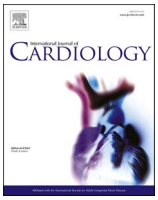
International Journal of Cardiology 410 (2024) 132234

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Perinatal outcomes after in-utero exposure to beta-blockers in women with heart disease: Data from the ESC EORP registry of pregnancy and cardiac disease (ROPAC)☆

Karishma P. Ramlakhan [a,b], Jolien W. Roos-Hesselink [a,*], Thomas Basso [c], Jaimi Greenslade [d,e], Robert B. Flint [f,g], Eric V. Krieger [h], Avraham Shotan [i], Werner Budts [j], Julie De Backer [k], Roger Hall [l], Mark R. Johnson [m], William A. Parsonage [c,e], on behalf of the ROPAC Investigators[1]

[a] Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[b] Department of Obstetrics and Gynaecology, Erasmus MC – Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands
[c] Department of Cardiology, Royal Brisbane and Women's Hospital, Brisbane, Australia
[d] Emergency and Trauma Centre, Royal Brisbane and Women's Hospital, Brisbane, Australia
[e] Australian Centre for Health Services Innovation, School of Public Health and Social Work, Centre for Healthcare Transformation, Faculty of Health, Queensland University of Technology, Brisbane, Australia
[f] Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[g] Department of Neonatology, Erasmus MC – Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands
[h] Division of Cardiology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA
[i] Heart Institute, Laniado Medical Center, Netanya, Adelson School of Medicine, Ariel University, Israel
[j] Congenital and Structural Cardiology, University Hospitals Leuven, and Department of Cardiovascular Sciences, Catholic University of Leuven, Leuven, Belgium
[k] Department of Cardiology, Ghent University Hospital, Ghent, Belgium
[l] Department of Cardiology, University of East Anglia, Norwich, United Kingdom
[m] Department of Obstetric Medicine, Imperial College London, Chelsea and Westminster Hospital, London, United Kingdom

ARTICLE INFO

Keywords:
Pregnancy
beta-blockers
Perinatal outcomes
Small for gestational age

ABSTRACT

Background: Beta-blockers are commonly used drugs during pregnancy, especially in women with heart disease, and are regarded as relatively safe although evidence is sparse. Differences between beta-blockers are not well-studied.

Methods: In the Registry of Pregnancy And Cardiac disease (ROPAC, $n = 5739$), a prospective global registry of pregnancies in women with structural heart disease, perinatal outcomes (small for gestational age (SGA), birth weight, neonatal congenital heart disease (nCHD) and perinatal mortality) were compared between women with and without beta-blocker exposure, and between different beta-blockers. Multivariable regression analysis was used for the effect of beta-blockers on birth weight, SGA and nCHD (after adjustment for maternal and perinatal confounders).

Results: Beta-blockers were used in 875 (15.2%) ROPAC pregnancies, with metoprolol ($n = 323$, 37%) and bisoprolol ($n = 261$, 30%) being the most frequent. Women with beta-blocker exposure had more SGA infants (15.3% vs 9.3%, $p < 0.001$) and nCHD (4.7% vs 2.7%, $p = 0.001$). Perinatal mortality rates were not different (1.4% vs 1.9%, $p = 0.272$). The adjusted mean difference in birth weight was −177 g (−5.8%), the adjusted OR for SGA was 1.7 (95% CI 1.3–2.1) and for nCHD 2.3 (1.6–3.5). With metoprolol as reference, labetalol (0.2, 0.1–0.4) was the least likely to cause SGA, and atenolol (2.3, 1.1–4.9) the most.

Conclusions: In women with heart disease an association was found between maternal beta-blocker use and perinatal outcomes. Labetalol seems to be associated with the lowest risk of developing SGA, while atenolol should be avoided.

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

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

[1] Listed in the Appendix of the Supplementary file

https://doi.org/10.1016/j.ijcard.2024.132234
Received 24 January 2024; Received in revised form 20 May 2024; Accepted 3 June 2024
Available online 4 June 2024

1. Introduction

Maternal cardiac disease is estimated to affect 1–4% of all pregnancies. This prevalence is likely to increase as maternal age rises and the life expectancy of patients with congenital heart disease (CHD) improves, and more of these women become pregnant. [1,2] Pharmacotherapy is often necessary during pregnancy for women with cardiovascular disease, yet data on the perinatal effects of maternal cardiovascular medication use are scarce.

Beta-blockers have been used widely in pregnancy and are generally considered relatively safe, but their use has been associated with an increased risk of growth restriction, preterm birth and neonatal morbidity and mortality. [3–6] There may be a detrimental effect on both the placental circulation and the fetus itself, as most beta-blockers cross the placenta. Most observations regarding adverse effects have been derived from patients with hypertensive disorders of pregnancy [3–6], limiting their applicability to other pregnancies as these conditions independently affect perinatal outcomes, and mostly involve 3rd trimester beta-blocker exposure.

In women with heart disease, beta-blockers have an important impact on the symptoms and prognosis of heart failure, arrhythmias, myocardial ischemia and aortopathy, as well as of systemic hypertension when it coexists. [3] Small studies concerning the effect of beta-blockade on pregnancy outcomes in women with heart disease show varying results, with some evidence suggesting adverse perinatal effects, especially on birthweight. This effect has been related to any beta-blocker use [7,8], the ancillary properties of the particular beta-blocker used [9], the beta-blocker dose [10] and the maternal condition being treated. [3] As maternal heart disease may also cause adverse perinatal outcomes, elucidating the degree attributable to beta-blocker use specifically, versus the maternal condition, is challenging. [11] Additionally, it would be of great clinical value to know whether specific beta-blockers are associated with a worse perinatal outcome. The aim of this study is to evaluate the effect of beta-blocker use, including specific beta-blockers, on perinatal outcomes in a large cohort of women with heart disease.

2. Methods

The Registry of Pregnancy and Cardiac disease (ROPAC) is part of the EURObservational Research Programme of the European Society of Cardiology [12] and is a prospective worldwide registry of pregnancies in women with structural heart disease, which includes six diagnostic groups: CHD, valvular heart disease, ischemic heart disease, cardiomyopathy, aortopathy and pulmonary arterial hypertension. Women with arrhythmias without structural heart disease were excluded. A total of 5739 pregnancies were included between January 2008 and January 2018, from 138 centers in 53 countries. The ROPAC study protocol was published previously. [13] This study complies with the Declaration of Helsinki. Participating centres managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations.

2.1. Data and definitions

Study parameters were prospectively collected by a local investigator from the participating center, using patient record files and clinical information, and entered in a central online database. Pre-pregnancy characteristics included age, parity, cardiovascular risk factors, comorbidity, primary cardiac diagnosis, New York Heart Association (NYHA) functional classification and modified World Health Organization (mWHO) risk classification. [2] The International Monetary Fund classification was used to identify the low- and middle-income countries (LMIC) among the participating countries. The use of cardiac medications was recorded per trimester. Beta-blocker use was defined as use at any point during a trimester, excluding exposure only prior to pregnancy or during labour. The duration of exposure was defined as the number of trimesters with exposure. The type and daily dose of beta-blocker were documented, but the specific indication for medication use was not specifically recorded.

Gestational systemic hypertension and (pre-)eclampsia were defined according to the International Society for the Study of Hypertension in Pregnancy (ISHHP) guidelines. [14] Stillbirth was defined as fetal death after 20 weeks of gestation, perinatal mortality as stillbirths and neonatal mortality combined, preterm birth as delivery before 37 weeks of gestation, low Apgar score as an Apgar score of <7 at 5 min after birth and low birth weight as fetal birth weight < 2500 g. Small for gestational age (SGA) was collected as a dichotomous parameter of birth weight < 10th percentile according to local reference values for the fetal sex and gestational age at birth, which accounts for regional differences in fetal birth weight. Neonatal CHD did not include a patent foramen ovale or patent ductus arteriosus that closed spontaneously postpartum. Perinatal outcome included preterm delivery, low Apgar score, SGA, low birth weight, absolute birth weight, neonatal CHD and perinatal mortality.

2.2. Statistical analysis

Categorical data are presented as percentages and compared using χ^2 tests. When normally distributed, continuous data are presented as mean (standard deviation) and compared using unpaired *t*-tests or one-way ANOVA. When not normally distributed, data are presented as median (Q1-Q3) and compared with Mann-Whitney tests. Multiple imputation was used to handle missing values, which were at random (reported in the Supplementary Table S1 legend). 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).

Baseline characteristics and outcomes were compared between women who used beta-blockers during pregnancy and those who did not. SGA, birth weight and neonatal CHD with and without beta-blocker exposure were examined in the total cohort and between the six diagnostic groups.

The primary analysis was a multivariable logistic regression analysis, applied to explore the association between beta-blocker treatment and SGA. This analysis was corrected for the maternal diagnosis, the baseline parameters that were $p < 0.1$ in the univariable analysis, and those variables with a known influence on birth weight (maternal age, body mass index (BMI), LMIC and smoking). [15] Additionally, a propensity score estimation for beta-blocker use was added to the model for regression adjustment [16], using factors that influence the likelihood of beta-blocker use: maternal age, BMI, LMIC, smoking, chronic hypertension, atrial fibrillation/flutter, signs of heart failure, estimated left ventricular ejection fraction (LVEF) <40%, prior cardiac interventions and gestational hypertensive disorders.

Several secondary analyses were also conducted. First, a multivariable linear regression analysis examined the association between beta-blocker use and birth weight. This analysis was corrected for maternal age, BMI, gestational age, smoking, fetal sex, diabetes, non-beta-blocker cardiac medication use, hypertensive disorders of pregnancy and the propensity score.

Second, the most frequently used beta-blockers (used in >5% of pregnancies) were compared, excluding pregnancies in which multiple beta-blockers were used. Perinatal outcome was compared between the types and a multivariable logistic regression analysis was performed for the comparative effect on SGA, using metoprolol and alternately as the reference value. To correct for dosage, the daily dose of each type of beta-blocker was converted to its metoprolol equivalent dose (Supplementary Table S2) [17–19], along with other confounders and factors that influence the choice of beta-blocker: chronic hypertension, atrial fibrillation or flutter, heart failure, estimated left ventricular ejection fraction <40%, gestational hypertension or preeclampsia, cardiomyopathy, aortopathy and ischemic heart disease.

Third, a multivariable logistic regression was performed for the association between beta-blocker use and neonatal CHD, corrected for maternal age, BMI, nulliparity, smoking, diabetes, maternal CHD, aortopathy and cardiomyopathy, and the propensity score. A sensitivity analysis was performed for pregnancies with non-beta-blocker cardiac medication exposure. Two additional sensitivity analyses were performed in an attempt to rule out residual confounding by maternal disease by excluding autosomal dominant neonatal CHD and including 1) pregnancies with beta-blocker exposure during the first trimester (the period of organogenesis) and 2) pregnancies with beta-blocker exposure outside of the first trimester exposure only (where a causal effect on neonatal CHD is unlikely).

3. Results

Beta-blockers were used in 875 (15.2%) out of 5739 pregnancies in women with structural heart disease and were the most frequently used class of cardiac medication. The underlying maternal cardiac diagnosis was congenital heart disease in 32.2%, valvular heart disease in 34.9%, cardiomyopathy in 19.8%, aortopathy in 8.5%, ischemic heart disease in 3.8% and pulmonary arterial hypertension in 0.8% (Table 1). Metoprolol ($n = 323$) and bisoprolol ($n = 261$) were used more often than carvedilol ($n = 64$), propranolol (n = 64), labetalol ($n = 49$) and atenolol (n = 49) (Supplementary Fig. S1). The daily doses per trimester are listed in Supplementary Table S3, with the most frequently used type in each diagnostic group shown in Supplementary Table S4.

Baseline characteristics for pregnancies with and without beta-blocker exposure are compared in Table 1. Women using beta-blockers in pregnancy were older, more often from an LMIC and more likely to have cardiovascular comorbidities (systemic hypertension, atrial fibrillation/flutter, or heart failure) or LVEF <40%. Unadjusted obstetric and perinatal outcomes are described in Table 2. There was no difference in fetal mortality between pregnancies with and without exposure (0.7% vs 1.4%, $p = 0.165$). There were more therapeutic terminations of pregnancy in women with beta-blocker use than in those without (2.5% vs 0.9%, $p < 0.001$), mainly for maternal health reasons (1.9% vs 0.6%, $p < 0.001$) but not for fetal abnormalities (0.3% vs 0.2%, $p = 0.608$). Delivery by Caesarean section was more frequent in women treated with beta-blockers (64.2% vs 47.1%, $p < 0.001$).

In women treated with beta-blockers, preterm birth (26.4% vs 16.5%, $p < 0.001$), low Apgar scores (9.3% vs 6.5%, $p = 0.003$) and SGA infants (15.3% vs 9.3%, $p < 0.001$) were more common, but the neonatal mortality rate was similar (0.7% vs 0.6%, $p = 0.638$). The unadjusted difference in mean birth weight was −296 g or − 9.7% (2738 vs 3034 g, $p < 0.001$); −386 g (−12.6%; p < 0.001) for high-income countries and − 185 g (−6.2%; p < 0.001) for low/middle-income

Table 1
Baseline pre-pregnancy characteristics of women with structural heart disease.

	Beta-blocker use during pregnancy (n = 875, 15.2%)	No beta-blocker use during pregnancy (n = 4864, 84.8%)	p-value
Pre-pregnancy characteristics			
Age, years (±sd)	30.8 (±5.6)	29.3 (±5.6)	<0.001
BMI, kg/m^2 (Q1-Q3)	24.8 (21.9–28.3)	23.8 (21.5–27.4)	<0.001
Nulliparity	337 (38.6)	2236 (46.1)	<0.001
Multiple gestation	12 (1.4)	84 (1.7)	0.450
LMIC	407 (46.5)	1874 (38.5)	<0.001
Current smoker	52 (6.7)	176 (4.2)	0.003
Chronic hypertension	127 (14.8)	253 (5.3)	<0.001
Diabetes mellitus	20 (2.3)	70 (1.5)	0.073
Atrial fibrillation/ flutter	37 (4.2)	69 (1.4)	<0.001
Signs of heart failure	143 (16.6)	453 (9.4)	<0.001
Estimated LVEF <40%	127 (14.5)	126 (2.6)	<0.001
NYHA class > I	299 (34.2)	1096 (22.5)	<0.001
Prior cardiac intervention	395 (45.4)	2765 (57)	<0.001
Pre-pregnancy cardiac medication use	875 (100)	1194 (24.5)	<0.001
Beta-blockers	499 (57)	64 (1.3)	<0.001
Non-beta-blockers	376 (43)	1130 (23.2)	<0.001
Diagnosis details			
Congenital heart disease	283 (32.3)	3012 (61.9)	<0.001
Valvular heart disease	305 (34.9)	1344 (27.6)	<0.001
Cardiomyopathy	173 (19.8)	265 (5.4)	<0.001
Aortopathy	74 (8.5)	143 (2.9)	<0.001
Ischaemic heart disease	33 (3.8)	62 (1.3)	<0.001
Pulmonary hypertension	7 (0.8)	38 (0.8)	0.954
mWHO I	59 (6.7)	1126 (23.1)	<0.001
mWHO II	36 (4.1)	792 (16.3)	<0.001
mWHO II-III	555 (63.4)	2143 (44.1)	<0.001
mWHO III	80 (9.1)	513 (10.5)	0.209
mWHO IV	141 (16.1)	266 (5.5)	<0.001

Data are n (%) unless otherwise specified. *P*-values were calculated between the groups with and without beta-blocker use, using chi-square tests and unpaired t-tests as appropriate. 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 class, New York Heart Association Functional Classification; Q1-Q3, inter-quartile range.

Table 2
Obstetric and perinatal outcome.

	Beta-blocker use (n = 875)	No beta-blocker use (n = 4864)	*P* value
Obstetric and fetal outcome			
Reported miscarriage	24 (2.7)	190 (3.9)	0.094
Therapeutic termination of pregnancy	22 (2.5)	46 (0.9)	<0.001
For fetal abnormalities	3 (0.3)	12 (0.2)	0.608
For maternal health	17 (1.9)	31 (0.6)	<0.001
Intra-uterine growth restriction	62 (7.1)	192 (3.9)	<0.001
Pregnancy-induced hypertension	11 (1.3)	66 (1.4)	0.813
(Pre-)eclampsia and HELLP syndrome	29 (3.3)	143 (2.9)	0.550
Gestational diabetes mellitus	45 (5.2)	115 (2.4)	<0.001
Stillbirth	6 (0.7)	66 (1.4)	0.165
Gestational age at stillbirth, median weeks^{+days} (Q1-Q3)	30^{+3} (24^{+2}–36^{+6})	26^{+3} (23–31^{+2})	0.316
Delivery			
Gestational age at delivery, median weeks^{+days} (Q1-Q3)	38 (36^{+5}–39)	38^{+5} (37^{+5}–39^{+5})	<0.001
Assisted vaginal delivery	55 (6.3)	398 (8.2)	0.055
Caesarean section	529 (64.2)	2152 (47.1)	<0.001
Emergency Caesarean section	129 (14.7)	637 (13.1)	0.187
Neonatal outcome			
Preterm birth	207 (26.4)	698 (16.5)	<0.001
Apgar score < 7 at 5 min	81 (9.3)	316 (6.5)	0.003
Mean birth weight, grams (±sd)	2738 (±628)	3034 (±627)	<0.001
Birth weight < 2500 g	217 (24.8)	456 (9.4)	<0.001
Small for gestational age	134 (15.3)	450 (9.3)	<0.001
Neonatal congenital heart disease	41 (4.7)	129 (2.7)	0.001
Other neonatal congenital disease	21 (2.4)	105 (2.2)	0.654
Neonatal mortality	6 (0.7)	27 (0.6)	0.638
Total perinatal mortality	12 (1.4)	93 (1.9)	0.272

Data are n (%) unless otherwise specified. P-values were calculated between the groups with and without beta-blocker use, using chi-square tests and unpaired t-tests as appropriate. Miscarriage: fetal mortality <20 weeks. Stillbirth: fetal mortality >20 weeks. Total perinatal mortality: stillbirths + neonatal mortality. HELLP syndrome, haemolysis, elevated liver enzymes and low platelets syndrome.

countries. Adjusted for gestational age alone, the difference in mean birth weight was −170 g (5.6%). There was more neonatal CHD in the beta-blocker treated group (4.7% vs 2.7%, $p = 0.001$), but no difference in the non-cardiac congenital malformation rate. Details on neonatal CHD are reported in Supplementary Table S5; septal defects ($n = 11$ out of 41) were the most frequently observed type of neonatal CHD.

Supplementary Fig. S2 compares SGA, birth weight and neonatal CHD between pregnancies with and without beta-blocker exposure, stratified by maternal cardiac disease. SGA rates were higher and birth weight lower after beta-blocker use in women with CHD, valvular heart disease or cardiomyopathy. Neonatal CHD was higher after beta-blocker use in women with CHD or valvular heart disease. For women with aortopathy, ischemic heart disease and pulmonary arterial hypertension, there was no significant difference in SGA, birth weight or neonatal

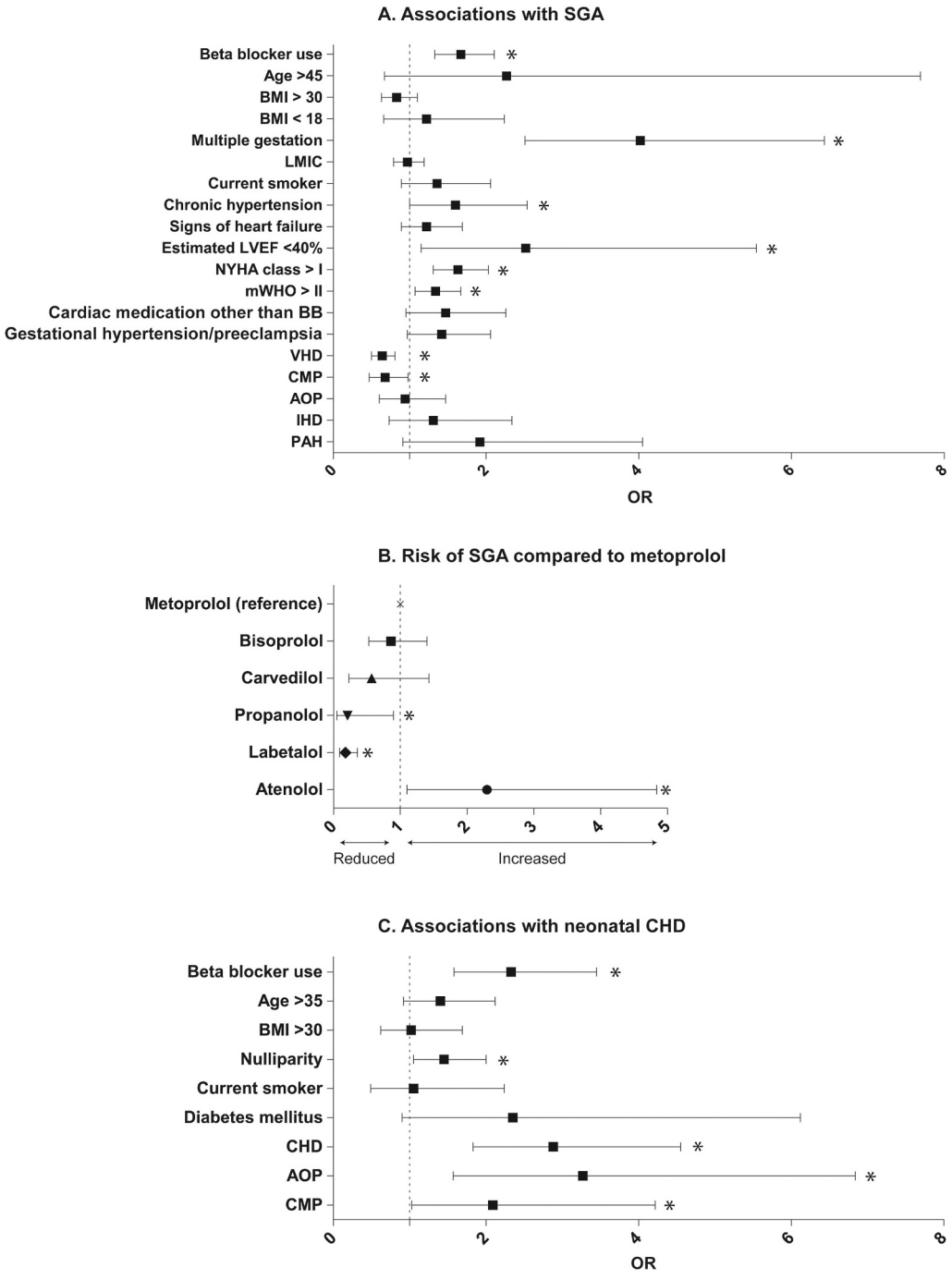


Fig. 1. Results of the multivariable logistic regression analysis. *denotes $p < 0.05$. **A:** associations with small for gestational age, after propensity score adjustment and adjustment for all factors displayed in the plot. **B:** comparative effect of the most common beta-blockers on small for gestational age, after adjustment for the following factors (not displayed in the plot): metoprolol equivalent dose, low- or middle income country and possible indications for beta-blocker use: chronic hypertension, atrial fibrillation or flutter, signs of heart failure, estimated left ventricular ejection fraction <40%, gestational hypertension or preeclampsia, cardiomyopathy, aortopathy and ischemic heart disease. **C:** associations with neonatal CHD, after propensity score adjustment and adjustment for all factors displayed in the plot. BB, beta-blocker; 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 class, New York Heart Association Functional Classification; SGA, small for gestational age; AOP, aortopathy; CMP, cardiomyopathy; IHD, ischemic heart disease; PAH, pulmonary arterial hypertension; VHD, valvular heart disease.

CHD with or without beta-blocker use.

After adjustment for multiple confounders, the adjusted difference in mean birth weight after beta-blocker use was −177 g (−218;-137), or − 5.8% (Supplementary Table S6). Fig. 1A shows that after adjustment, beta-blocker use (OR 1.7, 95% CI 1.3–2.1) was independently associated with SGA, as were multiple gestation (OR 4.0, 2.5–6.4), reduced LVEF (OR 2.5, 1.2–5.5), chronic hypertension (OR 1.6, 1.0–2.5), NYHA class >I (OR 1.6, 1.3–2.0), mWHO class >II (OR 1.3, 1.1–1.7), valvular heart disease (OR 0.6, 0.5–0.8) and cardiomyopathy (OR 0.7, 0.5–1.0) using a maternal diagnosis of CHD as the reference (full data in Supplementary Table S1).

For the analysis of beta-blocker type, 28 out of 875 pregnancies with beta-blocker exposure were excluded because multiple beta-blockers were used. Perinatal outcome is stratified by beta-blocker type in Table 3, showing differences for preterm birth, low Apgar score, low birth weight and SGA. Fig. 1B illustrates that after adjustment for metoprolol equivalent dosage and confounders and compared to metoprolol, labetalol (OR 0.2, 95% CI 0.1–0.4) and propranolol (OR 0.2, 0.1–0.9) were significantly less likely and atenolol (OR 2.3, 1.1–4.9) was more likely to cause SGA (Fig. 1B, full data in Supplementary Table S7). There was no difference between metoprolol and bisoprolol, the two most commonly used beta-blockers. Using bisoprolol as reference, labetalol was less likely to cause SGA (OR 0.2, 0.1–0.8) and atenolol more likely (OR 2.7, 1.2–5.6, Supplementary Table S7).

Beta-blocker exposure was associated with neonatal CHD after adjustment for confounders (OR 2.3, 95% CI 1.6–3.5, Fig. 1C and Supplementary Table S8). Non-beta-blocker cardiac medication use was not independently associated with neonatal CHD (OR 0.7, 0.2–2.2; Supplementary Table S8). After excluding autosomal dominant disease, first trimester beta-blocker exposure was associated with neonatal CHD (OR 1.7, 1.0–3.0); however, exposure outside of the first trimester was also associated (OR 2.1, 1.1–3.9; Supplementary Table S8).

4. Discussion

The prospective ROPAC data showed that beta-blockers were used in 15% of pregnant women with structural heart disease. Beta-blocker exposure was independently associated with SGA (adjusted OR 1.7) and with an adjusted difference in mean birth weight of −177 g, or − 5.8%. There were substantial differences in outcomes between the types of beta-blockers, with the comparative risk of SGA being lowest for labetalol and propranolol, and highest for atenolol.

In our study, beta-blockers were the most-used medication in women with structural heart disease. The differences in baseline characteristics between the pregnancies with and without beta-blocker exposure reflect differences in geographical regions, disease complexity and severity, which likely affect perinatal outcome independent of beta blocker use. The importance of these differences is not easily quantified, because characteristics known to have positive (raised maternal BMI, multiparity and gestational diabetes) as well as negative (LMIC, smoking, hypertension and heart failure) effects on birth weight were both significantly higher in the beta-blocker treated group (Table 1). [7,20]

4.1. SGA and birth weight

There was no difference in perinatal mortality between women that used beta-blockers and those that did not. However, our findings strengthen the association between beta-blockers use during pregnancy and potential adverse effects, including lower birth weight and SGA. Importantly our observations relate specifically to women with structural heart disease as opposed to hypertensive disorders of pregnancy, on which most previous studies are based. [4–6] Women with heart disease are at risk of having SGA infants [7,11], but it was previously unclear whether this was attributable to the maternal disease or to medication use. Earlier studies in women with heart disease showed conflicting findings, reporting either no effect (one study) or a significantly increased risk of SGA (three studies; OR 2.7–9.2) [7–9,21]. These studies were limited by small numbers, retrospective design and/or incomplete adjustment for confounding factors. Our adjusted analyses suggest that beta-blockers increased the odds of SGA independent of maternal cardiac function or diagnosis, although residual confounding due to other factors cannot be excluded. The adjusted difference in mean birth weight of −5.8%, or − 177 g, is in line with earlier reports of −8.6% [8] or − 237 g (adjusted only for maternal age, parity and maternal cardiac lesion). [7]

4.2. Drug-specific effect

We found differences in the magnitude of the risk of SGA for different beta-blockers. Metoprolol and bisoprolol, as most commonly used beta-blockers, were similar in their association with SGA. After correcting for equivalent dosage and different indications for beta-blocker use, atenolol was associated with the largest detrimental effect on perinatal outcome, as suggested in previous studies. [2,9,22] β1-selective beta-blockers could be expected to cause greater impairment to placental perfusion, because they lack the protective α1 blocking effects of the non-selective beta-blockers. Indeed, one previous retrospective study reported an adjusted OR of 9.21 for SGA after β1-selective beta-blocker exposure. [9] However, we did not find the same degree of association with a harmful effect for the other β1-selective types, metoprolol and

Table 3
Perinatal outcome stratified by beta-blocker type.

Drug receptor selectivity	Drug name (n)	Daily dose, grams (±SD)	Metoprolol equivalent daily dose, grams (±SD)	Preterm birth, %	Low Apgar score, %	Birth weight, grams, mean (±SD)	Low birth weight, %	SGA, %	Neonatal CHD, %	Perinatal mortality, %
Selective: β1 blockade	Metoprolol (n = 323)	62.4 (±44.6)	62.4 (±44.6)	29.2	10.5	2779 (±649)	26	18.6	6.2	1.5
	Bisoprolol (n = 261)	3.3 (±2.3)	66.7 (±46.7)	23.7	7.7	2707 (±626)	24.5	14.2	4.2	1.1
	Atenolol (n = 49)	37.4 (±19.3)	74.8 (±38.6)	34.9	22.4	2547 (±641)	40.8	26.5	6.1	2
Non-selective: β1,2 blockade	Propranolol (n = 64)	38 (±37.2)	47.5 (±46.5)	10	4.7	2776 (±527)	10.9	3.1	0	0
Non-selective: α1 and β1,2 blockade	Carvedilol (n = 64)	21 (±18.2)	83.9 (±73)	35.2	3.1	2746 (±620)	21.9	10.9	1.6	1.6
	Labetalol (n = 49)	335.8 (±232.1)	167.9 (±116)	8.7	6.1	2877 (±458)	14.3	8.2	2	2
	p-value	**<0.001**	**<0.001**	**0.001**	**0.005**	**0.127**	**0.005**	**0.003**	**0.181**	**0.348**

Data are % unless otherwise specified. *p*-values were calculated between the types of beta-blockers taken by >5% of the total beta-blocker cohort. Chi-square tests or one-way ANOVA were used as appropriate, significant if at least one of the types is significantly different compared to the other groups. *Low Apgar: <7 at 5 min. Low birth weight: <2500 g. CHD, congenital heart disease; SGA, small for gestational age.

bisoprolol. It is notable that atenolol is the only hydrophilic drug, while the others are lipophilic – possibly, subsequent differences in pharmacokinetics (such as distribution behavior and placental passage), apart from receptor selectivity, may explain the amplified effect.

Labetalol and propranolol were associated with the least harmful effect. Labetalol, as a dual α1/β1,2 receptor blocker, is expected to have less impact on the placental perfusion, but there are reports that dispute this and describe similar rates to other beta-blockers. [23]

4.3. Neonatal CHD

Earlier data are conflicting on the association between beta-blocker exposure and neonatal congenital disease. A recent meta-analysis of over 900,000 pregnancies in the general population showed that the overall risk of congenital disease was not associated with beta-blocker use, but the risk of cardiac lesions was associated (OR 1.3) – however, this effect disappeared when only adjusted data were pooled. [24] In the only other study to report an increased rate of congenital disease in the offspring after beta-blocker use in women with heart disease, neonatal CHD was found in 11.8% ($n = 6/51$) after beta-blocker use versus 4.8% ($n = 6/124$) in the control population, however this difference was not significant ($p > 0.05$). [8] We found that non-beta-blocker medications were not associated with neonatal CHD. We found 4.7% neonatal CHD after beta-blocker use, most often minor defects such as septal defects and persistent ductus arteriosus, and increased odds (OR 2.3) compared to non-users. The question remains whether this is a true effect of beta-blockers or, more likely, still mediated through the underlying condition of the mother. To address the role that maternal (hereditary) disease may play in this cohort, we adjusted for confounders, included a propensity score for beta-blocker use, and performed several sensitivity analyses excluding autosomal dominant diseases. However, both first-trimester use and outside of first-trimester use were significantly associated with neonatal CHD, which suggests that a genetic effect of the underlying condition that we could not correct for remains the most logical explanation. With this study, we cannot rule out that a causal relationship might indeed exist between beta-blocker exposure and neonatal CHD and more research on this is warranted.

4.4. Clinical implications

SGA is known to be associated with a multitude of adverse perinatal outcomes, such as mortality, neonatal intensive care unit admission, asphyxia, hypoglycemia, hypothermia, coagulopathy and immunological disorders, but also with cognitive and neurodevelopmental impairment later in childhood. [25] Added surveillance through fetal growth scans is therefore recommended for early identification of fetal growth restriction in women with heart disease using beta blockers. Alternative drugs that are not associated with growth impairment could be considered in women with fetal growth restriction or at risk of developing it, such as methyldopa for hypertension and calcium channel blockers for arrhythmias. [26,27] When a beta-blocker specifically is clearly indicated, a switch to labetalol or propranolol, and avoidance of atenolol is advised.

The prognosis of neonatal CHD depends on the complexity of the defect and the available health care facilities, and although survival is good, there may be a lifelong impact on health. [28] In women with structural cardiac disease and first trimester beta-blocker exposure, specialist fetal echocardiography at 20–22 weeks of pregnancy should be used to identify fetal CHD. Septal defects, the most frequent type, can be difficult to detect on fetal echocardiograms, so in addition a neonatal echocardiogram is advised. The optimal timing and location of delivery should be decided in close collaboration in a pregnancy heart team, including at least an obstetrician, cardiologist, anaesthesiologist and neonatologist.

Beta-blockers are an important cardiac medication and their benefits may very well outweigh the risk for many women. If a clear indication exists, beta-blockers should not be avoided, because good maternal health is essential also for fetal health, but increased foetal surveillance is prudent. Counselling women and their partners about the benefits and risks remains important.

4.5. Study limitations

Our findings are in general limited, because we performed a sub-analysis on observational data, which warrants caution while interpreting the results. Despite striving for adjustment that is as complete as possible based on the available data, we cannot rule out residual confounding effects. Beta-blocker use might act as a proxy for the severity of maternal illness, which impacts the perinatal outcomes and has an inherent risk of SGA and neonatal CHD. The specific indication for the beta-blocker use was not collected in the ROPAC and timing of exposure was limited to the trimester level. We don't have enough data to report the association between various dosages of the beta blockers and fetal outcome. The comparison between beta-blocker types is limited by the sample size of some of the lesser used types. Early pregnancy complications, such as miscarriage, may be underrepresented because these pregnancies are less likely to have been included in the registry. Other neonatal outcome parameters suspected to be related to beta-blocker use were unavailable, such as neonatal bradycardia, hypoglycemia and hypotension. It was unknown how many of the neonates with CHD required postnatal surgical or medical intervention. Women without structural heart disease who had arrhythmias or hypertensive disorders of pregnancy, who are often treated with beta blockers, were not included in the registry.

Data was collected by different local ROPAC investigators worldwide and a selection bias cannot be ruled out. Despite these shortcomings to prove a causal effect, our data probably represent the best available, due to the inherent ethical constraints in drug research during pregnancy that preclude randomized trials.

5. Conclusions

Beta-blockers are used by 15% of pregnant women with heart disease, which makes them the most common type of cardiac medication used. Beta-blocker use was associated with an adverse effect on perinatal outcomes independent of maternal factors. Beta-blocker exposure was associated with an increased the rate of SGA (adjusted OR 1.7) and reduced birth weight (by an adjusted 5.8%). Additionally, higher rates of preterm birth and low Apgar scores were observed compared to non-exposed pregnancies. Clear differences between the different types of beta-blockers were determined. Beta-blocker use was also associated with neonatal CHD (adjusted OR 2.3), but further research here is clearly needed. In women with other risk factors for growth restriction, and without specific indications for beta-blockade, alternate medications should be considered. When beta-blockers specifically are indicated, based on these data we would advise to use labetalol during pregnancy, avoiding the first trimester if possible, using a dose that is as low as possible, but as high as necessary to address clinical concerns. Increased surveillance for growth restriction and neonatal CHD should be considered.

Finally, a randomized controlled trial is advised to further investigate the hypothesis of adverse outcomes of beta-blocker use in women with heart disease, to overcome the limitations of our study. It would be of great clinical value to further examine the exposure-effect relationship, considering the dose and duration of beta-blocker use.

Data sharing

The de-identified participant data that support the findings of this study are available from the corresponding author on reasonable request.

Funding

This work was supported by the ESC EORP. 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) and Vifor (2019-2022).

CRediT authorship contribution statement

Karishma P. Ramlakhan: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jolien W. Roos-Hesselink:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Thomas Basso:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Jaimi Greenslade:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Robert B. Flint:** Writing – review & editing, Methodology, Investigation. **Eric V. Krieger:** Writing – review & editing, Investigation. **Avraham Shotan:** Writing – review & editing, Investigation. **Werner Budts:** Writing – review & editing, Investigation. **Julie De Backer:** Writing – review & editing, Investigation. **Roger Hall:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Mark R. Johnson:** Writing – review & editing, Methodology, Investigation. **William A. Parsonage:** Writing – review & editing, Methodology, Investigation, Conceptualization.

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

The ROPAC Investigators are listed in the Appendix. 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.ijcard.2024.132234.

References

[1] D. Celermajer, G. Strange, R. Cordina, L. Selbie, G. Sholler, D. Winlaw, et al., Congenital heart disease requires a lifetime continuum of care: a call for a regional registry, Heart Lung Circ. 25 (2016) 750–754.
[2] V. Regitz-Zagrosek, J.W. Roos-Hesselink, J. Bauersachs, C. Blomstrom-Lundqvist, R. Cifkova, M. De Bonis, et al., 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy, Eur. Heart J. 39 (2018) 3165–3241.
[3] C.A. Fitton, M.F.C. Steiner, L. Aucott, J.P. Pell, D.F. Mackay, M. Fleming, et al., In-utero exposure to antihypertensive medication and neonatal and child health outcomes: a systematic review, J. Hypertens. 35 (2017) 2123–2137.
[4] K. Meidahl Petersen, E. Jimenez-Solem, J.T. Andersen, M. Petersen, K. Brødbæk, L. Køber, et al., β-Blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study, BMJ Open (2012) 2.
[5] H. Orbach, I. Matok, R. Gorodischer, E. Sheiner, S. Daniel, A. Wiznitzer, et al., Hypertension and antihypertensive drugs in pregnancy and perinatal outcomes, Am. J. Obstet. Gynecol. 208 (301) (2013) e1–e6.
[6] R. Lennestål, P. Otterblad Olausson, B. Källén, Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants, Eur. J. Clin. Pharmacol. 65 (2009) 615–625.
[7] M. Cauldwell, P. Steer, M. Sterrenburg, S. Wallace, G. Malin, G. Ulivi, et al., Birth weight in pregnancies complicated by maternal heart disease, Heart 105 (2019) 391–398.
[8] A.S. Ersboll, M. Hedegaard, L. Sondergaard, M. Ersboll, M. Johansen, Treatment with oral beta-blockers during pregnancy complicated by maternal heart disease increases the risk of fetal growth restriction, BJOG 121 (2014) 618–626.
[9] K. Tanaka, H. Tanaka, C. Kamiya, S. Katsuragi, M. Sawada, M. Tsuritani, et al., Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease, Circ. J. 80 (2016) 2221–2226.
[10] I.K. Sorbye, R. Haualand, H. Wiull, A.S. Letting, E. Langesaeter, M.E. Estensen, Maternal beta-blocker dose and risk of small-for gestational-age in women with heart disease, Acta Obstet. Gynecol. Scand. 101 (7) (2022 Jul) 794–802, https://doi.org/10.1111/aogs.14363. Epub 2022 Apr 25.
[11] I.M. van Hagen, J.W. Roos-Hesselink, V. Donvito, C. Liptai, M. Morissens, D. J. Murphy, et al., Incidence and predictors of obstetric and fetal complications in women with structural heart disease, Heart 103 (2017) 1610–1618.
[12] J. Roos-Hesselink, L. Baris, M. Johnson, J. De Backer, C. Otto, A. Marelli, 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. 0 (2019) 1–8.
[13] J.W. Roos-Hesselink, T.P. Ruys, J.I. Stein, U. Thilen, G.D. Webb, K. Niwa, 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. 34 (2013) 657–665.
[14] M.A. Brown, L.A. Magee, L.C. Kenny, S.A. Karumanchi, F.P. McCarthy, S. Saito, et al., Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice, Hypertension 72 (2018) 24–43.
[15] M.S. Kramer, Determinants of low birth weight: methodological assessment and meta-analysis, Bull. World Health Organ. 65 (1987) 663–737.
[16] P.C. Austin, An introduction to propensity score methods for reducing the effects of confounding in observational studies, Multivar. Behav. Res. 46 (2011) 399–424.
[17] B. Harvald, Comparison of labetalol and propranolol in treatment of hypertension, Postgrad. Med. J. 56 (Suppl. 2) (1980) 65–68.
[18] W.H. Frishman, E.L. Michelson, B.F. Johnson, M.P. Poland, Multiclinic comparison of labetalol to metoprolol in treatment of mild to moderate systemic hypertension, Am. J. Med. 75 (1983) 54–67.
[19] J.J. Goldberger, R.O. Bonow, M. Cuffe, L. Liu, Y. Rosenberg, P.K. Shah, et al., Effect of Beta-blocker dose on survival after acute myocardial infarction, J. Am. Coll. Cardiol. 66 (2015) 1431–1441.
[20] S. Cnattingius, O. Axelsson, G. Eklund, G. Lindmark, O. Meirik, Factors influencing birthweight for gestational age, with special respect to risk factors for intrauterine growth retardation, Early Hum. Dev. 10 (1984) 45–55.
[21] J. Baard, F. Azibani, A. Osman, W. Dowling, B. Rayner, K. Sliwa, The effect of beta-blockers on foetal birth weight in pregnancies in women with structural heart disease: a prospective cohort study, Cardiovasc. J. Afr. 31 (2020) 136–141.
[22] G.Y.H. Lip, M. Beevers, D. Churchill, L.M. Shaffer, D.G. Beevers, Effect of atenolol on birth weight, Am. J. Cardiol. 79 (1997) 1436–1438.
[23] K. Meidahl Petersen, E. Jimenez-Solem, J.T. Andersen, M. Petersen, K. Brodbaek, L. Kober, et al., beta-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study, BMJ Open (2012) 2.
[24] Y. Wu, J.W. Yao, L.J. Xu, M. Chen, L. Wan, Risk of congenital malformations in offspring of women using β-blockers during early pregnancy: an updated meta-analysis of observational studies, Br. J. Clin. Pharmacol. 87 (3) (2021 Mar) 806–815, https://doi.org/10.1111/bcp.14561. Epub 2020 Oct 27.
[25] E.K. Pallotto, H.W. Kilbride, Perinatal outcome and later implications of intrauterine growth restriction, Clin. Obstet. Gynecol. 49 (2006) 257–269.
[26] B.M. Sibai, Treatment of hypertension in pregnant women, N. Engl. J. Med. 335 (1996) 257–265.
[27] M. Rezk, M. Emarh, A. Masood, R. Dawood, E. El-Shamy, A. Gamal, et al., Methyldopa versus labetalol or no medication for treatment of mild and moderate chronic hypertension during pregnancy: a randomized clinical trial, Hypertens. Preg. 39 (2020) 393–398.
[28] I. Bracher, M. Padrutt, F. Bonassin, B. Santos Lopes, C. Gruner, S.F. Stampfli, et al., Burden and impact of congenital syndromes and comorbidities among adults with congenital heart disease, Int. J. Cardiol. 240 (2017) 159–164.