Epidemiology of Congenital Heart Disease with Emphasis on Sex-Related Aspects

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Epidemiology of congenital heart disease. Art work by Piet Michiels, Leuven, Belgium

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Abstract

Gender differences in prevalence, manifestation, treatment outcomes, and prognosis have been well known for acquired heart disease

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such as coronary artery disease. Regarding congenital heart disease (CHD), it is recognized that the incidence of each congenital heart defect varies according to sex observed during a time span of more than 40 years. As diagnostic and surgical methods for CHD have achieved dramatic advances for the past decades, more newborns with CHD were able to survive and reach adulthood. Thereafter gender differences have begun to be reported on mortality, progress to pulmonary arterial hypertension, treatment outcomes, and prognosis in patients with CHD. However, it has been less known in the field of CHD yet, and this contribution describes information that is relatively well studied to date.

Keywords

Congenital heart disease · Gender · Sex ratio · Women · Ethnicity · Incidence · Prevalence · Manifestation · Pulmonary arterial hypertension · Outcome · Complication · Prognosis

Incidence and Prevalence of Congenital Heart Disease (CHD)

The incidence of CHD is generally estimated at 8/1000 live births [1], although it varies according to geographic regions, the time of investigation, target population, and case definition (e.g., exclusion of functionless abnormalities, unspecified anomalies, and spontaneously closed defect or not). However, the incidence of CHD has been rising to 10–14/1000 live births in recent studies [2–5], and this change is more evident in the reports from registries with continuous monitoring of the same populations over time [6–9]. Also a meta-analysis study, including worldwide 114 papers, reported that birth prevalence (<5 years of age) increased substantially over time from 0.6/1000 live births in 1930 to 9.1/1000 live births after 1995 (Fig. 3.1) [10].

When analyzed according to the severity of CHD, simple CHD with subtle physical findings such as atrial septal defect (ASD) or patent ductus arteriosus (PDA) significantly increased, along with the increase of overall CHD incidence (Fig. 3.2) [3, 10–13]. It is suggested that improvements in diagnostic and screening modalities, especially echocardiography and color-Doppler technique since the 1980s, enabled diagnosis of lesions, and therefore case detection increases rather than a true incidence of disease. On the other hand, some studies reported that the incidence of severe and complex CHD decreased over time resulting from availability of fetal echocardiography and pregnancy termination by intervention [10, 12, 13].

Similar changes are also observed in prevalence. According to the data from Quebec (Canada), prevalence of CHD was 6.88/1000

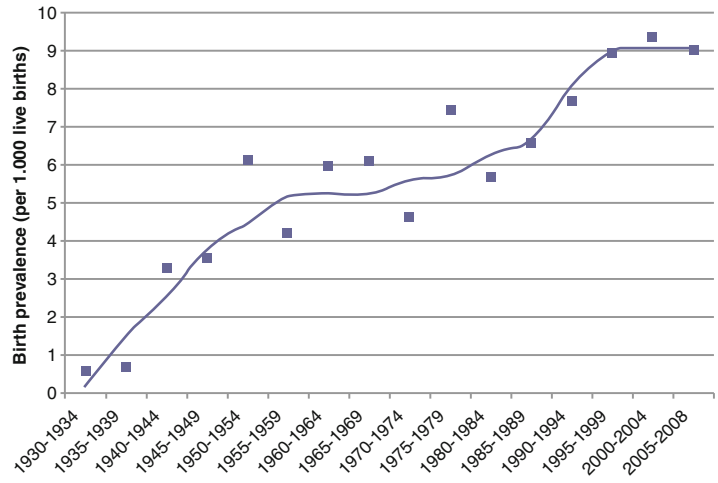

Fig. 3.1 Birth prevalence of total congenital heart disease over time. Time course of reported total congenital heart disease (CHD) birth prevalence from 1930 until 2010. The blue line shows the time trend, and the squares represent the calculated birth prevalence values for each time period. (Reprinted from Ref. [10] with permission from Elsevier)

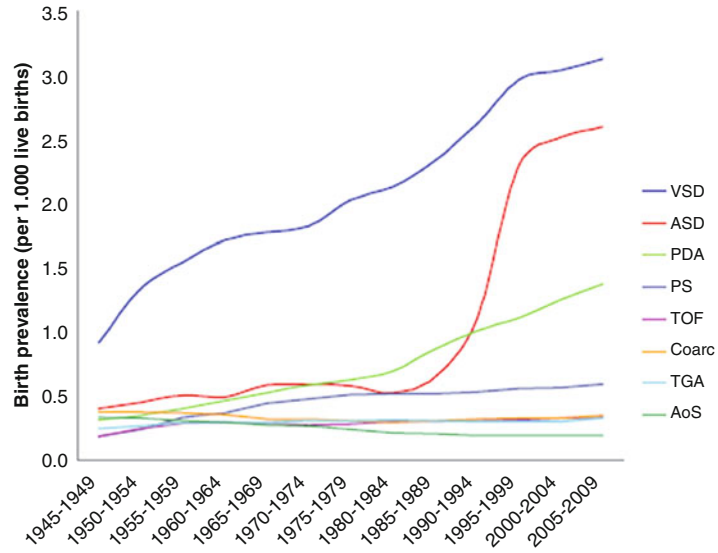

Fig. 3.2 Birth prevalence of specific congenital heart defects over time. Time course of birth prevalence of the eight most common CHD subtypes from 1945 until 2010. *AoS* aortic stenosis, *ASD* atrial septal defect, *Coarc* coarctation of aorta, *PDA* patent ductus arteriosus, *PS* pulmonary valve stenosis, *TGA* transposition of great arteries, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect. (Reprinted from Ref. [10], with permission from Elsevier)

children (<18 years of age) in 1985 and abruptly rose to 11.89/1000 children in 2000 [4]. In addition, the prevalence of all CHD was consistently higher in females over time for both adult and pediatric populations (4.83/1000 females versus 3.94/1000 males in 1985; 4.55/1000 females versus 3.61/1000 males in 2000). While many prevalence studies reported that the sex ratio for overall CHD was greater than 1 [4, 11, 12], some recent studies have reported that total CHD is more prevalent in females [3, 5, 14]. This result could be attributed by that the proportion of simple CHD such as shunt lesions which show female preponderance is recently getting larger in the CHD population. Thus, we need to monitor if this change will continue in the years ahead.

Preponderance of Specific Defects Between Boys and Girls

It is well known that the incidences of CHD are different between male and female, according to each diagnosis, and this observation has been relatively consistent over time. ASD and atrioventricular septal defect (AVSD) have shown a female preponderance, and aortic stenosis (AS), coarctation of aorta (COA), transposition of great arteries (TGA), tetralogy of Fallot (TOF), and double outlet right ventricle (DORV) have shown a male preponderance (Fig. 3.3) [4, 5, 11–21]. Although we have not found the answers to explain these differences yet, it is suggested that a genetic factor is responsible for the male preponderance of aortic valve disease (e.g., AS, COA). The absence of a normal second X chromosome is then thought to be associated with aortopathy [22]. This explanation is based on the speculation that a genetic factor that modulates the development of the aorta and aortic valve is located on the X chromosome, as evidenced by the Turner syndrome (a sex aneuploidy syndrome), in which aortic valve disease occurs 146 times more frequently compared to the general population [23].

Table 3.1 summarizes results from previous studies for gender preponderance of specific congenital heart defects [4, 5, 11–21]. It is generally recognized that male predominance is associated with more complex and severe CHD, whereas female with more simple CHD. However, we should consider that gender preponderance could be different according to the race/ethnicity or geographic regions. In the comparative study from three large birth defect registries in

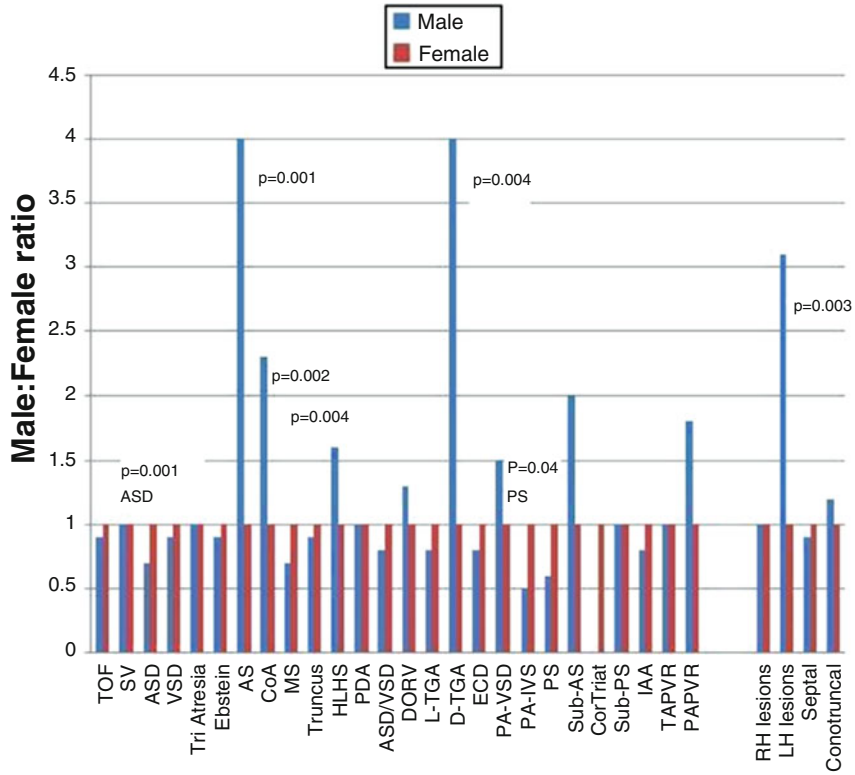

Fig. 3.3 Gender preponderance in congenital heart disease. *AS* aortic stenosis, *CoA* coarctation of aorta, *Cor Triat* cor triatriatum, *d-TGA* complete transposition of great arteries, *ECD* endocardial cushion defect, *DORV* double outlet right ventricle, *HLHS* hypoplastic left heart syndrome, *IAA* interrupted aortic arch, *LH* left heart, *L-TGA* congenitally corrected transposition of great arteries, *MS* mitral stenosis, *PA-IVS* pulmonary atresia with intact ventricular septum, *PA-VSD* pulmonary atresia with ventricular septal defect, *PS* pulmonic stenosis, *RH* right heart, *SV* single ventricle, *TAPVR* total anomalous pulmonary venous return, *TOF* tetralogy of Fallot. (Reprinted from Ref. [4], with permission from Springer)

California, Sweden, and France, the sex ratio of ASD showed a significant heterogeneity between registries (0.54 in French, 0.74 in Swedish, and 1.06 in California registry) [11]. Also, differences in sex ratios between ethnic groups were revealed in some studies [15, 17, 18]. An epidemiologic study of left ventricular outflow tract obstruction lesions, including AS, COA, and hypoplastic left heart syndrome (HLHS) from the Texas Birth Defect Registry, demonstrated racial/ethnic differences not only in prevalence but also in sex ratio of these defects [17]. In these defects which commonly have male preponderance, black males showed lower prevalence than white or Hispanic males and even lower than black females (Fig. 3.4).

Manifestation of CHD

Although atypical symptoms without chest pain occur more frequently in women with acute coronary syndromes resulting in higher mortality, gender difference in the manifestation of CHD has not been researched well. The study from a nationwide registry of adult patients with congenital heart disease in the Netherlands (CONCOR registry) showed a significant gender difference in functional class of patients with pulmonary arterial hypertension (PAH) associated with CHD [24]. More females than males were symptomatic even though mean systolic pulmonary arterial pressure was not different between males and

females (Fig. 3.5). Female sex (odds ratio = 1.5) and increased systolic pulmonary arterial pressure (odds ratio = 0.04) were independently associated with a worse NYHA class. Also, in database of the European Heart Survey on adult congenital heart disease (ACHD), females were more likely to have functional limitation than males (OR 1.27; 95% CI 1.09–1.48) [25]. Hormonal fluid retention and predisposition to thrombosis might have contributed to this gender difference in manifestation. However, there has been no study to demonstrate this speculation [26].

Table 3.1 Preponderance of specific congenital heart defects between male and female

Male	Equivocal (or controversial)	Female
AS	VSD[a]	ASD secundum
COA	PS[a]	AVSD
TGA	PA[b]	PDA
TOF	TA[c]	MV anomalies
DORV	Truncus arteriosus[c]	
HLHS		
SV		
Anomalous PV return		

AS aortic stenosis, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *COA* coarctation of aorta, *DORV* double outlet right ventricle, *HLHS* hypoplastic left heart syndrome, *MV* mitral valve, *PA* pulmonary atresia, *PDA* patent ductus arteriosus, *PS* pulmonary valve stenosis, *PV* pulmonary venous, *SV* single ventricle, *TA* tricuspid atresia, *TGA* transposition of great arteies, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect

[a]Defects show equivocal sex ratio or female preponderance (female preponderance of VSD in Refs. [5, 12, 14]; of PS in Refs. [4, 5])

[b]Defects show equivocal sex ratio or male preponderance (male preponderance in Refs. [11, 18])

[c]Gender preponderance of defects is controversial [11, 12, 14, 18]

Progression to PAH

It has been recognized that females have a predisposition to PAH. The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL registry), the largest ongoing study of PAH in the United States, demonstrated that more women had PAH associated with CHD and connective tissue disease [27]. In the study from the Dutch registry (CONCOR), the prevalence of PAH among 5970 registered patients with ACHD was 4.2% (6.1% among 1824 patients with septal defect), and 60% of these patients were female [24]. It was also noted that women had a 33% higher risk of PAH (OR 1.33; 95% CI 1.07–1.65) than men in the same registry [28]. The sex steroid hormone is considered as a related factor. Estrogen affects angiogenesis, vasculogenesis, and remodeling in response to shear stress via proliferation and migration of both endothelial cells and vascular smooth muscle cells [29]. As another potential influence of estrogen on PAH, it is suggested

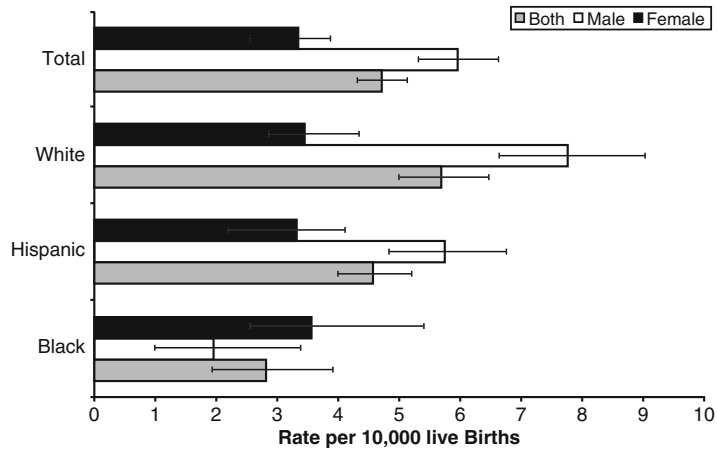

Fig. 3.4 Prevalence of left ventricular outflow tract obstruction malformations by sex and race/ethnicity, Texas, 1999–2001. (From Ref. [17], with permission from John Wiley and Sons)

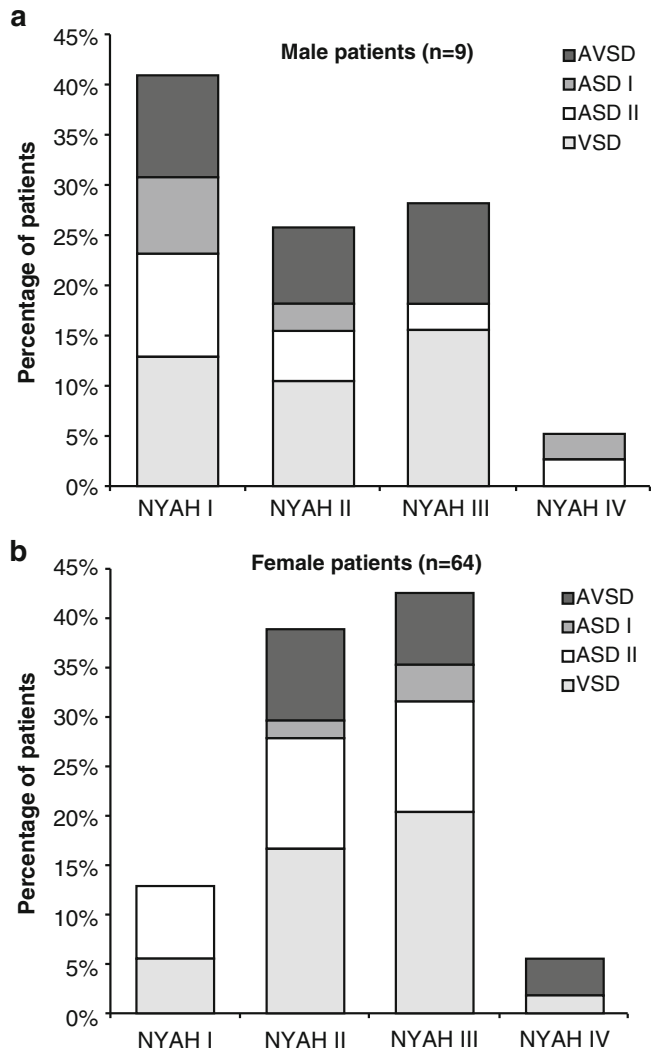

Fig. 3.5 Functional class of patients with pulmonary arterial hypertension due to CHD according to sex. Bars represented percentages. The whole bars sum to 100%. Subdivisions of the bars represent the proportions taken up by the individual defects within each NYHA class. (Reprinted from Ref. [24], with permission from Elsevier)

that estrogen enhances the proliferative capacity of cardiac fibroblasts via estrogen receptor- and mitogen-activated protein kinase (MAPK)-dependent mechanisms [30].

However, we should consider the gender distribution among CHD when investigating the incidence of CHD-associated PAH. In the Dutch study mentioned above, the prevalence of PAH among male and female patients with a septal defect was similar, both overall and per defect (7.8 vs. 7.6%, Fig. 3.6). However, there were more females than males with CHD-associated PAH since the patients with septal defect (especially ASD secundum) were more female.

Taking these two factors into consideration, a "two-hit hypothesis" is suggested for female preponderance in PAH. That is, the female has vulnerability (i.e., genetic susceptibility) to the development of PAH, and then the trigger of a shunt lesion initiates the vascular injury in the lungs resulting in higher prevalence of female in PAH [22].

Treatment Outcomes and Complications

Sex difference in surgical mortality related to CHD is still controversial. The prevalence study

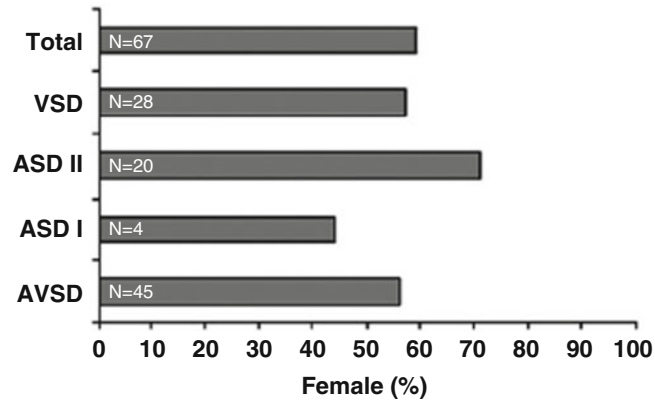

Fig. 3.6 Percentage of females among the patients with pulmonary arterial hypertension and a septal defect. *VSD* ventricular septal defect, *ASD II* atrial septal defect secundum, *ASD I* atrial septal defect primum, *AVSD* complete atrioventricular septal defect. (Reprinted from Ref. [24], with permission from Elsevier)

from Quebec (Canada) revealed the female predominance in ACHD patients with severe disease, but it was not observed in children. On the other hand, for simple disease (e.g., shunt lesions), female predominance was observed in both children and adults [3]. It was suggested that the rising prevalence of severe CHD in the female population is caused by gender difference in mortality, based on that mortality among males has been reported to be 5% greater than in females in a population of high-risk CHD infants [31]. However, some studies have revealed conflicting results [25, 28]. Of the 33,848 hospitalizations for CHD surgery, female infants who had high-risk procedures were at higher risk for death than male (OR, 1.21; 95% CI 1.08–1.36), although males underwent high-risk procedures and CHD surgery more frequently than females [28]. Also, in a recent study, surgical mortality was not different between male and female among 20,399 young patients (<18 years of age) [32]. Based on the results to date, we could infer that the females are affected by severe congenital heart diseases less frequently, but when affected, females could confront with a higher surgical mortality rate.

Regarding the complications of CHD, women had a 33% higher risk of PAH (OR, 1.33), a 33% lower risk of aortic outcomes (OR, 0.67; 95% CI, 0.50–0.90), a 47% lower risk of endocarditis (OR, 0.53; 95% CI, 0.40–0.70), a 55% lower risk of an implantable cardioverter defibrillator (OR, 0.45; 95% CI, 0.26–0.80), and a borderline significant 12% lower risk of arrhythmias (OR, 0.88; 95% CI, 0.77–1.02) in the CONCOR registry (Fig. 3.7) [33].

Prognosis of CHD

Gender differences in the long-term prognosis of CHD have not been studied widely yet. A published lecture provided some information about this issue as follows: In patients with repaired TOF (165 male, 104 female), symptomatic ventricular tachycardia and sudden unexpected death are frequent causes of death and morbidity in males, while the pulmonary vascular disease is the main cause of death in females. In AS, females have less severe manifestation. Females have a greater longevity of the pulmonary artery homograft than males [26]. It was reported that surgery for ACHD is at higher risk in males, and overall mortality in adulthood is greater in male patients with CHD, so the long-term survival rate is higher in females (Fig. 3.8) [34, 35].

As far as TOF is concerned, there are a few studies for gender differences in the long-term prognosis. The study from a cohort of 272 patients with repaired TOF (158 male, 114 female) demonstrated that females with repaired TOF had larger right ventricular (RV) end-systolic volumes (standard deviation scores: women, 4.35; men, 3.25), lower RV ejection fraction (women, −2.83; men, −2.12), lower RV muscle mass (women, 1.58; men, 2.45), and poor exercise capacity relative to sex-matched controls [36]. The other study of the effects of pregnancy

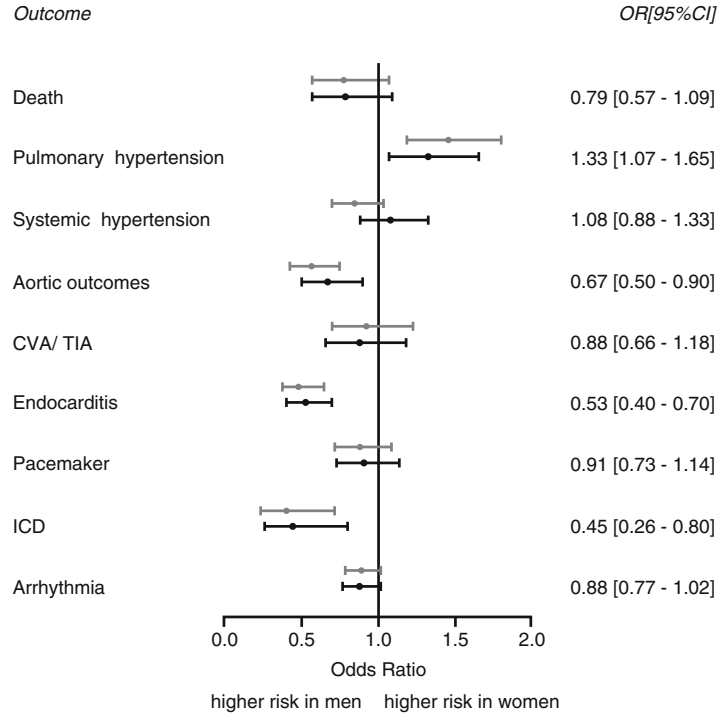

Fig. 3.7 Treatment outcomes and complications of adult congenital heart disease in women compared with men. ORs of outcomes in women compared with men. The gray lines represent ORs with 95% CIs adjusted for age only. The black lines represent ORs with 95% CIs additionally adjusted for underlying congenital heart defects. The numbers adjacent to the figure correspond to the black lines. *CVA* cerebrovascular accident, *TIA* transient ischemic attack. (From Ref. [28])

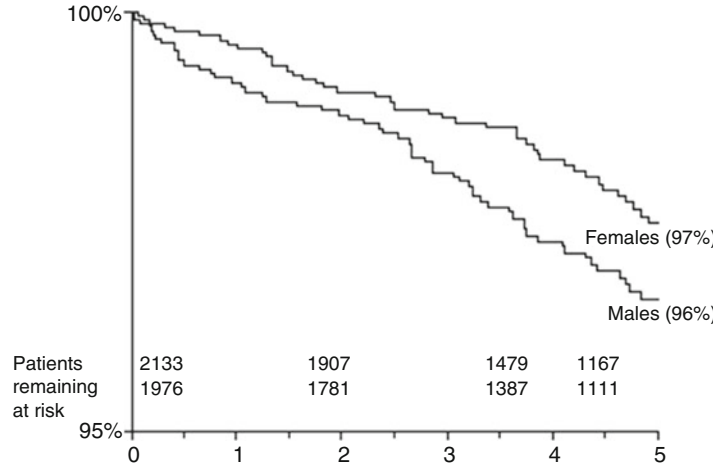

Fig. 3.8 Five-year cumulative survival curves for men and women with adult congenital heart disease, aggregated over all defects. Using Cox regression, cumulative mortality was greater in the male population (hazard ratio, 1.63; 95% CI 1.12–2.38). (Reproduced from Ref. [34], with permission from Bohn Stafleu van Loghum)

on RV remodeling in women with repaired TOF revealed that women with completed pregnancy showed accelerated RV remodeling (an increase in RV end-diastolic volume) compared with nulliparous women with repaired TOF, whereas RV systolic function does not deteriorate [37]. Gender difference in volumetric assessment of ventricles in patients with repaired TOF has been reported, showing that volumes for LV and RV in women are on average smaller, even after indexation for body surface area (Fig. 3.9) [38, 39]. Thus, even if the RV volume overload deteriorates more rapidly in women, it may be less noticeable than in men when evaluated with the same ventricular

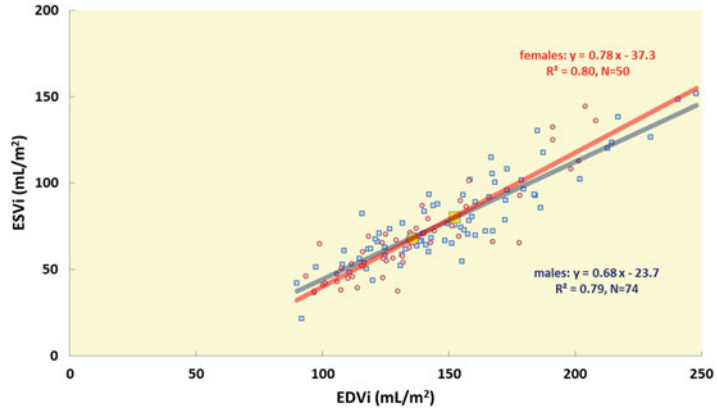

Fig. 3.9 Volume regulation graph. This representation shows end-systolic volume index (ESVi) versus end-diastolic volume index (EDVi) for the right ventricle in 124 patients with repaired tetralogy of Fallot, stratified for sex. Both ESVi ($P = 0.012$) and EDVi ($P = 0.006$) are smaller in females (see yellow circle and square), while ejection fraction is similar. (Data from Ref. [41])

volume criteria as men. Therefore, it is needed to apply sex-specific criteria during long-term follow-up of these patients.

Regarding ASD secundum, a study from CONCOR registry with 2207 adult patients with ASD closed or not revealed that male patients had a lower survival rate compared with the age- and sex-matched general population, although females had equal survival rate with controls. Moreover, males had a higher risk of conduction disturbances (OR, 1.63), supraventricular dysrhythmias (OR 1.41), cerebrovascular thromboembolic events (OR 1.53), and heart failure (OR 1.91) than females [40].

Summary

In addition to the sex-specific preponderance in the incidence of CHD, gender differences have been reported in manifestations, complications, progress to PAH, treatment outcome, and prognosis of CHD. For the gender preponderance of specific congenital heart defects, male predominance is associated with more complex and severe CHD such as AS, COA, TGA, and TOF, whereas female with more simple CHD such as ASD, PDA. Female patients with ACHD were more likely to have functional limitation than male patients and may be attributed by hormonal fluid retention and predisposition to thrombosis. It has been recognized that females have a predisposition to PAH, because female has vulnerability (i.e., genetic and hormonal susceptibility) to the development of PAH, and then the trigger of a shunt lesion initiates the vascular injury in the lungs. Sex differences in surgical mortality related to CHD are still controversial. Regarding the complications of CHD, females show higher risk of PAH and lower risk of aortic outcomes, endocarditis, and an implantable cardioverter defibrillator, while males show generally a higher prevalence of rhythm disorders. Gender differences in the long-term prognosis of CHD have not been studied widely yet, but studies on some diseases have emerged recently. Although there is little information to date, our understanding on the gender differences in CHD will be gradually improved, because the gender-specific prevention and management are essential to devise the optimal strategies for the individual characteristics of CHD.

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