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Does gender affect the prognosis and risk of complications in patients with congenital heart disease in the modern era?

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ABSTRACT

Gender differences in the outcome of acquired cardiovascular disease are well known, but available literature on the influence of gender in congenital heart disease (CHD) is limited. Registries have provided valuable, albeit at times conflicting data. Higher mortality rates have been reported in older males with CHD, while sudden cardiac death is more prevalent in young males. However, mortality around surgery for CHD is higher in girls compared to boys, likely due to smaller body size. Women are at higher risk of developing pulmonary arterial hypertension, but at lower risk of adverse aortic outcomes, even though they are less likely to receive aortic surgery. Finally, women have a lower risk of presenting with infective endocarditis compared to men. The underlying reasons for gender differences in CHD can be attributed to genetic, hormonal, behavioural and other causes. The aim of the present paper is to provide an overview of available evidence on gender differences in CHD and their impact on outcome.

1. Introduction

In recent years, there has been increasing attention to gender differences in relation to the prevalence, clinical manifestations, management and prognosis of acquired cardiovascular disease [1]. However, available data on the influence of gender in congenital heart disease (CHD) are limited and, at times, conflicting [2].

Gender-related differences are evident also regarding surgery for CHD. In the CONgenital CORvitia (CONCOR) registry, a large Dutch database including more than 8000 adult CHD patients, males had a higher likelihood of undergoing surgery in adulthood and had a consistently worse long-term survival after reoperations compared with females [3]. This may explain, at least in part, why male patients with CHD are more frequently managed conservatively [4]. It has been hypothesized that the discrepancy in outcome between genders may reflect unequal access to tertiary care [5]. In a more recent paper, the risks around reoperation for congenital heart disease were reported to be higher in the female population [6]. There is also growing awareness of the psychosocial impact of CHD. Female patients are more likely to be treated with anti-depressant medication compared to their male counterparts, for reasons that are not well understood [7].

The aim of the present review is to provide an overview of the existing evidence on gender differences among patients with CHD, and their impact on outcome. For this purpose, we have focused on common types of CHD and their complications (e.g. endocarditis), for which data on the impact of gender are available.

2. Aortic coarctation with or without aortic valve disease

Male dominance has been demonstrated in patients with aortic coarctation, with a prevalence of approximately 2.5:1 at birth [2]. In women with aortic coarctation, either operated or in natural history, mortality is not increased compared to men despite the potential impact of pregnancy. Mortality in aortic coarctation is mainly related to

List of abbreviations: AV, atrioventricular; AVSD, atrioventricular septal defect; CHD, congenital heart disease; ICD, implantable cardioverter defibrillator; IE, infective endocarditis; PA, pulmonary artery; PM, pacemaker; RV, right ventricle; TCPC, total cavo-pulmonary connection; ToF, tetralogy of Fallot.

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reintervention for associated aortic valve disease, which is higher in males who are more likely to present with an association of coarctation and aortic valve disease. On the contrary, women with aortic aneurysm have a 33% lower risk of adverse aortic outcomes (odds ratio 0.67), largely due to their smaller aorta, with consequent lower rates of aortic surgery [8].

Criteria for elective aortic surgery are not gender-specific and, since the female aorta is significantly smaller, women have a lower probability of reaching the threshold for intervention. On the other hand, fatal aortic rupture is more common in women, with a worse surgical outcome and higher mortality observed around acute dissection. These findings may suggest a suboptimal management of aortic aneurysms in female patients with aortic coarctation and support the need for gender-specific thresholds or correction for body surface area when deciding on the indications for elective aortic surgery.

Aortic coarctation affects 12% of women with Turner syndrome, which is caused by the complete absence of a sex-linked chromosome, or presence of a structurally abnormal one [9]. Even in the absence of a typical isthmic narrowing, about one half of patients with Turner syndrome have an elongated transverse arch and/or kinking of the aortic isthmus. In addition, Turner syndrome is associated with a higher risk of developing aortic dissection, which occurs at an earlier age and has a 100-fold higher incidence compared to the general population. Indeed, aortic dissection can even occur in women with Turner syndrome with mild arch abnormalities, most likely as the result of an intrinsic aortopathy, combined with abnormal shear stress related to the elongated transverse arch, predisposing these patients to potentially catastrophic aortic events.

Since aortic disease is clearly a "male domain" and the absence of a normal second X chromosome is associated with aortopathy in patients with Turner syndrome, one might speculate that one or more genes involved in the development of the aorta are located on chromosome X. X-linked genes that might be implicated in cardiovascular development include those encoding for vascular endothelial growth factor D and the angiotensin type-2 receptor, both of which are involved in fetal development [10].

3. Atrioventricular septal defects

Atrioventricular septal defects (AVSDs) include a wide spectrum of congenital anomalies, characterised by abnormalities of the atrioventricular (AV) functional septum and abnormal AV valves. Gender distribution of AVSDs appears well-balanced, even though some series report a slight female preponderance. The long-term outcome of patients with this condition is extremely heterogeneous due to significant anatomical variation, associated genetic syndromes (e.g. Down syndrome and Ellis-Van Creveld syndrome), heterotaxy (isomerism), associated defects (e.g. tetralogy of Fallot [ToF], parachute deformity, or double orifice of the left-sided AV valve), ventricular hypoplasia and/or imbalance. Surgical repair includes closure of atrial and ventricular communications as well as, often highly demanding, valve surgery with the goal of achieving two neither stenotic nor regurgitant AV valves.

There is no compelling evidence of gender-related differences in outcome after primary repair of AVSD in infancy. Surgical reintervention is frequently carried out for symptomatic left AV valve regurgitation or, more rarely, valve stenosis, left ventricular outflow tract obstruction, or large residual atrial or ventricular septal communication.

Pregnancy is usually well tolerated in female patients with repaired AVSD (WHO risk class II–III). The risk is higher in women with severe atrioventricular valve regurgitation or impaired ventricular function. The risk for offspring mortality is 6% of cases, primarily due to the recurrence of CHD [11].

4. Tetralogy of Fallot

ToF is the most common cyanotic congenital heart defect, accounting for about 10% of all CHD. Males slightly outnumber female patients by a ratio of approximately 1.3:1 [12]. No gender difference has been reported with regard to age at palliation or repair, surgical technique, and the number and type of reoperations. No gender imbalance has been found in the incidence of ventricular arrhythmias, even though QRS duration is longer in men than in women and male patients are more likely to receive an implantable cardioverter defibrillator (ICD), and do so at a younger age, compared to women ($p = 0.0001$) [13]. However, lower ICD implant rates in women may also result from gender bias, as previously reported in coronary artery disease [2].

Daliento et al. described gender differences in the clinical presentation of ToF in adulthood, with women complaining more frequently of fatigue (45% vs. 28% in men, $p = 0.05$) and exertional dyspnoea (60% vs. 36%, $p = 0.038$). They also present more frequently with psychological disorders [13]. These findings are supported by a lower peak oxygen uptake, a flatter chronotropic response and higher ventilation per unit of CO2 production (VE/VCO2 slope) on cardiopulmonary exercise testing in women compared to men with ToF. Since these exercise parameters are also strong predictors of outcome, it may be speculated that women are potentially at higher risk for adverse outcome compared with men [12].

In a German multicentre prospective study conducted on 407 adult patients with corrected ToF, differences in ventricular function and remodelling were observed between males and females. In particular, higher indexed ventricular volumes and mass were reported in males, supporting the use of gender-specific right ventricular volumetric thresholds for pulmonary valve replacement, since female patients are likely to be erroneously diagnosed with more severe right ventricular dilatation when unisex thresholds are considered [14]. However, even when gender-specific percentiles are used, males with ToF display higher RV volumes and mass compared to females at cardiac magnetic resonance [14]. To the best of our knowledge, there are no studies focusing on sex-related differences regarding RV development/hypoplasia in ToF patients. However, some reports suggested a higher prevalence of hypoplastic (mono and bi-partite) RV in men [15].

Over the period 2000–2014, in patients who underwent surgery for ToF, the standardized mortality ratio was found to be higher in women, with a higher proportion of cardiac, obstetric and sudden death [16].

5. Patients with a right ventricle-to-pulmonary artery prosthetic conduit

A prosthetic conduit between the right ventricle and pulmonary artery (RV-PA conduit) is surgically implanted to correct or palliate a number of different congenital heart defects with "complex" right ventricular outflow tract obstruction. However, such conduits invariable degenerate and are responsible for long-term complications, including the need for reintervention. Female gender recipients of prosthetic RV-PA conduits are at reduced risk of long-term intervention, whereas smoking and higher body mass index appear to be risk factors for accelerated conduit dysfunction [17]. Interestingly, in patients who have undergone a Ross procedure for congenital aortic stenosis (where an RV-PA conduit is implanted to replace the native pulmonary valve, used as an autograft in the aortic position after excision of the native aortic valve), female gender is associated with increased propensity of conduit regurgitation, whereas male gender is a risk factor for conduit stenosis [18].

Pregnancy in women with well-functioning RV-PA conduits is generally well tolerated. However, in the presence of chronic right ventricular volume overload (conduit regurgitation), pregnancy may result in accelerated right ventricular dilatation [19]. In case of conduit stenosis, careful assessment of the anatomy and functional capacity is recommended, and patients with severe obstruction and pressure overload should be considered for pre-conception transcatheter or surgical intervention.

6. Systemic right ventricle

In the general population, men have greater right ventricular mass and volumes than women, with poorer right ventricular systolic

function [20]. However, there are no data regarding sex-related differences in patients with a RV in the systemic circulation. Long-term data after atrial switch repair (Senning or Mustard) for transposition of the great arteries did not show any significant sex-related difference in morbidity or mortality [21]. In addition, there were no gender differences in mortality, systemic right ventricular dysfunction or overall morbidity in patients with congenitally corrected transposition of the great arteries.

Prolonged volume overload generated by pregnancy in women with a systemic RV is associated with increased right ventricular dimensions, reduced right ventricular ejection fraction and higher rates of tricuspid valve regurgitation, that may not recover post-delivery in up to 70% of cases. Furthermore, arrhythmic events are frequent during pregnancy in patients with previous atrial switch repair, while AV block may complicate pregnancy in women with congenitally corrected transposition of the great arteries. Nevertheless, pregnancy is often successful in patients with a systemic RV followed by specialist services, but still carries a significant risk of clinical deterioration (worsening functional class) [22], even in women who were previously asymptomatic. Pregnancy may, indeed, accelerate the process of clinical deterioration, which is part of the natural history of a systemic RV; this should be discussed with the patient during pre-conception counselling.

In patients who have undergone a Senning or Mustard procedure, gender differences in angiotensin II and aldosterone secretion have been demonstrated, with female patients having significantly higher aldosterone levels than male patients [23]. Furthermore, a negative correlation between angiotensin II levels and right ventricular fractional area change, and a positive correlation between aldosterone levels and right ventricular end-diastolic area were observed in female patients only. A similar negative correlation between angiotensin II levels and ventricular ejection fraction and geometry had previously been described in Fontan patients.

7. Univentricular heart

This group includes a wide range of congenital heart defects, with highly diverse anatomical substrates and pathophysiology. The vast majority of patients undergo a staged approach to a single-ventricular palliation, achieving two separate circulations, improving or abolishing cyanosis and decreasing systemic ventricular volume load.

The total cavo-pulmonary connection (TCPC) is a staged surgical palliation aimed at re-routing the systemic venous return to the pulmonary arteries without the interposition of a ventricle. The surgical creation of such a palliation has undergone multiple modifications since its original description by Fontan. Nowadays, the "extracardiac conduit" and "lateral tunnel" versions have been uniformly adopted in most congenital heart programmes. However, in adult patients, older versions of the Fontan operation (e.g. atrio-pulmonary connection) are often encountered.

Gender-related demographic and outcome differences have been reported in patients with Fontan palliation, although not always linked to the underlying congenital heart defect. Recent data suggest that the overall risk for major cardiovascular complications, including mortality, is expected to increase in males compared to females receiving a TCPC [24]. Moreover, male patients with atrio-pulmonary Fontan undergoing TCPC conversion have a higher perioperative mortality compared to female patients [25]. Male patients with TCPC are at increased risk of progressive aortic dilatation and aortic valve regurgitation, even though severe regurgitation is rarely reported [26]. Male gender has been associated with an increased propensity towards haemorrhagic complications in patients receiving long-term anticoagulation [25]. However, conflicting evidence exists on this issue, since other authors have not confirmed that gender is an independent predictor of mortality in Fontan palliation [27].

Pregnancy is generally not contraindicated in women with TCPC but carries a risk of cardiovascular and obstetric complications, including arrhythmias, thrombosis, and congestive heart failure, as well as a significant risk of miscarriage. Accordingly, all Fontan patients should undergo expert pre-pregnancy evaluation in a tertiary centre.

8. Infective endocarditis

Patients with CHD are at increased risk of developing IE [28,29]. Women are at reduced risk of developing infective endocarditis (IE) [29]. Tutarel et al. reported a male preponderance of IE (71%) in a single tertiary grown-up CHD centre [30]. It has been postulated that better dental and skin hygiene in women compared to men and lower predilection for smoking and/or intravenous drug use may be the reasons why women are less likely to develop IE. Indeed, women are less likely to develop IE in the community compared to healthcare-associated IE. Male predominance of IE decreases with age: while the incidence of IE over the last 3–4 decades in men has remained somewhat stable, it increased in women [28]. This may be secondary to the increased life expectancy and a rise in healthcare related infections.

The majority of IE cases occur in patients with underlying left ventricular outflow tract lesions, shunts (e.g. ventricular septal defects) and ToF, or pulmonary atresia [30]. Differences in sex distribution between these lesions may influence gender distribution of IE, with men being more likely to have a bicuspid aortic valve compared to women and hence presenting more often with IE.

Gender, however, does not appear to influence the outcome of IE among adults with CHD [30]. IE during pregnancy is very rare, affecting approximately 1/100,000 pregnancies, and is more common in patients with known valvular or CHD (0.5%) and in drug addicts [31].

Prophylaxis for dental procedures should follow standard guideline recommendations. There is no evidence for antibiotic prophylaxis outside dental procedures, including delivery, and hence it is not generally recommended during vaginal or caesarean delivery. Timely diagnosis and treatment of IE in pregnancy is essential, as maternal morbidity and mortality and fetal mortality are high [32].

However, the clinical picture may be confounded by symptoms relating to pregnancy itself and its effects on the underlying cardiac defect.

IE should be treated in pregnant women in the same way as in non-pregnant patients, keeping in mind the potential foetotoxic effects of certain antibiotics. Penicillin, ampicillin, amoxicillin, erythromycin, mezlocillin, and cephalosporins appear safe in all trimesters, while vancomycin, imipenem, rifampicin, and teicoplanin are group C drugs, hence risk to the foetus cannot be excluded. Aminoglycosides, quinolones, and tetracyclines are group D drugs and should only be used for extreme cases and life-threatening situations, carefully weighing the risks and potential benefits [11].

Valve surgery during pregnancy should only be performed when medical therapy has failed or there are pressing indications (e.g. high risk of embolic events); if the foetus is viable, delivery prior to, or at the time of surgery should be considered [31].

9. Device implantation

Women are more likely to receive a single chamber pacemaker (PM), and less likely to receive a rate-responsive PM. This may be due to a higher likelihood of women presenting with sinus node dysfunction rather than AV node dysfunction and older age at implantation. Softer indications for PM implantation are likely to result in less device implantation in women compared to men [33].

Moreover, women often present with different symptoms compared to men and may be subjected to fewer investigations; under-investigation and suboptimal management have been described in women with cardiovascular disease (the so-called "Yentl syndrome"), resulting from a longstanding (erroneous) perception that cardiovascular disease and complications are less common in women than in men.

The indications for implantation of an ICD in CHD patients remain empiric and are still debated, especially for primary prevention. Patients with severe ventricular dysfunction or ToF with certain risk factors,

Table 1
Gender differences in patients with congenital heart disease.

Specific disease/condition	Male	Female	Reference
Overall mortality	Higher	Lower	[1,7]
Sudden cardiac death	Higher	Lower	[12]
Surgery-related mortality	Lower	Higher	[1,5]
Occurrence of pulmonary arterial hypertension	Lower	Higher	[1–8]
Poorer outcome in aortic disease	Higher	Lower	[1,7]
Occurrence of infective endocarditis	Higher	Lower	[2,28]
Need for pacing/defibrillator	Lower	Higher	[30]

presenting with sustained ventricular arrhythmias or syncope, may receive an ICD for secondary prevention [33]. Women are less likely to receive an ICD, even though no gender difference exists in the risk of malignant arrhythmias between genders [2]. In one study, women were more likely than men to refuse an ICD and more women were considered medically ineligible for a device [34]. Defibrillator use in CHD patients, who are generally younger than their non-CHD counterparts, is associated with anxiety and low device acceptance compared to PMs [35]. Women under the age of 50 may be at greater risk of developing psychosocial distress and anxiety related to the risk of shocks, death and impact on body image. However, device acceptance is equally low among men and women [35].

Pregnant women who develop complete heart block with a slow ventricular rate and a wide QRS complex should undergo PM implantation during pregnancy, while in patients with a stable narrow junctional escape rhythm, PM implantation can be deferred to the post-partum period [36]. Permanent pacing during pregnancy carries low risks, especially after 8 weeks of gestation. Fluoroscopy may be avoided or minimised using echocardiography or electro-anatomical navigation. Patients with congenital heart block are deemed at low risk of complications around pregnancy and do not normally require pacing. Pregnant patients presenting with malignant tachycardias should be considered for ICD implantation for protecting the mother's life. The presence of an ICD is not a contraindication for pregnancy, even though the condition that led to ICD implantation (e.g. severe ventricular dysfunction) may be of concern. Pregnancy does not appear to affect ICD operation, and this is unlikely to impact on the outcome of pregnancy, although one miscarriage likely due to shock therapy has been reported [37].

10. Pulmonary arterial hypertension

Women with CHD are at increased risk of developing pulmonary arterial hypertension [2]. In the Dutch nationwide CONCOR national registry for adults with CHD [3], women were 35% more likely to present with pulmonary hypertension, defined as a systolic pulmonary artery pressure above 40 mmHg. Atrial and ventricular septal defects were the most common lesions in the overall cohort and were more likely to be associated with pulmonary hypertension compared to other defects. These findings are in keeping with previous reports [38]. Interestingly, in the CONCOR registry [3] there was no difference in gender distribution for Eisenmenger syndrome (severe pulmonary hypertension with reversal of the original left-to-right shunt and cyanosis). This finding seems to suggest similar rates of progression of pulmonary vascular disease in men and women. A similarly equal distribution of Eisenmenger syndrome between genders was described by the Euro Heart Survey [39], while the Mayo Clinic reported a significantly higher frequency of isolated secundum atrial septal defects with Eisenmenger syndrome in females [39].

The association of pulmonary hypertension with female sex is fascinating. Idiopathic pulmonary arterial hypertension is more common in women, and one wonders whether women are more predisposed to develop pulmonary vascular disease in response to haemodynamic or other triggers, compared to men. However, no known genetic mutations associated with idiopathic pulmonary arterial hypertension are sex-linked. Some authors speculate that a left-to-right shunt at atrial level in Eisenmenger patients is an "innocent bystander" and the underlying pathophysiology is primarily that of idiopathic pulmonary arterial hypertension. However, a "two-hit hypothesis" is more likely: a large left-to-right shunt through the atrial septal defect may induce pulmonary vascular injury in a "predisposed" pulmonary circulation, which, in turn, leads to endothelial and vascular smooth muscle dysfunction, with pulmonary vascular remodelling [40]. The female tendency to develop pulmonary vascular injury more frequently compared to men may relate to hormonal factors and the potential burden of pregnancy. Pregnancy-induced haemodynamic cardiovascular changes may precipitate pulmonary vascular disease, especially in women with a pulmonary vascular bed previously exposed to excessive pressure or volume [40].

Table 2
Clinical characteristics of the enrolled studies.

Author	Main characteristic(s) of the research
Daly C, et al. [1]	Gender differences in management/outcome of stable angina
Michalski AM, et al. [2]	Gender differences in congenital heart disease prevalence at birth
Verheugt CL, et al. [5]	Gender differences in surgery for congenital heart disease
Beurtheret S, et al. [6]	Gender differences in outcome among grown-up congenital heart disease
Verheugt CL, et al. [7]	Gender differences in outcome among grown-up congenital heart disease
Ho VB, et al. [8]	Features of vascular anomalies in Turner's syndrome
Sachdev V, et al. [9]	Features of aortic valve disease in Turner's syndrome
Diller GP, et al. [10]	Gender differences in anti-depressant therapy among grown-up congenital heart disease after surgery
Sarikouch S, et al. [12]	Gender differences in right ventricular function and exercise capacity in tetralogy of Fallot
Daliento L, et al. [13]	Gender differences in pregnancy outcome in tetralogy of Fallot
Mercuro G, et al. [15]	Gender differences in congenital heart defects and arrhythmias
Wu MH, et al. [16]	Gender differences in epidemiology, arrhythmias appearance, mortality among grown-up congenital heart disease
Buber J, et al. [17]	Gender differences in right ventricle-pulmonary artery conduit durability after Ross procedure
Mokhles MM, et al. [18]	Gender differences in right ventricle-pulmonary artery conduit durability after Ross procedure
Egidy Assenza G, et al. [19]	Effect of pregnancy in tetralogy of Fallot
Kawut SM, et al. [20]	Gender differences in right ventricle structure and function
Turina M, et al. [21]	Gender differences in outcome in transposition of the great vessels after atrial switch
Guedes A, et al. [22]	Effect of pregnancy in transposition of the great vessels after atrial switch
Szymansi P, et al. [23]	Gender differences in angiotensin II and aldosterone secretion in systemic right ventricle
Schilling C, et al. [24]	Gender differences in Fontan patients
Said SM, et al. [25]	Gender differences in Fontan patients
Kim YY, et al. [26]	Gender differences in aortic dilatation in Fontan patients
Correa de Sa DD, et al. [28]	Gender differences in infective endocarditis
Habib G, et al. [29]	European Society of Cardiology guidelines on infective endocarditis
Tutarel O, et al. [30]	Gender differences in infective endocarditis among grown-up congenital heart disease
Regitz-Zagrosek G, et al. [31]	European Society of Cardiology guidelines on pregnancy in grown-up congenital heart disease
Lamas GA, et al. [33]	Gender differences in permanent pace-maker insertion
Horton HL, et al. [34]	Gender differences in permanent defibrillator insertion
Bedair R, et al. [35]	Gender differences in psychological acceptance of permanent defibrillator insertion
Brignole M, et al. [36]	European Society of Cardiology guidelines on cardiac pacing/resincronization therapy
Natale A, et al. [37]	Implantable cardioverter-defibrillators in pregnancy
Sommerville J, et al. [38]	Peculiarities in women suffering from congenital heart disease
Engelfriet PM, et al. [39]	Gender differences in pulmonary arterial hypertension
Warnes CA, et al. [40]	Gender differences in congenital heart disease

11. Conclusions

In conclusion, gender differences do exist in CHD and may affect outcome of these patients, but little is known on the underlying mechanisms (genetic, hormonal, behavioural or other) (Tables 1 and 2). Therefore, gender should be part of the risks stratification patients in conditions in which there is evidence of sex-related increased risk exists. While gender should be considered when reporting on imaging (e.g. ventricular volumes or aortic dimensions), it is unclear whether published gender differences in outcome should advocate a more aggressive surgical approach.

Pregnancy can impact significantly on the well-being of women with CHD and appropriate personalised counselling should be part of the routine follow-up of all women with CHD of reproductive age, starting from the time of transition from paediatric to adult CHD services. Large registries are required to clarify the male-female divide in CHD and define whether gender-specific management strategies are needed.

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References

[1] C. Daly, F. Clemens, Lopez Sendon JL Tavazzi L, Boersma E, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM; Euro Heart Survey Investigators. Gender differences in the management and clinical outcome of stable angina, Circulation 113 (2006) 490–498.
[2] A.M. Michalski, S.D. Richardson, M.L. Browne, S.L. Carmichael, M.A. Canfield, A.R. VanZutphen, M.T. Anderka, E.G. Marshall, C.M. Druschel, Sex ratios among infants with birth defects, National Birth Defects Prevention Study, 1997-2009, Am. J. Med. Genet. A 167A (2015) 1071–1081.
[3] A.C. Zomer, C.L. Verheugt, I. Vaartjes, C.S. Uiterwaal, M.M. Langemeijer, D.R. Koolbergen, M.G. Hazekamp, J.P. van Melle, T.C. Konings, L. Bellersen, D.E. Grobbee, B.J. Mulder, Surgery in adults with congenital heart disease, Circulation 124 (2011) 2195–2201.
[4] G. Giannakoulas, K. Vasiliadis, A. Frogoudaki, C. Ntellos, A. Tzifa, S. Brili, A. Manginas, M. Papaphylactou, D. Parcharidou, N. Kampouridis, A. Pitsis, A. Chamaidi, M. Kolios, G. Papadopoulos, A. Douras, P. Davlouros, D. Ntiloudi, H. Karvounis, A. Kalangos, C. Tsioufis, S. Rammos, CHALLENGE investigators, Adult congenital heart disease in Greece: preliminary data from the CHALLENGE registry, Int. J. Cardiol. 245 (2017) 109–113.
[5] C.L. Verheugt, C.S. Uiterwaal, I. Vaartjes, E.T. van der Velde, A.C. Zomer, F.J. Meijboom, P.G. Pieper, M.C. Post, H.W. Vliegen, M.G. Hazekamp, D.E. Grobbee, B.J. Mulder, Chance of surgery in adult congenital heart disease, Eur. J. Prev. Cardiol. 24 (2017) 1319–1327.
[6] S. Beurtheret, O. Tutarel, G.P. Diller, C. West, E. Ntalarizou, N. Resseguier, V. Papaioannou, R. Jabbour, V. Simpkin, A.J. Bastin, S.V. Babu-Narayan, B. Bonello, W. Li, B. Sethia, H. Uemura, M.A. Gatzoulis, D. Shore, Contemporary cardiac surgery for adults with congenital heart disease, Heart 103 (2017) 194–202.
[7] C.L. Verheugt, C.S.P.M. Uiterwaal, E.T. van der Velde, F.J. Meijboom, P.G. Pieper, H.W. Vliegen, A.P. van Dijk, B.J. Bouma, D.E. Grobbee, B.J. Mulder, Gender and outcome in adult congenital heart disease, Circulation. 118 (2008) 26–32.
[8] V.B. Ho, V.K. Bakalov, M. Cooley, P.L. Van, M.N. Hood, T.R. Burklow, C.A. Bondy, Major vascular anomalies in Turner's syndrome: prevalence and magnetic resonance angiographic features, Circulation 110 (2004) 1694–1700.
[9] V. Sachdev, L.A. Matura, S. Sidenko, V.B. Ho, A.E. Arai, D.R. Rosing, C.A. Bondy, Aortic valve disease in Turner syndrome, J. Am. Coll. Cardiol. 51 (2008) 1904–1909.
[10] G.P. Diller, A. Brautigam, A. Kempny, A. Uebing, R. Alonso-Gonzalez, L. Swan, S.V. Babu-Narayan, H. Baumgartner, K. Dimopoulos, M.A. Gatzoulis, Depression requiring anti-depressant drug therapy in adult congenital heart disease: prevalence, risk factors, and prognostic value, Eur. Heart J. 37 (2016) 771–782.
[11] Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA; ESC Scientific Document Group. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur. Heart J. 2018;39:3165–41.
[12] S. Sarikouch, D. Boethig, B. Peters, S. Kropf, K.O. Dubowy, P. Lange, T. Kuehne, A. Haverich, Beerbaum P; Investigators of the German Competence Network for Congenital Heart Defects. Poorer right ventricular systolic function and exercise capacity in women after repair of tetralogy of Fallot: a sex comparison of standard deviation scores based on sex-specific reference values in healthy control subjects, Circ. Cardiovasc. Imaging 6 (2013) 924–933.
[13] L. Daliento, L. Dal Bianco, F. Bagato, E. Secco, B. Sarubbi, E. Mazzotti, B. Bauce, G. Rizzoli, Gender differences and role of pregnancy in the history of post-surgical women affected by tetralogy of Fallot, PLoS One 7 (2012), e49729.
[14] C. Lee, C.H. Lee, J.G. Kwak, S.H. Kim, W.S. Shim, S.Y. Lee, S.I. Jang, S.J. Park, Y.M. Kim, Factors associated with right ventricular dilatation and dysfunction in patients with chronic pulmonary regurgitation after repair of tetralogy of Fallot: analysis of magnetic resonance imaging data from 218 patients, J. Thorac. Cardiovasc. Surg. 148 (6) (2014) 2589–2595.
[15] G. Mercuro, P.P. Bassareo, E. Mariucci, M. Deidda, A.M. Zedda, M. Bonvicini, Sex differences in congenital heart defects and genetically induced arrhythmias, J. Cardiovasc. Med. 15 (2014) 855–863.
[16] M.H. Wu, C.W. Lu, H.C. Chen, F.Y. Kao, S.K. Huang, Adult congenital heart disease in a nationwide population 2000-2014: epidemiological trends, arrhythmia, and standardized mortality ratio, J. Am. Heart Assoc. 7 (2018), e007907.
[17] J. Buber, G.E. Assenza, A. Huang, A.M. Valente, S.M. Emani, K. Gauvreau, A.C. Marshal, D.B. McElhinney, M.J. Landzberg, Durability of large diameter right ventricular outflow tract conduits in adults with congenital heart disease, Int. J. Cardiol. 175 (2014) 455–463.
[18] M.M. Mokhles, E.I. Charitos, U. Stierle, J. Rajeswaran, E.H. Blackstone, A.J. Bogers, J.J. Takkenberg, H.H. Sievers, The fate of pulmonary conduits after the Ross procedure: longitudinal analysis of the German-Dutch Ross registry experience, Heart. 99 (2013) 1857–1866.
[19] G. Egidy Assenza, D. Cassater, M. Landzberg, T. Geva, J. Schreier, D. Graham, M. Volpe, N. Barker, K. Economy, A.M. Valente, The effects of pregnancy on right ventricular remodeling in women with repaired tetralogy of Fallot, Int. J. Cardiol. 168 (2013) 1847–1852.
[20] S.M. Kawut, J.A. Lima, R.G. Barr, H. Chahal, A. Jain, H. Tandri, A. Praestgaard, E. Bagiella, J.R. Kizer, W.C. Johnson, R.A. Kronmal, D.A. Bluemke, Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study, Circulation 123 (22) (2011) 2542–2551.
[21] M. Turina, R. Siebenmann, P. Nussbaumer, A. Senning, Long-term outlook after atrial correction of transposition of great arteries, J. Thorac. Cardiovasc. Surg. 95 (1988) 828–835.
[22] A. Guédès, L.A. Mercier, L. Leduc, L. Bérubé, F. Marcotte, A. Dore, Impact of pregnancy on the systemic right ventricle after a Mustard operation for transposition of the great arteries, J. Am. Coll. Cardiol. 44 (2004) 433–437.
[23] P. Szymański, A. Klisiewicz, B. Lubiszewska, M. Lipczyńska, M. Kowalski, J. Janas, P. Hoffman, Gender differences in angiotensin II and aldosterone secretion in patients with pressure overloaded systemic right ventricles are similar to those observed in systemic arterial hypertension, Int. J. Cardiol. 147 (2011) 366–370.
[24] C. Schilling, K. Dalziel, R. Nunn, K. Du Plessis, W.Y. Shi, D. Celermajer, D. Winlaw, R.G. Weintraub, L.E. Grigg, D.J. Radford, A. Bullock, T.L. Gentles, G.R. Wheaton, T. Hornung, R.N. Justo, Y. d'Udekem, The Fontan epidemic: population projections from the Australia and New Zealand Fontan Registry, Int. J. Cardiol. 219 (2016) 14–19.
[25] S.M. Said, H.M. Burkhart, H.V. Schaff, F. Cetta, D.J. Driscoll, Z. Li, W.C. Oliver Jr., N.M. Ammash, J.A. Dearani, Fontan conversion: identifying the high-risk patient, Ann. Thorac. Surg. 97 (2014) 2115–2121.
[26] Y.Y. Kim, R.H. Rathod, K. Gauvreau, E.M. Keenan, P. Del Nido, T. Geva, Factors associated with severe aortic dilation in patients with Fontan palliation, Heart 103 (2017) 280–286.
[27] Y.T. Lan, R.K. Chang, H. Laks, Outcome of patients with double-inlet left ventricle or tricuspid atresia with transposed great arteries, J. Am. Coll. Cardiol. 43 (2004) 113–119.
[28] D.D. Correa de Sa, I.M. Tleyjeh, N.S. Anavekar, J.C. Schultz, J.M. Thomas, B.D. Lahr, A. Bachuwar, M. Pazdernik, J.M. Steckelberg, W.R. Wilson, L.M. Baddour, Epidemiological trends of infectiveendocarditis: a population-based study in Olmsted County, Minnesota, Mayo Clin. Proc. 85 (2010) 422–426.
[29] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; ESC Scientific Document Group. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM), Eur. Heart J. 36 (2015) 3075–3128.
[30] O. Tutarel, R. Alonso-Gonzalez, C. Montanaro, R. Schiff, A. Uribarri, A. Kempny, M.R. Grübler, A. Uebing, L. Swan, G.P. Diller, K. Dimopoulos, M.A. Gatzoulis, Infective endocarditis in adults with congenital heart disease remains a lethal disease, Heart 104 (2018) 161–165.
[31] V. Regitz-Zagrosek, C. Blomstrom Lundqvist, C. Borghi, R. Cifkova, R. Ferreira, J.M. Foidart, J.S. Gibbs, C. Gohlke-Baerwolf, B. Gorenek, B. Iung, M. Kirby, A.H. Maas, J. Morais, P. Nihoyannopoulos, P.G. Pieper, P. Presbitero, J.W. Roos-Hesselink, M. Schaufelberger, U. Seeland, L. Torracca, ESC Committee for Practice Guidelines. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during pregnancy of the European Society of Cardiology (ESC). Endorsed by the European Society of Gynecology (ESG), the Association for European Paediatric Cardiology (AEPC), and the German Society for Gender Medicine (DGesGM), Eur. Heart J. 32 (2011) 3147–3197.
[32] K.Y. Kebed, K. Bishu, R.I. Al Adham, L.M. Baddour, H.M. Connolly, M.R. Sohail, J.M. Steckelberg, W.R. Wilson, M.H. Murad, N.S. Anavekar, Pregnancy and postpartum infective endocarditis: a systematic review, Mayo Clin. Proc. 89 (2014) 1143–1152.

[33] G.A. Lamas, C.L. Pashos, S.L. Normand, B. McNeil, Permanent pacemaker selection and subsequent survival in elderly Medicare pacemaker recipients, Circulation 91 (1995) 1063–1069.
[34] H.L. Horton, R.A. Marinchak, S.J. Rials, P.R. Kowey, Gender differences in device therapy for malignant ventricular arrhythmias, Arch. Intern. Med. 155 (1995) 2342–2345.
[35] R. Bedair, S.V. Babu-Narayan, K. Dimopoulos, S. Quyam, A.M. Doyle, L. Swan, M.A. Gatzoulis, T. Wong, Acceptance and psychological impact of implantable defibrillators amongst adults with congenital heart disease, Int. J. Cardiol. 181 (2015) 218–224.
[36] M. Brignole, A. Auricchio, G. Baron-Esquivias, P. Bordachar, G. Boriani, O.A. Breithardt, J. Cleland, J.C. Deharo, V. Delgado, P.M. Elliott, B. Gorenek, C.W. Israel, C. Leclercq, C. Linde, L. Mont, L. Padeletti, R. Sutton, Vardas PE; ESC Committee for Practice Guidelines (CPG). 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA), Eur. Heart J. 34 (2013) 2281–2329.
[37] A. Natale, T. Davidson, M.J. Geiger, K. Newby, Implantable cardioverter-defibrillators and pregnancy: a safe combination? Circulation 96 (1997) 2808–2812.
[38] J. Somerville, The Denolin lecture: the woman with congenital heart disease, Eur. Heart J. 19 (1998) 1766–1775.
[39] P.M. Engelfriet, M.G. Duffels, T. Möller, E. Boersma, J.G. Tijssen, E. Thaulow, M.A. Gatzoulis, B.J. Mulder, Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease, Heart 93 (2007) 682–687.
[40] C.A. Warnes, Sex differences in congenital heart disease: should a woman be more like a man? Circulation 118 (2008) 3–5.