018). In our study, the average parental age of infants with CCHD was comparable to the average parental age of all births in Japan, and parents of infants with UVH were younger than the average age of parents of infants with BVH.

Association between CCHD and other risk factors

Causes of CHD include genetic factors (13%); environmental factors (2%), such as rubella, maternal systemic disease, maternal smoking history, maternal history of alcohol and drug use, and other unknown factors (85%) (Matsuoka et al., 2003). Based on the National Health and Nutrition Survey in Japan, there was no difference in maternal systemic disease, maternal

smoking history, and maternal history of alcohol between patients with CCHD in our study and all birth in Japan (Japanese Ministry of Health, Labour and Welfare. National Health and Nutrition Survey, 2020).

Conception by ART and prenatal diagnosis by fetal echocardiography

Our findings indicate that the proportion of ART in infants with CCHD, especially UVH, is higher than the reported rate of ART in Japan as a whole. ART is expensive and repeated cycles may be required to achieve pregnancy, resulting in mental and physical stress. Therefore, it devastating to parents when their infant that was conceived by ART is diagnosed with a CCHD after birth. Hence, prenatal diagnosis of CCHD is desirable in this population and may improve infant mortality rate and the prognostic outcome of CHD (Colaco et al., 2017; Eckersley et al., 2016). In addition, infants with CCHD often present low birth weight, and SGA are associated with several obstetric complications such as preterm delivery and preeclampsia (Giorgione et al., 2020; Inversetti et al., 2020). Therefore, prenatal diagnosis of CHD may also help in providing better timing of delivery and planning of postnatal treatment.

The 2013 ISUOG guidelines which mandate 4 chamber cardiac views, outflow and 3 vessel views on all routine anatomy scans as part of routine care, would pick up more than 90% of the CCHD diagnoses (all but the TAPVC). However,-average rate of fetal diagnosis for CCHD in Japan was reported to be about 60% even recently and Makarin et al. reported that average rate of fetal diagnosis for CCHD in the world was 50% (Aoki et al, 2010; Marian et al. 2019). In our study, 220 patients (52.3%) had a prenatal diagnosis of CCHD and many infants with CCHD all over the world were diagnosed with CCHD after birth, which indicate that there is room for improvement in the ratio of prenatal diagnosis. Based on our findings and considering the impact of ART on parents, we believe that detailed fetal echocardiography screening is better performed during pregnancies conceived by ART.

Limitations and Strengths

It is important to note the limitations and strengths of our study. The main limitation of this study is its retrospective design. Furthermore, the data analysed, were obtained from only two institutions-and we did not have the data about the proportion of ART conception in infants without CCHD as a control group. In addition, information about maternal weight, that is a

known risk factor for CHD, was not available and was not included in the analyses. Moreover, we excluded minor and major CHD, except for CCHD, and did not include fetal death or abortion. Thus, our findings must be interpreted with caution. Nevertheless, most infants diagnosed with CCHD in the Aichi prefecture were treated in the two centres included in our study. Therefore, our data shows the trend of CCHD in our locality that has a population of 7,550,000 individuals with 60,000 births per year. Further, it is unclear whether the ART procedure increases the rate of CCHD/UVH or whether the CCHD/UVH rate increases due to the background factors of infertility that were the indication for ART.

The strengths of our study are as follows. First, this is the report that focused on the proportion of infants conceived by ART with rare CCHD that required early intervention. Second, our study is one of the few reports to investigate the proportion of ART in infants with CCHD by the type of ventricle in Japan. Some prospective studies have shown the overall number of CHD in natural conception and ART in some institutions (Iwashima et al., 2017; Sharmshirsaz et al., 2018; Tararbit et al., 2011; Wen et al., 2010). However, it is difficult to evaluate the risk of subgroups of CCHD in infants born through ART because only 1.2-1.5 in 1000 infants have CCHD (Lytzem et al., 2018). The proportion of ART in all births in Japan is highest in the

world, and our study also indicates that there are some risks for CCHD, especially UVH, that are associated with ART.

Conclusion

Our study identified that the proportion of ART in infants with CCHD was higher than the reported rate of ART in Japan as a whole. In addition, infants with UVH were more likely to have been conceived by ART than infants with BVH.

Currently, many infants with CCHD that were conceived by ART were not diagnosed with CCHD before birth. Based on these findings, fetal echocardiography would be indicated for these conceptions. Further large-scale prospective studies are needed to confirm our findings.

Declarations of Interest

Author contributions

Y.M. and T.K. designed and performed the study; Y.M., M.N. and T.K. also analysed the data; Y.M. collected and managed clinical data; Y.M. and T.K. wrote the paper. K.G., H.Y., Y.F.,

E.M., K.Y., H.N., N.O. and Y.T. critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that there is no conflict of interest.

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Figure Legends

Figure 1. Flow chart of patients selection

CHD, congenital heart disease, CCHD, critical congenital heart disease;

Figure 2. The spectrum of all critical congenital heart disease (CCHDs)

This figure indicates the prevalence for each type of CCHD in our study group

AVSD, atrioventricular septal defect; CCHD, critical congenital heart disease; CoA, aortic coarctation; DORV, double-outlet right ventricle; Ebstein; Ebsteins' anomamly; f-SV(+H), functional single ventricle with heterotaxy syndrome; f-SV(-H), functional single ventricle without heterotaxy syndrome; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA/IVS, pulmonary atresia with intact ventricular septum; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot

Figure 3. The proportion of infants conceived by fertility treatment

The proportion of cases of fertility treatment is shown for each type of ventricle (A) and for each type of CCHD (B). Black, natural conception; White, low-technology assisted reproduction; Grey, ART.

ART, assisted reproductive technology; AVSD, atrioventricular septal defect; BVH, biventricular heart defect; CCHD, critical congenital heart disease; CoA, aortic coarctation; DORV, double-outlet right ventricle; Ebstein; Ebsteins' anomamly; f-SV(+H), functional single ventricle with heterotaxy syndrome; f-SV(-H), functional single ventricle without heterotaxy syndrome; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA/IVS, pulmonary atresia with intact ventricular septum; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart defect

Supplemental Figure 1. The prenatal detection rate of CCHD

The prenatal detection rate is shown for each type of ventricle (A) and for each type of CCHD (B). Black, prenatal diagnosis; White, postnatal diagnosis

AVSD, atrioventricular septal defect; BVH, biventricular heart defect; CCHD, critical congenital heart disease; CoA, aortic coarctation; DORV, double-outlet right ventricle; Ebstein; Ebsteins' anomamly; f-SV(+H), functional single ventricle with heterotaxy syndrome; f-SV(-H), functional single ventricle without heterotaxy syndrome; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA/IVS, pulmonary atresia with intact ventricular

septum; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; UVH, univentricular heart defect

Table1

Table 1. Patients' characteristics in infants diagnosed with CCHD

Variables	Total (n=418)	Natural Conception Group (n=357)	Fertility Treatment Group (n=61)	*P*-value
Maternal age, years	32±5	31±5	36±4	<0.001
Paternal age, years	34±6	33±6	37±5	<0.001
Conception method, n		natural 357	CC 6 / AIH 9 / IVF 40 / ICSI 6	
Maternal history of miscarriage (yes), n (%)	77 (18.4)	55 (15.4)	22 (36.1)	<0.001
Maternal medical history, n (%)	39 (9.3)	26 (7.3)	13 (21.0)	<0.001
Thyroid disease, n (%)	7 (1.7)	5 (1.4)	2 (3.3)	0.291
Diabetes, n (%)	5 (1.2)	5 (1.4)	0 (0.0)	0.352
Maternal social history				
Alcohol consumption, n (%)	7 (1.7)	4 (1.1)	3 (4.9)	0.033
Smoking, n (%)	27 (6.5)	26 (7.3)	1 (1.6)	0.098
Diagnosis (prenatal), n (%)	220 (52.3)	183 (51.3)	37 (60.7)	0.174
Sex (male), n (%)	229 (54.8)	197 (55.2)	32 (52.5)	0.693
Gestational age, weeks	38±2	38±2	38±2	0.274
Preterm birth, n (%)	55 (13.2)	44 (12.3)	11 (18.0)	0.223
Birth weight, g	2736±457	2748±452	2663±477	0.184
Small-for-gestational age, n (%)	127 (30.4)	109 (30.5)	18 (29.5)	0.872
Genetic disorder, n (%)	78 (18.7)	67 (18.8)	11 (18.0)	0.892
21trisomy, n (%)	40 (9.6)	37 (10.4)	3 (4.9)	0.182
22q11.2 deletion syndrome, n (%)	11 (2.6)	8 (2.2)	3 (4.9)	0.227
CHARGE syndrome, n (%)	5 (1.2)	4 (1.1)	1 (1.6)	0.731

Data are presented as mean ± standard deviation or number (*n*) and percentage (%);

AIH, Artificial Insemination; CC, Clomiphene citrate; CCHD, Critical congenital heart disease;

ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization

Table2

Table 2. Comparison of variables between infants with UVH and infants with BVH

Variables	UVH Group (n=111)	BVH Group (n=307)	*P*-value
Maternal age, years	31±5	32±5	0.026
Paternal age, years	33±6	34±6	0.413
Conception method			
ART, n (%)	18 (16.2)	28 (9.1)	0.041
low-technology assisted reproduction, n (%)	5 (4.5)	9 (2.9)	0.423
Maternal history of miscarriage (yes), n (%)	29 (26.1)	48 (15.6)	0.016
Maternal medical history	8 (7.2)	31 (10.1)	0.370
Thyroid disease, n (%)	4 (3.6)	3 (1.0)	0.065
Diabetes, n (%)	1 (0.1)	4 (1.3)	0.739
Maternal social history			
Alcohol consumption, n (%)	4 (3.6)	3 (1.0)	0.065
Smoking, n (%)	12 (10.8)	15 (4.9)	0.030
Diagnosis (prenatal), n (%)	88 (79.2)	132 (43.0)	<0.001
Sex (male), n (%)	64 (57.7)	165 (53.7)	0.478
Gestational age, weeks	38±2	39±2	0.004
Preterm birth, n (%)	16 (14.4)	39 (12.7)	0.648
Birth weight, g	2700±405	2748±474	0.343
Small-for-gestational age, n (%)	36 (32.3)	91 (29.6)	0.584
Genetic disorder	6 (5.4)	72 (23.5)	<0.001
21trisomy, n (%)	3 (2.7)	37 (12.0)	0.004
22q11.2 deletion syndrome, n (%)	0 (0.0)	11 (3.6)	0.043
CHARGE syndrome, n (%)	0 (0.0)	5 (1.6)	0.176

Data are presented as mean ± standard deviation (SD) or number (*n*) and percentage (%),

ART, Assisted reproductive technology; BVH, biventricular heart defect;

UVH, univentricular heart defect

Table3

Table 3. Univariate/Multivariable logistic regression analysis for variables: Infants with UVH compared with infants with BVH

	Univariate			Multivariable		
Variables	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Maternal age (years)	0.95	0.91–0.99	0.027	0.93	0.89–0.98	0.006
Conception method (ART)	1.93	1.02–3.65	0.043	2.28	1.11–4.68	0.025
Maternal history of miscarriage (yes)	1.90	1.12–3.20	0.017	1.79	1.02–3.17	0.044
Maternal social history (Smoking)	2.36	1.07–5.21	0.034	1.98	0.86–4.53	0.106
Maternal social history (Alcohol consumption)	3.79	0.83-17.20	0.086			
Maternal medical history (Thyroid disease)	3.79	0.83-17.20	0.086			
Maternal medical history (Diabetes))	0.69	0.08-6.23	0.730			

ART, Assisted reproductive technology; BVH, biventricular heart defect; CI, Confidence interval; OR, Odds ratio; UVH, univentricular heart defect

Figure1

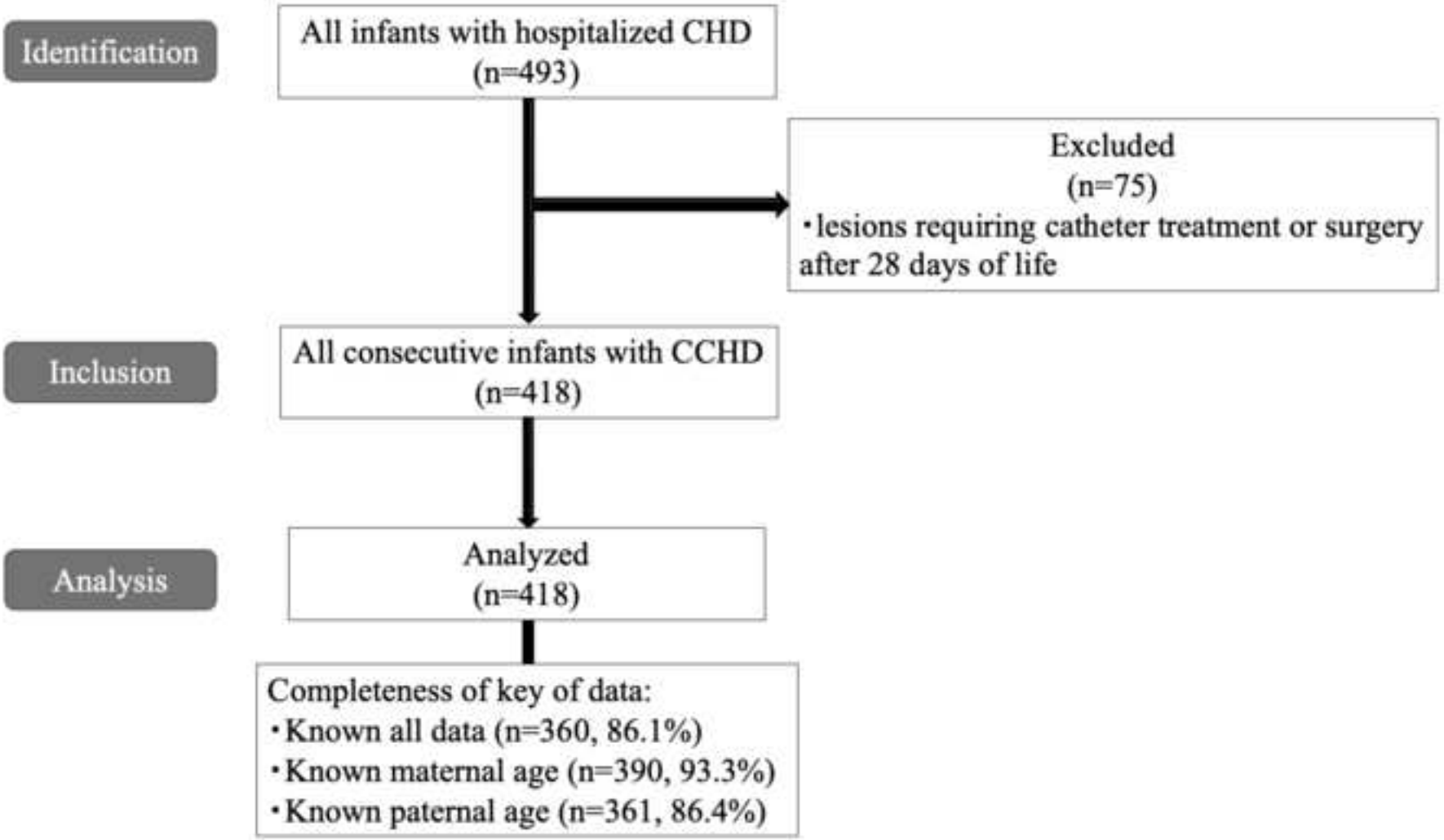

Identification
All infants with hospitalized CHD
(n=493)
Excluded
(n=75)
·lesions requiring catheter treatment or surgery after 28 days of life
Inclusion
All consecutive infants with CCHD
(n=418)
Analysis
Analyzed
(n=418)
Completeness of key of data:
·Known all data (n=360, 86.1%)
·Known maternal age (n=390, 93.3%)
·Known paternal age (n=361, 86.4%)

Figure2

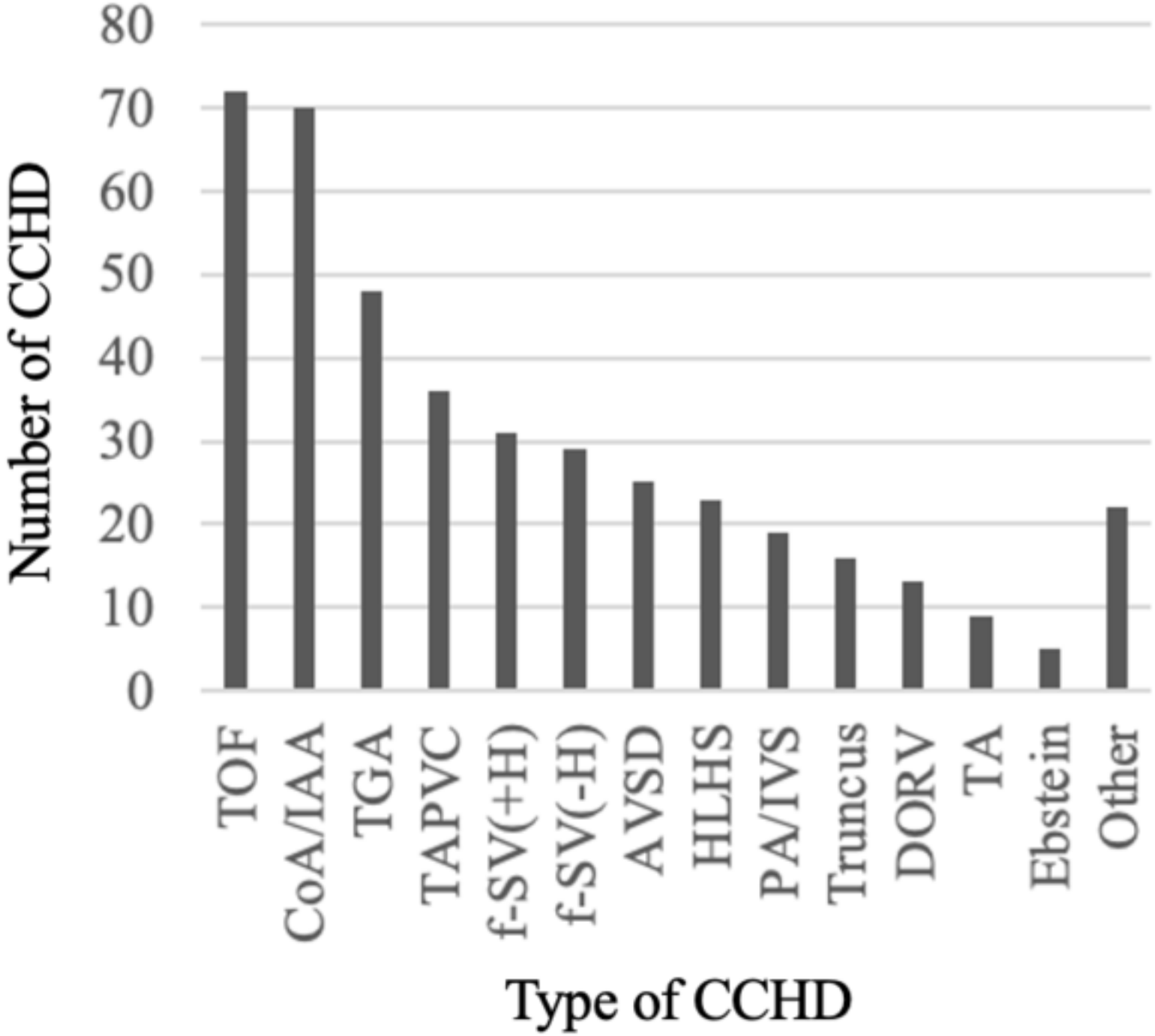
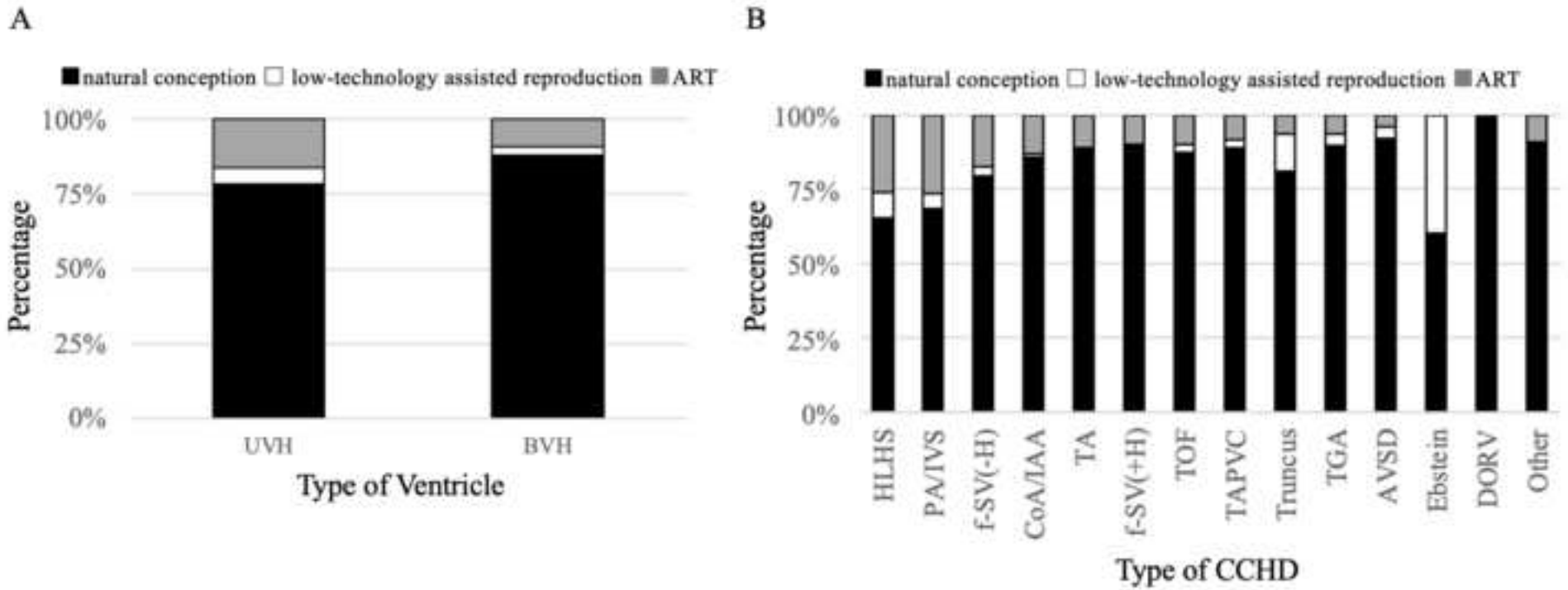

80
70
60
50
40
30
20
10
0
Number of CCHD
TOF
CoA/IAA
TGA
TAPVC
f-SV(+H)
f-SV(-H)
AVSD
HLHS
PA/IVS
Truncus
DORV
TA
Ebstein
Other
Type of CCHD

Figure3


A
natural conception
low-technology assisted reproduction
ART
100%
75%
50%
25%
0%
Percentage
UVH
BVH
Type of Ventricle
B
natural conception
low-technology assisted reproduction
ART
100%
75%
50%
25%
0%
Percentage
HLHS
PA/IVS
f-SV(-H)
CoA/IAA
TA
f-SV(+H)
TOF
TAPVC
Truncus
TGA
AVSD
Ebstein
DORV
Other
Type of CCHD

Key Message

The proportion of Assisted reproductive technology was high in infants with critical congenital heart disease, especially univentricular heart defects. As such, foetal echocardiography would be indicated for these pregnancies.