International Journal of Cardiology Congenital Heart Disease 3 (2021) 100107

Contents lists available at ScienceDirect

International Journal of Cardiology Congenital Heart Disease

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-congenital-heart-disease

Congenital heart disease in the ESC EORP Registry of Pregnancy and Cardiac disease (ROPAC)☆

Karishma P. Ramlakhan [a], Mark R. Johnson [b], Malgorzata Lelonek [c], Aly Saad [d], Zaur Gasimov [e], Natalia V. Sharashkina [f], Patrick Thornton [g], Margaret Arstall [h], Roger Hall [i], Jolien W. Roos-Hesselink [a,*], on behalf of theROPAC Investigators Group, ROPAC Executive Committee, ROPAC Investigators

[a] Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Academic Department of Obstetrics and Gynaecology, Imperial College London, Chelsea and Westminster Hospital, London, United Kingdom
[c] Department of Noninvasive Cardiology, Medical University of Lodz, Lodz, Poland
[d] Department of Cardiovascular Medicine, Zagazig University, Zagazig, Egypt
[e] Department of Preventive Cardiology, Research Institute of Cardiology named after J. Abdullayev, Baku, Azerbaijan
[f] Russian Gerontology Research and Clinical Centre, Pirogov National Research Medical University, Moscow, Russia
[g] Department of Anaesthesia, Rotunda Hospital, Dublin, Ireland
[h] Cardiology Unit, Northern Adelaide Local Health Network, SA, Australia
[i] Department of Cardiology, Norwich Medical School, University of East Anglia, Norwich, United Kingdom

ARTICLE INFO

Keywords:
Congenital heart disease
Pregnancy
Maternal health
Observational registry

Introduction

Pregnancy is a major burden on the maternal cardiovascular system. Hormonal changes cause a drop in systemic vascular resistance and a compensatory volume expansion, leading to a 30–50% increase in cardiac output [1]. Cardiac output peaks at the end of the second trimester and remains on a plateau thereafter, until delivery. During labour, pain, stress and the uterine contractions increase cardiac output by another 25%. These changes, with the abrupt cessation of the increased utero-placental blood flow at delivery with the return of 500–700 mls into the systemic circulation, make the postpartum period high risk for the development of heart failure [2,3]. Additionally, the risk of arrhythmias, thrombosis and aortic dissection is increased during and shortly after pregnancy [3]. The impact of pregnancy on the cardiovascular system may explain why cardiac disease is the leading cause of maternal mortality in high income countries and why women with pre-existing cardiac disease, including congenital heart disease (CHD), are at particular risk [4,5].

For women with cardiac disease, hard data are very limited and the clinical management of pregnancy often remains based on expert opinion derived from clinical experience. The inherent difficulty in performing randomized controlled trials in pregnant women further compounds the situation. However, advances in medical and surgical treatment have increased the number of adult CHD patients, and consequently the number of pregnant CHD patients [6]. CHD is now the most common form of heart disease seen in pregnancy [7]. Advances in care mean that even women with complex CHD, such as a Fontan circulation, are now becoming pregnant and the need for data upon which to base clinical management is becoming urgent.

In an attempt to define optimal care for women with heart disease the ESC EORP Registry Of Pregnancy And Cardiac disease (ROPAC), which is a prospective, observational worldwide registry, was initiated in 2007. Patients with structural heart disease, congenital heart disease (CHD), valvular heart disease (VHD), cardiomyopathy (CMP), ischemic heart disease (IHD), aortic pathology (AOP) and pulmonary hypertension (PH) were included.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author. Erasmus University Medical Center Department of Cardiology, Rg-435 P.O. Box: 2040, 3000 CA, Rotterdam, the Netherlands.
E-mail address: j.roos@erasmusmc.nl (J.W. Roos-Hesselink).

https://doi.org/10.1016/j.ijcchd.2021.100107
Received 16 February 2021; Accepted 21 February 2021

Between 2007 and 2018, 5739 pregnancies from 138 centres in 53 countries were included in the ROPAC, and in 2019 the main results were published for the entire cohort [7]. There have been earlier ROPAC publications for specific CHD diagnoses, including aortic coarctation, transposition of the great arteries (TGA), tetralogy of Fallot, aortic stenosis and uncorrected CHD [8–12]. However, a detailed overview of the ROPAC data on characteristics and pregnancy outcomes for women with CHD has not been published previously and is the focus of this manuscript.

Methods

A detailed description of the ROPAC study protocol and design has been published previously [13]. Pregnancies in women with CHD, VHD, CMP, IHD, AOP or PH were prospectively included between 2007 and 2018. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and ethical approval or Institutional Review Board approval as well as patients' informed consent was obtained if necessary according to local requirements. Baseline characteristics before pregnancy included age, parity, primary cardiac diagnosis and concomitant cardiac disease, prior interventions, cardiovascular risk factors, New York Heart Association (NYHA) functional classification, cardiac medication and if available, echocardiographic parameters. Maternal cardiovascular risk was classified according to the modified World Health Organization (mWHO) classification scale [14].The International Monetary Fund classification was used to define a participating country as low or middle-income (LMIC). Stillbirth was defined as fetal mortality >20 weeks of gestation, a low Apgar score as <7 at 5 min and small for gestational age (SGA) as birth weight less than the 10th percentile.

Statistical analysis

Baseline characteristics and outcomes were compared between CHD and non-CHD (VHD, CMP, IHD, AOP and PH) ROPAC pregnancies. Cardiac, obstetric and fetal outcomes were examined for the total CHD cohort, as well as per mWHO category. A composite endpoint of maternal mortality and heart failure was further examined for specific CHD diagnoses. Categorical data are presented as percentages and were compared using χ^2 tests. Continuous data are presented as mean (standard deviation) when normally distributed or as median (Q1-Q3) when not and compared using independent samples t-tests or Mann-Whitney tests. Logistic regression analysis was used to identify associations with the composite endpoint, presented as odds ratio with 95% confidence intervals (CI) and p-value. The following parameters that were significant at the $p < 0.1$ level in the univariable analysis, as well as parameters known to influence the composite endpoint, were added to the multivariable analysis: signs of heart failure, NYHA class > II, pulmonary hypertension, cyanosis, atrial fibrillation, LMIC, estimated LVEF <40%, multiple gestation, cardiac medication use, mWHO > II, age, prior cardiac intervention, BMI, current smoking and chronic hypertension. A two-sided p-value <0.05 was considered significant for all analyses. All analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp).

Results

Of 5739 pregnancies included in the ROPAC, 3295 (57.4%) were in women with CHD (mean age 29 years). Baseline characteristics are presented in Table 1. Compared to the 2444 non-CHD women in the ROPAC, the women with CHD were younger, more often nulliparous and living in a high-income country (all $p < 0.001$, Table 1). The CHD group had less pre-pregnancy hypertension, atrial fibrillation, signs of heart failure, reduced LVEF and cardiac medication use than the non-CHD group (all $p < 0.001$), but more prior cardiac interventions (68.9% vs 36.9%, $p < 0.001$). Correspondingly, the CHD pregnancies were in lower mWHO risk categories. ASD (n = 495) was the most frequent main diagnosis, followed by VSD (n = 463) and tetralogy of Fallot (n = 426, Fig. 1 and supplementary table S1).

Table 1
Baseline characteristics.

	All ROPAC n = 5739	CHD n = 3295	Non-CHD n = 2444	p-value*
Age, years (sd)	29.5 (5.6)	29 (5.4)	30.2 (5.9)	**<0.001**
BMI, kg/m^2 (Q1-Q3)	24 (21–28)	23 (21–27)	25 (22–29)	**<0.001**
Nulliparity	2573 (45)	1704 (51.9)	869 (35.7)	**<0.001**
Multiple pregnancy	96 (1.7)	46 (1.4)	50 (2)	0.058
LMIC	2281 (39.7)	936 (28.4)	1345 (55)	**<0.001**
Current smoker	228 (4.6)	132 (4.8)	96 (4.4)	0.478
Chronic hypertension	380 (6.7)	183 (5.6)	197 (8.2)	**<0.001**
Diabetes mellitus	90 (1.6)	42 (1.3)	48 (2)	**0.042**
Atrial fibrillation	106 (1.8)	16 (0.5)	90 (3.7)	**<0.001**
Signs of heart failure	596 (10.5)	213 (6.5)	383 (15.9)	**<0.001**
Estimated LVEF <40%	253 (4.4)	64 (1.9)	189 (7.7)	**<0.001**
Cyanosis	63 (1.1)	54 (1.6)	9 (0.4)	**<0.001**
Pulmonary hypertension	575 (10)	177 (5.4)	398 (16.3)	**<0.001**
NYHA class > II	204 (3.6)	61 (1.9)	143 (5.9)	**<0.001**
Cardiac medication use	2069 (36.1)	831 (25.2)	1238 (50.7)	**<0.001**
Prior cardiac intervention	3160 (55.3)	2261 (68.9)	899 (36.9)	**<0.001**
mWHO I	1185 (20.6)	1055 (32)	130 (5.3)	**<0.001**
mWHO II	828 (14.4)	828 (25.1)	0 (0)	**<0.001**
mWHO II-III	2698 (47)	944 (28.6)	1754 (71.8)	**<0.001**
mWHO III	593 (10.3)	334 (10.1)	259 (10.6)	0.571
mWHO IV	407 (7.1)	134 (4.1)	273 (11.2)	**<0.001**

Data in n (%) unless otherwise specified. *P-value calculated between the CHD and non-CHD pregnancies. Bold script denotes $p < 0.05$. BMI, Body Mass Index; CHD, congenital heart disease; LMIC, low/middle-income country; LVEF, left ventricular ejection fraction; mWHO, modified World Health Organization classification for maternal cardiovascular risk; NYHA, New York Heart Association functional classification; ROPAC, Registry of Pregnancy and Cardiac disease.

Fig. 2 describes the pregnancy outcomes of women with CHD. Maternal mortality occurred in 0.3% and heart failure in 6.6%, the latter was the most common cardiac complication. The composite endpoint of mortality and/or heart failure was 6.7%. Other complications included ventricular tachyarrhythmia in 1.2%, thrombo-embolic events in 1.2%, atrial fibrillation or flutter in 1.1% and endocarditis in 0.6%. There was one pregnancy (0.03%) complicated by aortic dissection, in a woman with congenital mitral valve regurgitation and Marfan syndrome. Hypertensive disorders of pregnancy occurred in 4.1% and 46.3% were delivered by Caesarean section, of which the majority (30.2%) were planned: 9.6% for cardiac reasons and 20.6% for obstetric reasons. In terms of fetal outcomes, stillbirth occurred in 0.5%, preterm delivery in 16%, SGA in 10.3% and a low Apgar score in 5.9%. Fetal congenital heart disease occurred in 3.5% and non-cardiac congenital disease in an additional 2.2%. The most important complications stratified by mWHO category are displayed in Fig. 3.

The composite endpoint of maternal mortality and/or heart failure occurred most commonly in women with Eisenmenger syndrome (58.1%), followed by women with a congenitally corrected transposition of the great arteries (ccTGA, 12.8%), Fontan circulation (11.2%) and double outlet right ventricle (11.1%, Fig. 4). For all the other CHD diagnoses, the composite endpoint occurred in less than 10% of pregnancies.

The results from the univariable and multivariable regression analysis for the composite endpoint of maternal mortality and/or heart failure are displayed in supplementary table S2 and Fig. 5. Pre-pregnancy signs of heart failure (OR 10.7, 95% CI 7.1–16), multiple gestation (4.6, 2–10.8), pulmonary hypertension (2.5, 1.5–4), estimated LVEF <40% (2.4,

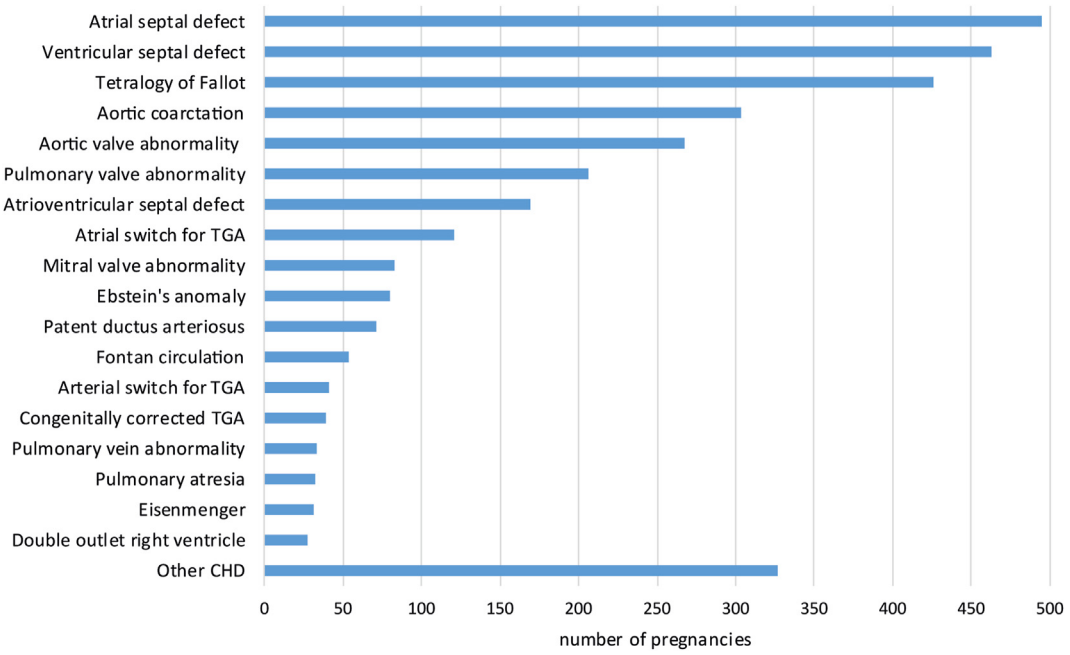

Fig. 1. Main diagnosis of congenital heart disease in pregnancies included in the Registry of Pregnancy and Cardiac disease. CHD, congenital heart disease; TGA, transposition of the great arteries.

1.1–5.1), cardiac medication use (2, 1.4–2.7) and low- or middle-income country (1.6, 1.1–2.4) were independently associated with the composite endpoint.

Discussion

The prospective observational ROPAC data on 3295 pregnancies in women with congenital heart disease show reassuring results in terms of a low rate of maternal mortality (0.3%). The most common maternal complication was heart failure (6.6%), which occurred in particular in women with Eisenmenger syndrome or other forms of complex congenital heart disease. Other cardiac complications were rare. The most important obstetric and fetal complications were a high rate of delivery by Caesarean section (46%) and preterm birth (16%).

The favourable outcome may be partly explained by the baseline characteristics of the CHD cohort. Compared to non-CHD ROPAC pregnancies, the CHD group had lower comorbidities such as hypertension (8.2 vs. 5.6%) and decreased LVEF (7.7 vs. 1.9%). Although prior cardiac interventions were more common (68.9 vs. 36.9%) use of cardiac medication was less frequent (50.5 vs. 25.2%), suggesting that these women generally had well-corrected CHD, with good residual cardiac function; indeed, the majority were in mWHO I or II risk class (57.1%) and lived in high income countries (71.6%).

Nevertheless, the composite endpoint of mortality and/or heart failure was observed in 6.7% of CHD pregnancies. Women with Eisenmenger's syndrome stand out dramatically in terms of adverse outcomes, with 9.7% mortality and 48.4% heart failure. Indeed the presence of pulmonary hypertension puts the mother into mWHO risk class IV and as such pregnancy is contra-indicated in this group, owing to the potentially fatal risk of pulmonary hypertensive crisis, thrombosis or right-sided heart failure [14,15]. After Eisenmenger's syndrome, the composite endpoint was most frequently observed in ccTGA and Fontan circulation. In ccTGA, the systemic right ventricle and tricuspid valve may be insufficiently equipped to handle the increase in volume load and cardiac output during pregnancy [16]. The same inability to adapt and meet the haemodynamic demands of pregnancy, but in the context of left-sided instead of right-sided heart failure, causes complications in the univentricular Fontan circulation, as well as its susceptibility to arrhythmia and thrombosis [17].

Caesarean section was performed in around half of the cohort, the majority were planned. In this series the most common reason for CS was obstetric, but nearly 10% of the total CHD cohort had a planned CS on cardiac indication. In general planned Caesarean sections in women with heart disease do not improve maternal outcome but are associated with worse fetal outcome [18]. Additionally, a Caesarean section increases the obstetric risks in a subsequent pregnancy. Therefore it is advisable to follow the current guidelines on mode of delivery in women with CHD, which on recommend vaginal delivery in most cases [14]. Exceptions are acute heart failure, severe aortic stenosis, critical aortic dilatation, Eisenmenger's syndrome, spontaneous labour under oral anticoagulant use or obstetric indications for Caesarean section [14]. For fetal outcome, preterm delivery was higher than the global average (16% vs 10.6%), but SGA was not higher (10.3 vs 14.6%) [19,20]. The recurrence rate of CHD was 3.3%, but it is known this can vary with the diagnosis and also may be incomplete because the ROPAC follow-up was only 6 months [21].

The mWHO classification seems to adequately predict adverse outcomes, with higher complication rates in higher mWHO classes and in women with a poor cardiac condition before pregnancy [22]. These observations are in line with the predictors identified in the earlier CARdiac disease in PREGnancy (CARPREG) and Zwangerschap bij Aangeboren HARtAfwijking (ZAHARA) studies on pregnancy outcomes in women with congenital heart disease [23,24]. The strong association between pre-pregnancy cardiac function and an adverse pregnancy outcome emphasises the importance of pre-pregnancy assessment and counselling to identify women at high risk of complications. In the case of CHD, the diagnosis is known in most patients and almost all are under the care of a cardiologist. This means that timely counselling on pregnancy and contraception, preferably before the transition from paediatric to adult cardiology services, may help to reduce the rate of unplanned pregnancy and allow women to make a fully informed decision [25].

The CARPREG study is based on Canadian and the ZAHARA study on Dutch and Belgian patient cohorts, whereas the ROPAC is an international registry with patients recruited from 53 countries. We found increased risks for women living in a low- or middle income country, independent of pre-pregnancy cardiac morbidity or the presence of uncorrected CHD, which are both probably higher in LMIC [8]. The increased risk could therefore be related to health care accessibility

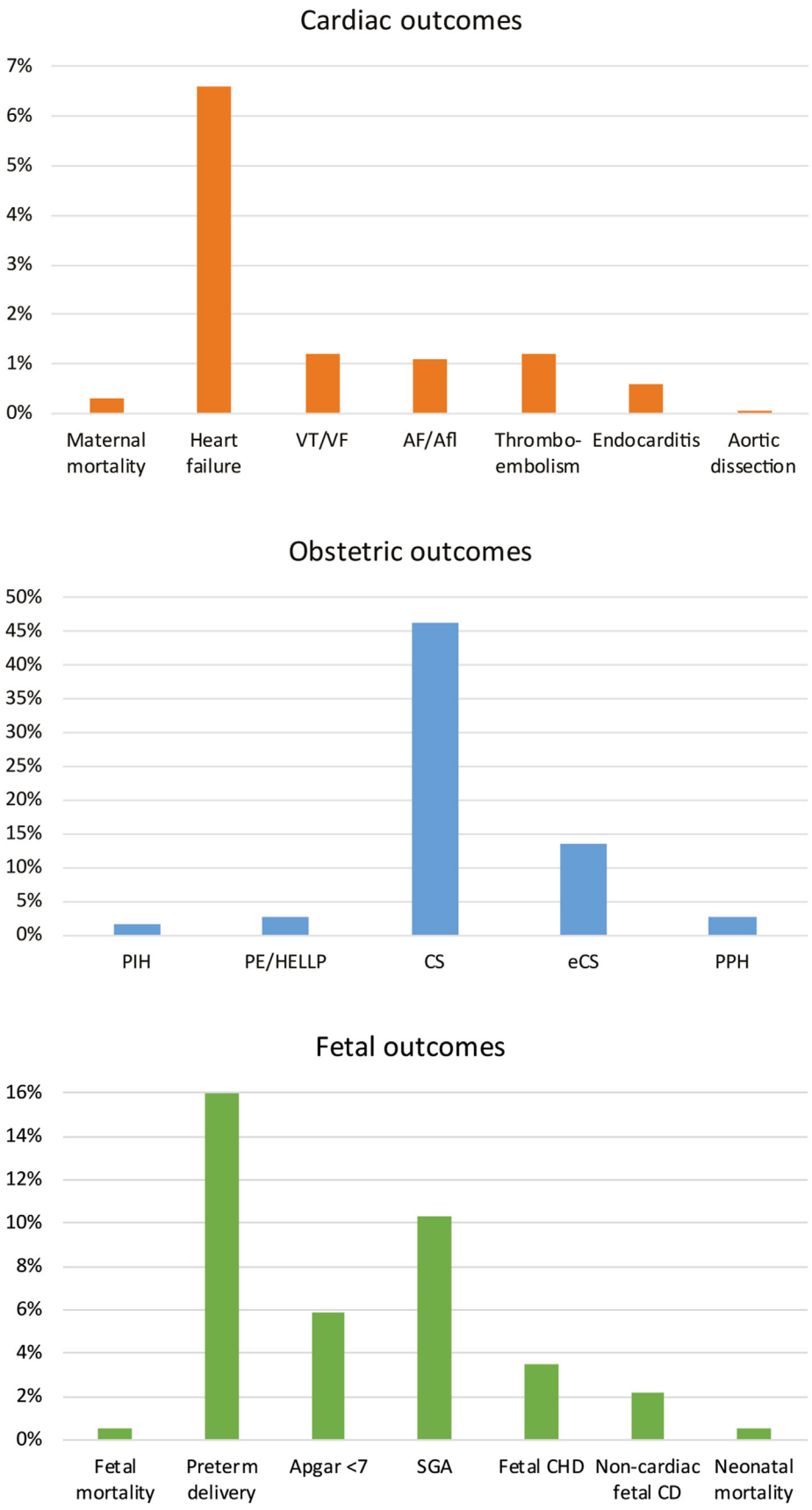

Fig. 2. Pregnancy outcomes of women with congenital heart disease. AF/Afl, Atrial fibrillation and/or flutter. C(H)D, congenital (heart) disease; (e)CS, (emergency) caesarean section; mWHO, modified World Health Organization classification; PE/HELLP, (pre-)eclampsia or Haemolysis, Elevated Liver enzymes and Low Platelet syndrome; PIH, pregnancy-induced hypertension; PPH, postpartum haemorrhage; SGA, small for gestational age; VT/VF, ventricular tachyarrhythmia.

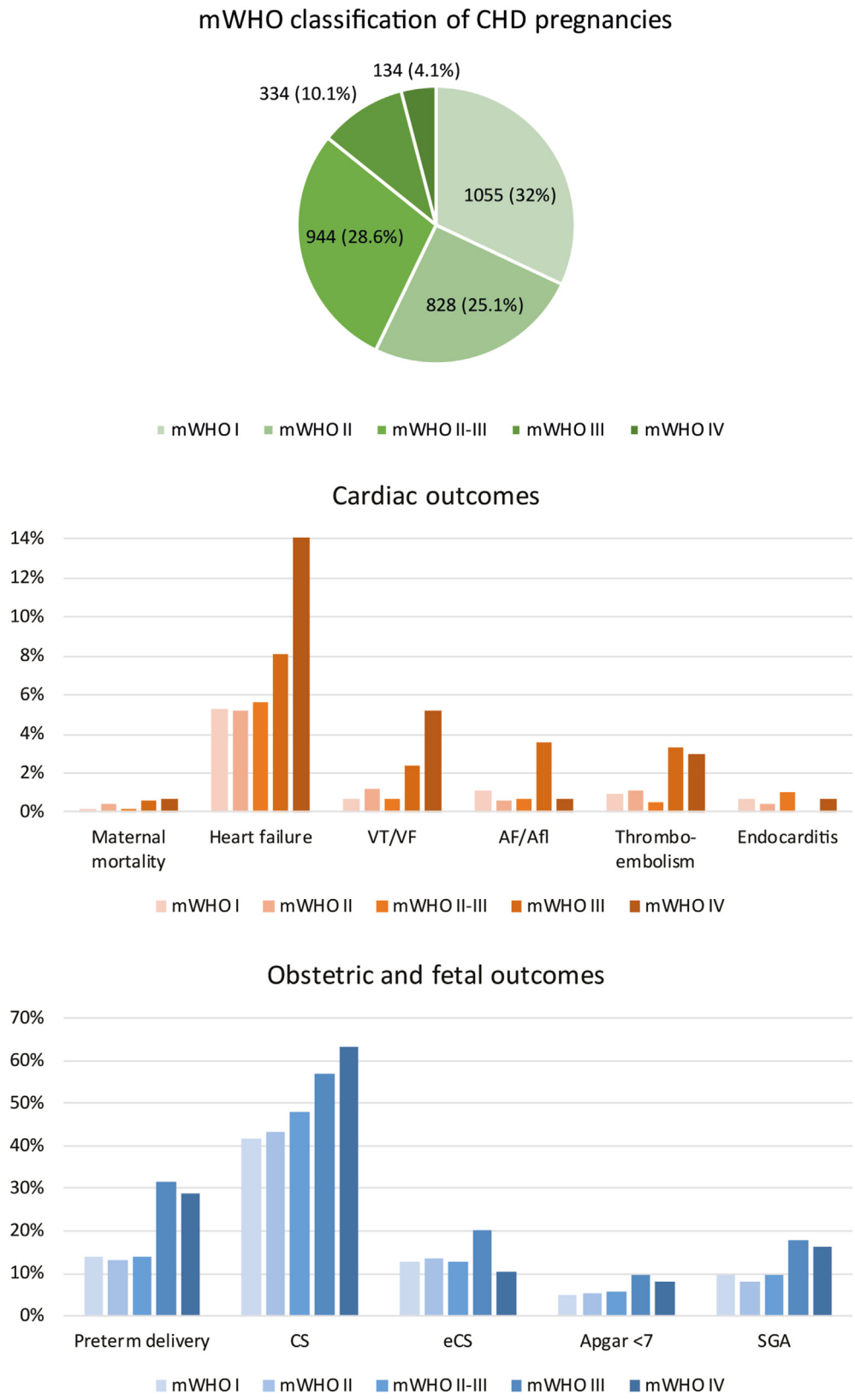

Fig. 3. Pregnancy outcomes of women with congenital heart disease by mWHO classification. Statistically significant differences between mWHO class were found for all outcomes except mortality and endocarditis. AF/Afl, Atrial fibrillation and/or flutter; (e)CS, (emergency) caesarean section; mWHO, modified World Health Organization classification; SGA, small for gestational age; VT/VF, ventricular tachyarrhythmia.

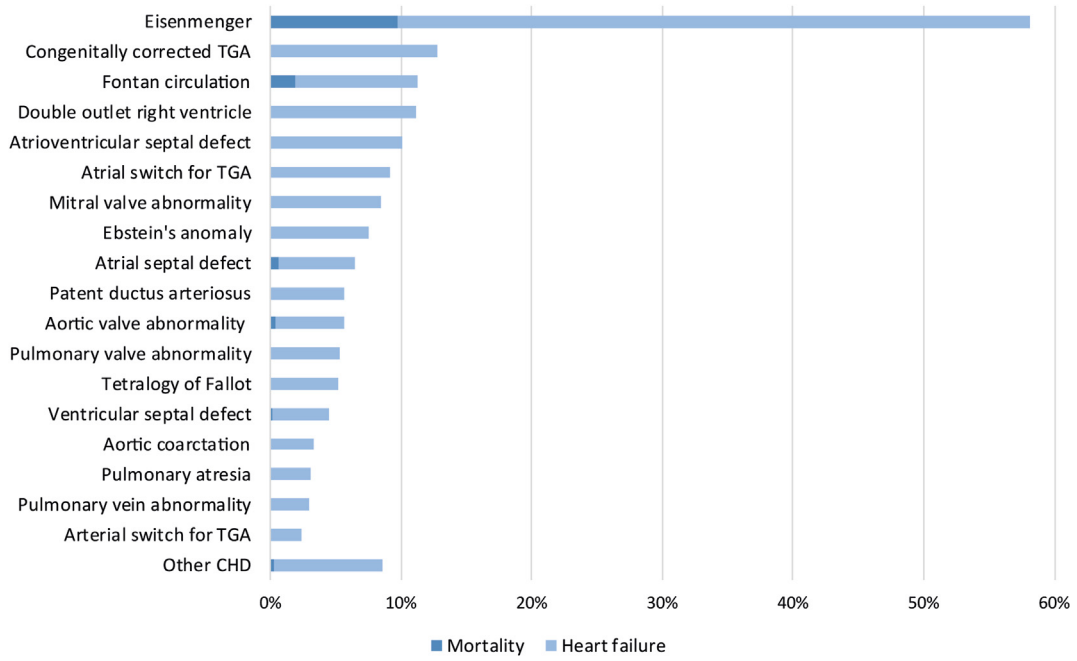

Fig. 4. Mortality and heart failure by main congenital heart disease diagnosis. CHD, congenital heart disease; TGA, transposition of the great arteries.

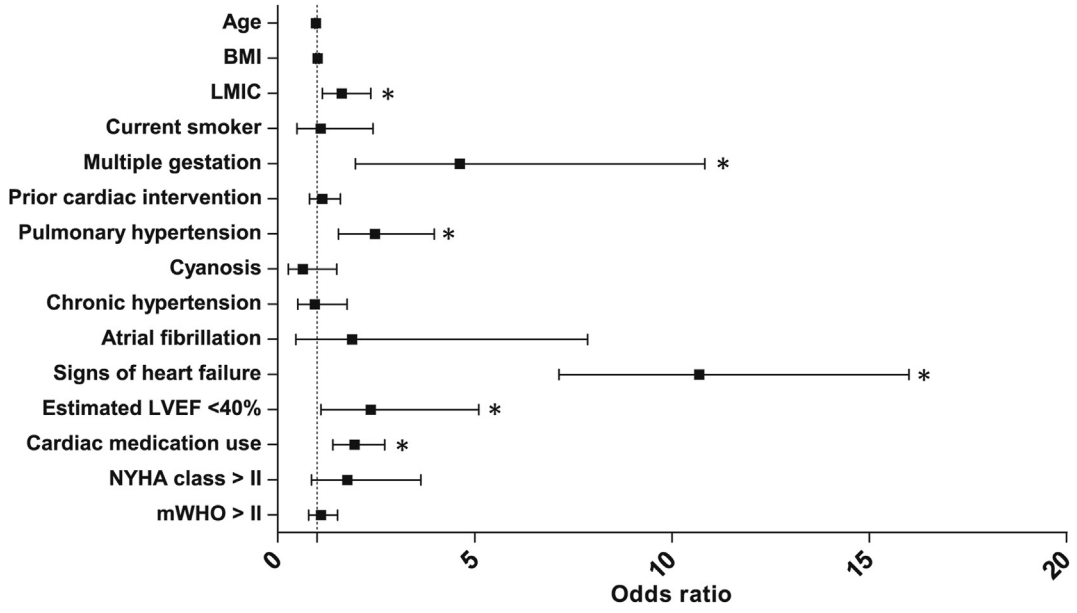

Fig. 5. Multivariable regression analysis for associations with the composite endpoint of maternal mortality and heart failure. *$p < 0.05$. BMI, Body Mass Index; LMIC, low/middle-income country; LVEF, left ventricular ejection fraction; mWHO, modified World Health Organization classification for maternal cardiovascular risk; NYHA, New York Heart Association functional classification.

before and during pregnancy, but more research on this subject is clearly needed. Further, the dissemination and implementation of up-to-date guidelines to all health care providers combined with patient education and pre-pregnancy counselling may help to improve pregnancy outcomes in LMIC. Telephone or (if available) digital consultations with a specialized pregnancy heart team at a tertiary referral centre could also make expert cardiac advice more accessible to secondary or rural health care centres.

We also identified multiple gestation as a risk factor for mortality and heart failure, which was not found in the ZAHARA study and not assessed in the CARPREG II study [23,24]. The haemodynamic changes in maternal physiology are more exaggerated during twin pregnancy, potentially explaining the higher risk of heart failure, with plasma volume (67% versus 48%) and cardiac output (70% vs. 30–50%) increasing to a greater extent in twin compared to singleton pregnancies [1,26,27]. We recommend increasing the frequency of follow-up visits during twin pregnancy and that this factor should be included when the mWHO classification is used to calculate the minimum number of antenatal visits [14].

Study limitations

The strength of this study is its inclusion of most known CHD lesions and that the ROPAC has collected relatively large numbers of even rare and complex diseases through international cooperation. The inclusion of many

different CHD lesions however means that data on disease-specific parameters is limited in this study. The outcomes reported may not be generalisable for all women with the same diagnosis, because cardiac function, comorbidities and previous cardiac and obstetric events are not considered in this study, while they can all contribute to the actual risk of pregnancy. Counselling and management should therefore always be individualized in a multidisciplinary context. It was unknown if the non-cardiac congenital disease in babies occurred independently or as part of a syndrome.

Conclusion

Although CHD is the most common type of cardiac disease seen during pregnancy, maternal outcome is relatively good. More complex CHD is at higher risk and women with Eisenmenger's syndrome are by far at highest risk for adverse outcomes. However, many women with other forms of CHD can be safely pregnant and should be reassured. Obstetric and fetal complications may be partly preventable, especially by reducing unnecessary planned Caesarean sections. The recurrence rate of congenital heart disease in the offspring is at least 3%. The pre-pregnancy cardiac state is strongly related to adverse pregnancy outcomes, which emphasises the importance of pre-pregnancy counselling. Follow-up during and after pregnancy should be individualized to the woman's needs and the complexity of her CHD, ideally performed by a multidisciplinary pregnancy heart team. If the required expertise is unavailable locally, telephone or digital consultations with a specialist tertiary centre may provide a solution.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

EORP oversight Committee, ROPAC Executive Committee, Data collection was conducted by the EORP department from the ESC by Elin Folkesson Lefrancq as Project Officer; Viviane Missiamenou, Gérard Gracia and Sébastien Authier as Data Managers. Overall activities were coordinated and supervised by Dr. Aldo P. Maggioni, Scientific Coordinator.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2021.100107.

Funding

Funding from “Zabawas Foundation” and “De Hoop Foundation” in addition to the support from EORP is greatly acknowledged. Since the start of EORP, the following companies have supported the programme: Abbott Vascular Int. (2011–2021), Amgen Cardiovascular (2009–2018), AstraZeneca (2014–2021), Bayer AG (2009–2018), Boehringer Ingelheim (2009–2019), Boston Scientific (2009–2012), The Bristol Myers Squibb and Pfizer Alliance (2011–2019), Daiichi Sankyo Europe GmbH (2011–2020), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014–2017), Edwards (2016–2019), Gedeon Richter Plc. (2014–2016), Menarini Int. Op. (2009–2012), MSD-Merck & Co. (2011–2014), Novartis Pharma AG (2014–2020), ResMed (2014–2016), Sanofi (2009–2011), Servier (2009–2021), Vifor (2019–2022).

References

[1] Meah VL, Cockcroft JR, Backx K, Shave R, Stohr EJ. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. Heart 2016;102:518–26.
[2] Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. Br Med J 1987;295:1169–72.
[3] Ramlakhan KP, Johnson MR, Roos-Hesselink JW. Pregnancy and cardiovascular disease. Nat Rev Cardiol 2020:1–14.
[4] Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011-2013. Obstet Gynecol 2017;130:366–73.
[5] On behalf of MBRRACE-UK. In: Knight MN M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk JJ, editors. Saving lives, improving mothers' care - lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2013-2015. Oxford: National Perinatal Epidemiology Unit, University of Oxford; 2017. p. 1–104. 2017.
[6] Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation 2014;130:749–56.
[7] Roos-Hesselink J, Baris L, Johnson M, et al. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry of Pregnancy and Cardiac disease (ROPAC). Eur Heart J 2019:1–8. 0.
[8] Sliwa K, Baris L, Sinning C, et al. Pregnant women with uncorrected congenital heart disease: heart failure and mortality. JACC Heart Fail 2020;8:100–10.
[9] Ramlakhan KP, Tobler D, Greutmann M, et al. Pregnancy outcomes in women with aortic coarctation. Heart; 2020.
[10] Orwat S, Diller GP, van Hagen IM, et al. Risk of pregnancy in moderate and severe aortic stenosis: from the multinational ROPAC registry. J Am Coll Cardiol 2016;68:1727–37.
[11] Baris L, Ladouceur M, Johnson MR, et al. Pregnancy in tetralogy of Fallot data from the ESC EORP ROPAC registry. International Journal of Cardiology Congenital Heart Disease 2021;2:100059.
[12] Tutarel O, Ramlakhan KP, Baris L, et al. Pregnancy outcomes in women after arterial switch operation for transposition of the great arteries: results from ROPAC (registry of pregnancy and cardiac disease) of the European society of cardiology EURObservational research programme. J Am Heart Assoc 2021;10:e018176.
[13] Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. Eur Heart J 2013;34:657–65.
[14] Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39:3165–241. 2018.
[15] Duan R, Xu X, Wang X, et al. Pregnancy outcome in women with Eisenmenger's syndrome: a case series from west China. BMC Pregnancy Childbirth 2016;16:356.
[16] Therrien J, Barnes I, Somerville J. Outcome of pregnancy in patients with congenitally corrected transposition of the great arteries. Am J Cardiol 1999;84:820–4.
[17] Garcia Ropero A, Baskar S, Roos Hesselink JW, et al. Pregnancy in women with a fontan circulation: a systematic review of the literature. Circ Cardiovasc Qual Outcomes 2018;11:e004575.
[18] Ruys TP, Roos-Hesselink JW, Pijuan-Domenech A, et al. Is a planned caesarean section in women with cardiac disease beneficial? Heart 2015;101:530–6.
[19] Chawanpaiboon S, Vogel JP, Moller A-B, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global Health 2019;7:e37–46.
[20] Blencowe H, Krasevec J, de Onis M, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. The Lancet Global Health 2019;7:e849–60.
[21] Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: A scientific statement from the American heart association. Circulation 2018;138:e653–711.
[22] van Hagen IM, Boersma E, Johnson MR, et al. Global cardiac risk assessment in the Registry of Pregnancy and Cardiac disease: results of a registry from the European Society of Cardiology. Eur J Heart Fail 2016;18:523–33.
[23] Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 2010;31:2124–32.
[24] Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II study. J Am Coll Cardiol 2018;71:2419–30.
[25] Ramlakhan KP, Ahmed I, Johnson MR, Roos-Hesselink JW. Congenital heart disease and family planning: preconception care, reproduction, contraception and maternal health. International Journal of Cardiology Congenital Heart Disease 2020;1:100049.
[26] Kametas N, McAuliffe F, Krampl E, Chambers J, Nicolaides K. Maternal cardiac function in twin pregnancy. Obstet Gynecol 2003;102:806–15.
[27] Rovinsky JJ, Jaffin H. Cardiovascular hemodynamics in pregnancy: I. Blood and plasma volumes in multiple pregnancy. Am J Obstet Gynecol 1965;93:1–15.