Maternal beta-blocker dose and risk of small-for-gestational-age in women with heart disease

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Abstract

Introduction: Beta-blockers are prescribed for many pregnant women with heart disease, but whether there is a dose-dependent effect on fetal growth remains to be examined. We aimed to investigate if antenatal beta-blocker use and dose were associated with delivering a small-for-gestational-age infant among women with heart disease.

Material and methods: Our cohort included women with heart disease who delivered at Oslo University Hospital between 2006 and 2015. Maternal heart disease was classified into modified WHO risk scores. Women with beta-blocker treatment were dichotomized into whether they had been treated with a low or high dose based on clinical factors. We compared the risk of delivering a small-for-gestational-age infant in women exposed to high doses, low doses, or with no exposure to antenatal beta-blockers while adjusting for severity of maternal heart disease in logistic regression models.

Results: Of a total of 540 pregnancies among women with heart disease, 163 (30.2%) were exposed to beta-blocker treatment. The majority were treated with metoprolol (86.5%). Almost twice as many babies in the beta-blocker group were small-for-gestational-age, compared with the non-exposed group (19.8 vs 9.5%, \(P < 0.001\)). Women using a high-dose beta-blocker had a five-fold increased risk of delivering a small-for-gestational-age infant compared with non-exposure (adjusted odds ratio [aOR] 4.89, 95% confidence interval [CI] 2.22–10.78, \(P < 0.001\)). Women using a low dose of beta-blocker had a two-fold increased risk of delivering a small-for-gestational-age infant; however, the confidence interval included the null (aOR 1.75, 95% CI 0.83–3.72, \(P = 0.143\)). Results when restricting the analyses to metoprolol showed the same pattern, but with attenuation of risks.

Conclusions: We found a five-fold increased risk of delivering a small-for-gestational-age infant in women with heart disease treated with a high dose of beta-blocker, and a two-fold increased risk among those treated with a low dose, showing an apparent

Abbreviations: CI, confidence interval; mWHO, modified World Health Organization risk score; NICU, neonatal intensive care unit; OR, odds ratio; SGA, small-for-gestational-age.
dose–response relation. Close monitoring of fetal growth is warranted among women with heart disease treated with beta-blockers. As drug therapy in pregnancy concerns both mother and fetus, an optimum balance for both should be the goal.

**KEYWORDS**
beta-blocker, birthweight, heart disease, modified World Health Organization risk score, pregnancy, small-for-gestational-age, Z score

# 1 | INTRODUCTION

Heart disease is an important indirect cause of maternal death and morbidity in high-income countries and complicates 0.2%–4.0% of pregnancies. In women with heart disease, the physiologic cardiovascular adaptations to pregnancy can be a challenge, both to the mother and the fetus. In normal pregnancy, maternal cardiac output and heart rate rise and peripheral resistance decreases partially due to the formation of a low-resistance circuit in the uteroplacental circulation. This placental perfusion is dependent on the maternal circulation. In women with congenital or acquired heart disease, the ability to meet the new demands of pregnancy may be challenging, leading to compromised uteroplacental flow, intrauterine fetal growth restriction, and delivery of a small-for-gestational-age (SGA) infant. As a result, fetal growth is disproportionally affected in women with severe heart conditions, as classified by the modified World Health Organization risk classification (mWHO). Use of beta-blockers is central to treatment of arrhythmias, heart failure, valvular heart disease, cardiomyopathy, and secondary hypertension. However, medication during pregnancy has the potential to negatively affect fetal growth. Beta-blockers differ in many aspects, including selectivity, half-life, and bioavailability. A cardioselective beta-blocker is considered the drug of choice in pregnancy due to selectivity for beta-1-adrenergic receptors mainly in the myocardium. The degree of beta-1 selectivity is dose dependent. Beta-1-selective beta-blockers include bisoprolol, atenolol, and metoprolol, where bisoprolol has a higher selectivity. Other beta-blockers such as labetalol, carvedilol, propranolol, and sotalol are unselective beta-blockers and may have antagonistic effects on beta-2 receptors in the uterus. Most studies investigating the effect of beta-blockers on fetal growth have examined women treated for hypertension where use is linked to increased risk of fetal growth restriction and of giving birth to an SGA infant. The mechanisms are suggested to be beta-blocker-induced reduction in uteroplacental blood flow due to selective vasoconstriction of vessels in the placenta, effects on maternal arterial blood pressure and cardiac output, and for beta-blockers that cross the placental barrier, a direct effect on fetal growth. A few studies have examined antenatal beta-blocker use in women with heart disease and found a significant correlation between maternal beta-blocker therapy and reduced fetal birthweight. However, previous studies have not included information about beta-blocker dose.

**Key message**
Pregnant women with heart disease using a high dose of beta-blocker had a five-fold increased risk of giving birth to a small-for-gestational-age infant, whereas those using low doses had a two-fold increased risk.

We hypothesized that administration of a beta-blocker was a risk factor for having an SGA infant independent of maternal cardiac risk class, and that there was a dose–response relation between maternal beta-blocker use and the risk of an SGA infant.

# 2 | MATERIAL AND METHODS

This was a cohort study of women with heart disease who delivered at a single center; Oslo University Hospital Rikshospitalet, Oslo, Norway. We included women diagnosed with congenital or acquired heart disease according to the International Classification of Diseases 10th revision before or during pregnancy and who gave birth to a live singleton infant. We identified 540 women–infant pairs that delivered at the facility between January 1, 2006 and December 31, 2015. Sixty-three women delivered more than once during this period, making the study population 474 unique women and 540 infants. The facility has a geographical uptake area of urban Oslo, in addition to referrals of high-risk pregnancies (mWHO risk groups II–IV) from regional and national hospitals. A multidisciplinary cardio-obstetric team provided pre-conception counseling, follow up during pregnancy, and an individual plan for labor, delivery, and postpartum management. Data were collected from electronic medical files and were manually entered into a custom-made case record form by two independent researchers (RH and HW). The multidisciplinary team was consulted in order to correctly classify cardiac disease or maternal/infant outcomes.

The primary outcome was the delivery of an SGA infant—defined as a Z score (birthweight according to gestational week and infant sex) below the 10th centile on national birthweight charts. Gestational length was calculated based on dating ultrasonography performed in gestational weeks 17–19, which was the national norm during the period. Secondary infant outcomes were Apgar score <7 at 5 minutes and transfer to neonatal intensive care unit (NICU).
We recorded antenatal beta-blocker use in terms of type of beta-blocker, the maximum and minimum dose prescribed, gestational week at initiation/discontinuation, and duration of treatment in calendar weeks. If beta-blocker was used before pregnancy, then gestational week 1 was registered as the starting week. Use of beta-blocker and maximum dosage were combined to produce a covariate with three categories: "high" beta-blocker dose, "low" beta-blocker dose, or "no beta-blocker". Dosage categories for metoprolol were constructed based on clinical significance. Equivalent doses were calculated for the other beta-blocker types according to expert opinion. We considered metoprolol doses of 75 mg and labetalol doses of 200 mg or higher as "high" (Table S1). Similar cut-off values were >80 mg for nadolol and sotalol, >50 mg for carvedilol, and >100 mg for atenolol.

Maternal heart disease during the period was classified according to an adapted mWHO classification used in Norwegian guidelines.10,20 The mWHO classification system stratifies pregnancy-related maternal morbidity and mortality risks, distinguishing between low-, moderate-, and high-risk conditions (Table S2). If arrhythmias were the only cardiac condition in the absence of structural heart disease, women were classified as mWHO risk group 1, unless stated otherwise by a cardiologist. Due to there being only a few cases in mWHO risk group 4, mWHO risk groups 3 and 4 were merged. Women with more than one heart condition were classified by the most serious condition, and women converting from one risk group to another during pregnancy were classified in the highest risk group. We included the following covariates known to be associated with fetal growth: maternal age at delivery, parity categorized into nulliparous and multiparous women, pre-pregnancy maternal body mass index, maternal smoking, and gestational weight gain. Obstetric covariates included preeclampsia, gestational and pre-gestational hypertension, gestational and pre-gestational diabetes, all categorized as "yes" or "no".

2.1 | Statistical analyses

We calculated mean values and proportions with standard deviations or 95% confidence intervals (CI) for continuous and categorical variables respectively. To compare means/medians and proportions we used Student’s t test/Kruskall–Wallis test and Mann–Whitney’s U test/chi-squared test or Fisher’s exact test, as appropriate. We performed multivariable linear regression analyses to assess any independent effect of a high dose, a low dose, or no beta-blocker use (reference) on infant birthweight z score. We evaluated mWHO class as particularly important because of confounding by indication, but also evaluated maternal age, parity, body mass index and weight change, preeclampsia, pre-gestational and gestational hypertension, and maternal cardiac arrhythmia for inclusion in the model. In the final model, maternal age, pre-gestational hypertension, and maternal arrhythmia were not significant and were excluded from the model. Due to the possibility for confounding by indication, mWHO was kept in the model although not statistically significant. We calculated the associated $r^2$ and performed residual plots to check model fit.

Proportions of SGA infants were compared among the exposed and unexposed groups and in the exposed group, stratified by dose level of beta-blocker. To assess the risk of SGA below the 10th centile according to high dose, low dose, or no beta-blocker (reference), we performed logistic regression analyses, adjusting for maternal body mass index and weight change, preeclampsia, gestational hypertension, and maternal mWHO risk group. Robust variance estimator was applied to the models to adjust for data dependency in women who had given birth more than once. In sensitivity analyses we ran the adjusted models after excluding women exposed to labetalol ($n = 14$), as this beta- and alpha-blocker was primarily used in the context of gestational hypertension and preeclampsia and also after excluding women treated with any beta-blocker other than metoprolol. Among women using beta-blockers, we further assessed if duration of therapy and/or timing of initiation of therapy were associated with offspring z score and risk of SGA. Cases with missing values were less than 5% for all variables and were excluded from the final analyses. A two-sided $p$ value of 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics 2/24.

2.2 | Ethical approval

The study was approved as a quality-assurance project by the Data Protection Office of Oslo University Hospital, approval no. 2015/19146, dated December 7, 2016. Individual patient’s consent was waived. Patient involvement was not considered because of the nature of the project.

3 | RESULTS

The majority of women were classified as mWHO risk group 1 (70.0%), followed by risk group 2 (20.4%) and risk groups 3–4 (9.8%) (Table 1). One out of three women had been diagnosed with arrhythmias. Overall, one-third (30.2%) of women received antenatal beta-blocker treatment. Women using beta-blockers had a higher mWHO risk score, a higher pre-pregnancy body mass index, were more often diagnosed with preeclampsia (10.4% vs 1.9%), pre-gestational or gestational hypertension, and were more often diagnosed with arrhythmias compared with women not using beta-blockers. Maternal age, parity, maternal smoking, and weight gain in pregnancy did not differ between women using beta-blockers and those who did not use them (Table 1). There were no maternal or neonatal deaths. The most commonly prescribed medication was the beta-1-selective beta-blocker metoprolol ($n = 141$; 86.5%) followed by the alpha/beta-blocker labetalol ($n = 14$; 8.6%), and other beta-blockers (5.5%; sotalol, $n = 5$; atenolol, $n = 2$; nadolol, $n = 1$; carvedilol, $n = 1$). The mean duration of treatment was 21 weeks (range 1–41 weeks). Approximately half of the women using beta-blockers were prescribed a high dose (Table 1). With regards to
women using metoprolol, only doses in multiples of 25 mg were prescribed. The mean gestational age at birth was 1 week shorter in the exposed vs the unexposed group.

The mean birthweight of infants exposed to beta-blockers was lower than those infants whose mothers did not use beta-blockers, with a difference of 338 g (3009 vs 3347 g, \( p < 0.001 \)) (Table 2). Both groups had z scores below zero; −0.52 in the beta-blocker group vs −0.24 in the non-treated group (\( p < 0.001 \)) (Figure 1). Almost twice as many infants in the beta-blocker group were classified as SGA, compared with the non-exposed group (19.8 vs 9.5%, \( p < 0.001 \)).

### TABLE 1 Maternal and infant characteristics of 540 pregnancies by antenatal beta-blocker treatment

| Maternal characteristics                  | Total     | Beta-blocker | No beta-blocker | \( p \) |
|-------------------------------------------|-----------|--------------|-----------------|--------|
| Number of pregnancies (%)                 | 540       | 163 (30.2)   | 377 (69.8)      |        |
| Maternal age, mean (SD)                   | 31.4 (5.1) | 31.5 (4.9)   | 31.4 (5.6)      | 0.831  |
| Parity, n (%)                             |           |              |                 | 0.418  |
| Para 0                                    | 275 (51.1)| 79 (48.5)    | 196 (52.3)      |        |
| Para 1+                                   | 263 (48.9)| 84 (51.5)    | 179 (47.7)      |        |
| Maternal BMI before pregnancy (kg/m\(^2\)), mean (SD) | 23.9 (4.6) | 24.8 (5.3)   | 23.5 (4.2)      | 0.003  |
| Maternal weight change, (kg), mean (SD)   | 12.5 (5.5)| 12.6 (6.0)   | 12.5 (5.3)      | 0.875  |
| Smoking during pregnancy, n (%)           | 38 (7.0)  | 13 (8.1)     | 25 (6.6)        | 0.555  |
| Modified WHO (mWHO) risk group, n (%)     |           |              |                 | <0.001 |
| mWHO risk group 1                         | 376 (70.0)| 100 (61.3)   | 276 (73.4)      |        |
| mWHO risk group 2                         | 110 (20.4)| 34 (20.9)    | 76 (20.2)       |        |
| mWHO risk group 3–4                       | 53 (9.8)  | 29 (17.8)    | 24 (6.4)        |        |
| Maternal arrhythmia, n (%)                | 196 (36.3)| 104 (63.8)   | 92 (24.4)       | <0.001 |
| Pre-gestational hypertension, n (%)       | 11 (2.0)  | 9 (5.6)      | 2 (0.5)         | <0.001 |
| Gestational hypertension, n (%)           | 53 (9.8)  | 25 (15.3)    | 28 (7.4)        | 0.005  |
| Preeclampsia, n (%)                       | 24 (4.4)  | 17 (10.4)    | 7 (1.9)         | <0.001 |
| Pre-gestational diabetes, n (%)           | 4 (0.7)   | 2 (1.2)      | 2 (0.5)         | 0.588  |
| Gestational diabetes, n (%)               | 11 (2.0)  | 2 (1.2)      | 9 (2.4)         | 0.384  |
| Type beta-blocker, n (%)                  |           |              |                 |        |
| Metoprolol                                | 141 (86.5)|            |                 |        |
| Labetalol                                 | 14 (8.6)  |              |                 |        |
| Other beta-blocker                       | 9 (5.5)   |              |                 |        |
| Beta-blocker dose, n (%)                  |           |              |                 |        |
| High dose                                 |            | 79 (48.8)    |                 |        |
| Low dose                                  |            | 83 (51.2)    |                 |        |
| Gestational week at initiation of beta-blocker, median (IQR) | 16.5 (28) |              |                 |        |
| Duration of beta-blocker use (wk); median (IQR) | 19.5 (29) |            |                 |        |
| Other medication, n (%)                   | 174 (32.2)| 67 (41.1)    | 107 (28.4)      | 0.005  |
| Antihypertensive medication, n (%)        | 29 (5.4)  | 24 (14.7)    | 5 (1.3)         | <0.001 |
| Mode of delivery, n (%)                   |           |              |                 | <0.001 |
| Spontaneous vaginal delivery              | 281 (52.0)| 69 (42.3)    | 212 (56.2)      |        |
| Operative vaginal delivery                | 67 (12.4) | 12 (7.4)     | 55 (14.6)       |        |
| Emergency cesarean delivery               | 89 (16.5)| 27 (16.6)    | 60 (15.9)       |        |
| Planned cesarean delivery                 | 103 (19.1)| 53 (32.5)    | 50 (13.1)       |        |
| Gestational age at birth (wk), mean (SD)  | 38.5 (2.5)| 37.7 (2.6)   | 38.9 (2.3)      | <0.001 |
| Infant sex, female, n (%)                 | 262 (48.5)| 80 (49.1)    | 182 (48.3)      | 0.312  |

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.

\(^a\)Missing n=2.

\(^b\)Includes sotalol (\( n = 5 \)), atenolol (\( n = 2 \)), carvedilol (\( n = 1 \)) and nadolol (\( n = 1 \)).

\(^c\)Low dose includes \(<75\text{ mg metoprolol}, \leq 200\text{ mg labetalol}, \leq 100\text{ mg atenolol}, \leq 50\text{ mg carvedilol}, \leq 80\text{ mg nadolol}, \text{ or } \leq 80\text{ mg sotalol}\). High dose includes \(\geq 75\text{ mg metoprolol}, \geq 200\text{ mg labetalol}, >100\text{ mg atenolol}, >50\text{ mg carvedilol}, >80\text{ mg nadolol}, \text{ or } >80\text{ mg sotalol}\).
Stratifying by beta-blocker dose, 24.1% of the infants exposed to a high dose were SGA, compared with 14.5% and 9.5% in the low-dose and no beta-blocker groups, respectively (Figure 2).

In multivariate linear regression analysis, z score was significantly lower in the high-dose group (−0.26) compared with women with no beta-blocker, whereas the z score in the low-dose group did not differ (−0.10) (Table 3). We explored an interaction between dosage and time of initiation of beta-blocker, and found that initiation of beta-blocker treatment early in pregnancy had a greater impact on the z score compared with late initiation; however, effects were small. The use of a high dose was slightly more common in mWHO risk group 3–4 (19%) compared with mWHO risk group 1 (15%) (Table 4). In terms of duration of treatment, fewer women in mWHO risk group 3–4 were exposed to treatment of 20 weeks or more compared with women in mWHO risk group 1 (37.5% vs 52.0%, respectively; Table 4).

In univariate logistic regression models, high-dose beta-blocker use was associated with a three-fold risk of delivering an SGA infant compared with no beta-blocker (odds ratio [OR] 3.00, 95% CI 1.61–5.58, \( p < 0.001 \)), whereas low-dose beta-blocker use was associated with a 1.6-fold increased risk, but not significantly so (Table 5). In adjusted models, high-dose beta-blocker use was associated with a five-fold risk of delivering an SGA infant compared with no beta-blocker (adjusted OR 4.89, 95% CI 2.22–10.78, \( P < 0.001 \)), whereas low-dose beta-blocker had a 1.8-fold insignificantly elevated risk (Table 5). These models included adjustment for mWHO risk group.

### Table 2: Infant outcomes in 540 pregnancies by antenatal beta-blocker exposure in women with heart disease

| Outcomes                                      | Total   | Beta-blocker | No beta-blocker | \( p \)  |
|-----------------------------------------------|---------|--------------|-----------------|--------|
| Number of infants                             | 540     | 163 (30.2)   | 377 (69.8)      |        |
| Infant birthweight (g), mean (SD)             | 3245 (630) | 3009 (687) | 3347 (577) | <0.001 |
| Infant birthweight groups (g), n (%)          |         |              |                 | <0.001 |
| <2500                                         | 62 (11.5) | 40 (24.5)    | 22 (5.8)        |        |
| 2500–2999                                     | 87 (16.1) | 34 (20.9)    | 53 (14.1)       |        |
| 3000–3499                                     | 203 (37.6) | 53 (32.5) | 150 (39.8)      |        |
| 3500–3999                                     | 146 (27.0) | 28 (17.2) | 118 (31.3)      |        |
| 4000+                                         | 42 (7.8) | 8 (4.9)      | 34 (9.0)        |        |
| z score, mean (SD)                            | −0.33 (0.89) | −0.52 (0.93) | −0.24 (0.86) | 0.001  |
| Small-for-gestational-age, 10th centile, n (%) | 68 (12.6) | 32 (19.8) | 36 (9.5) | 0.001  |
| Small-for-gestational-age, 2.5th centile, n (%) | 14 (2.6) | 9 (5.6) | 5 (1.3) | 0.005  |
| Large-for-gestational-age, 10th centile, n (%) | 26 (4.8) | 6 (3.7) | 20 (5.3) | 0.43   |
| Infant Apgar score <7 at 5 min, mean (SD)     | 9.3 (0.80) | 9.3 (0.74) | 9.3 (0.82) | 0.596  |
| Transfer neonatal intensive care, n (%)       | 85 (15.7) | 45 (27.6) | 40 (10.6) | <0.001 |

Abbreviation: SD, standard deviation.
When excluding women treated with any other beta-blocker than metoprolol, the risk estimates were slightly lower (Table 5), but remained significantly increased for the high-dose group.

As to secondary outcomes, a higher number of infants in the beta-blocker group were transferred to the NICU compared with the no beta-blocker group (Table 2). This difference was mainly due to a lower gestational age. In adjusted models we found no association between beta-blocker dose and Apgar score <7 or transfer to the NICU. In analyses where cases with labetalol were excluded (n = 14), the results did not change, so all cases were included in the final analyses.

4 | DISCUSSION

In the present cohort study of 540 pregnancies in women with known heart disease, we found that a high dose of beta-blocker was associated with a reduced offspring z-score and a five-fold increased risk of SGA, compared with no beta-blocker. The low-dose group had a two-fold increased risk, but differences were not significant. These results were adjusted for maternal cardiac risk group. Our study suggests a dose dependent effect of beta-blockers on fetal growth even after taking into consideration the severity of maternal heart disease.
The SGA rates we found in our study are in accordance with other studies investigating the association between beta-blocker treatment and birthweight/z score in pregnancies complicated by maternal heart disease. Balci et al. found a difference in birthweight of about 100 g between the treated and non-treated groups, whereas Ersbøll et al. found an almost three-fold risk of delivering an SGA infant in women with beta-blocker therapy. Tanaka et al. found an adjusted OR of delivering a growth-restricted infant to be 9.21 in the group treated with beta-blockers compared with an untreated control group.

Beta-blocker usage at high doses may directly increase the risk of SGA; however, beta-blocker usage at high doses may also act as a proxy to identify those with severe disease and where fetal growth is most compromised. Although the proportion of women in the mWHO risk group 3–4 using a high dose was somewhat higher than the proportion in the mWHO risk group 1, this does not fully explain the difference in SGA risk. Even after taking into account the severity of maternal heart disease, we found a dose–response relation between beta-blocker use and SGA. When restricting to metoprolol-treated pregnancies only, the risk estimates were somewhat reduced, but remained significantly elevated in the high-dose group. Nor have previous studies specifically explored a dose–response relation. Erbsøll et al. and Tanaka et al. found a modest correlation between duration of therapy and a negative deviation from expected birthweight or intrauterine growth restriction, respectively. In this study the duration of treatment did not differ between mWHO risk groups. In sensitivity analyses, we found that longer duration of treatment and treatment initiation before

### TABLE 4 Maternal beta-blocker doses and duration of use by maternal cardiac risk groups

| Duration beta-blocker use | No beta-blocker | Low dose | High dose |
|---------------------------|-----------------|----------|-----------|
| <20 weeks                 | 277 (73.5)      | 44 (11.7)| 56 (14.9) |
| ≥20 weeks                 | 48 (48.0)       | 52 (52.0)|           |

| mWHO risk group | n (%) | n (%) | n (%) |
|-----------------|-------|-------|-------|
| 1               | 277 (73.5) | 44 (11.7)| 56 (14.9) |
| 2               | 76 (69.1)  | 21 (19.1)| 13 (11.8) |
| 3–4             | 24 (46.2)  | 18 (34.6)| 10 (19.2) |

Note: High dose includes ≥75 mg metoprolol, ≥200 mg labetalol, >100 mg atenolol, >50 mg carvedilol, >80 mg nadolol, or >80 mg sotalol. Low dose includes <75 mg metoprolol, <200 mg labetalol, ≤100 mg atenolol, ≤50 mg carvedilol, ≤80 mg nadolol, or ≤80 mg sotalol.

### TABLE 5 Risk of small-for-gestational-age infant by maternal high beta-blocker dose, low beta-blocker dose vs no maternal beta-blocker use for (a) All beta-blocker use (cohort) and (b) Restriction to the beta-blocker metoprolol

| Outcomes | Cohort | SGA | SGA | OR | 95% CI | p | aOR | 95% CI | a p |
|----------|--------|-----|-----|----|--------|---|-----|--------|-----|
| (a) All beta-blockers |        |     |     |    |        |   |     |        |     |
| Infants  | 540    | 68  | 472 |    |        |   |     |        |     |
| High dose | 83     | 19  | 60  | 3.00 | 1.61–5.58 | 0.001 | 4.89 | 2.22–10.78 | <0.001 |
| Low dose | 79     | 12  | 67  | 1.60 | 0.79–3.23 | 0.189 | 1.75 | 0.83–3.72 | 0.143 |
| No beta-blocker | 377 | 36  | 341 | 1 | Ref | Ref | 1 | Ref | Ref |
| (b) Metoprolol |        |     |     |    |        |   |     |        |     |
| Infants  | 517    | 50  | 360 |    |        |   |     |        |     |
| High dose | 47     | 12  | 47  | 2.42 | 1.18–4.97 | 0.016 | 4.30 | 1.82–10.19 | 0.001 |
| Low dose | 68     | 12  | 69  | 1.65 | 0.82–3.33 | 0.164 | 1.70 | 0.79–3.65 | 0.173 |
| No beta-blocker | 295 | 36  | 341 | 1 | Ref | Ref | 1 | Ref | Ref |

Abbreviation: aCI, adjusted confidence interval; aOR, adjusted odds ratio; ap, adjusted p value; CI, confidence interval; mWHO, modified World Health Organization classification of heart disease in pregnancy; OR, odds ratio; SGA, small for gestational age.

*Adjusted for modified WHO cardiac risk group, preeclampsia, pre-gestational/gestational hypertension, maternal pre-pregnancy body mass index and maternal weight gain. SGA = 10th centile for birthweight and gestational length at birth in weeks. High dose includes ≥75 mg metoprolol, ≥200 mg labetalol, >100 mg atenolol, >50 mg carvedilol, >80 mg nadolol, or >80 mg sotalol. Low dose includes <75 mg metoprolol, <200 mg labetalol, ≤100 mg atenolol, ≤50 mg carvedilol, ≤80 mg nadolol, or ≤80 mg sotalol.

The SGA rates we found in our study are in accordance with other studies investigating the association between beta-blocker treatment and birthweight/z score in pregnancies complicated by maternal heart disease. Balci et al. found a difference in birthweight of about 100 g between the treated and non-treated groups, whereas Erbsøll et al. found an almost three-fold risk of delivering an SGA infant in women with beta-blocker therapy. Tanaka et al. found an adjusted OR of delivering a growth-restricted infant to be 9.21 in the group treated with beta-blockers compared with an untreated control group.

Beta-blocker usage at high doses may directly increase the risk of SGA; however, beta-blocker usage at high doses may also act as a proxy to identify those with severe disease and where fetal growth is most compromised. Although the proportion of women in the mWHO risk group 3–4 using a high dose was somewhat higher than the proportion in the mWHO risk group 1, this does not fully explain the difference in SGA risk. Even after taking into account the severity of maternal heart disease, we found a dose–response relation between beta-blocker use and SGA. When restricting to metoprolol-treated pregnancies only, the risk estimates were somewhat reduced, but remained significantly elevated in the high-dose group.

Nor have previous studies specifically explored a dose–response relation. Erbsøll et al. and Tanaka et al. found a modest correlation between duration of therapy and a negative deviation from expected birthweight or intrauterine growth restriction, respectively. In this study the duration of treatment did not differ between mWHO risk groups. In sensitivity analyses, we found that longer duration of treatment and treatment initiation before
20 weeks of pregnancy was associated with a lower z-score. Our study was underpowered to examine the interaction between z-score and initiation and duration of beta-blocker therapy. In stratified analyses with dose categories, an effect between duration of therapy and z-score was found only for the high-dose category. Analyses using dosage categories of beta-blocker showed a similar association to the risk of delivering SGA infants, where higher doses were associated with a significantly increased risk. An association between duration of treatment and z-scores in other studies may be obscured by the fact that these women also used high doses of beta-blocker.

Using Norwegian national growth charts to calculate z-score, we found that both women using beta-blockers and those not using beta-blockers had a mean z-score below zero. This confirms previous findings that maternal heart disease is a risk factor for SGA.\(^5,6,21\) Other studies have found a more marked effect of beta-blockers on birthweight/z score in women suffering from valvular heart disease and arrhythmias.\(^6\) In a study by Pieper et al, a reduction in unadjusted birthweight was significantly correlated with the severity of heart disease (mWHO).\(^6\) Hameed et al found the same association related to severity of aortic and mitral stenosis.\(^21\) In our study, arrhythmias were not found to influence z score in any particular way. A more meticulous coding of the indication for medication might reveal a stronger relation between some cardiac conditions and z score; however, a larger cohort would be needed.

When we adjusted for the mWHO risk groups, the effect of beta-blocker dose remained. Even though the logistic regression model included cells with n < 5, the model was evaluated by the Omnibus test and found to be stable. The proportion of SGA infants, in our study defined as 10th centile, in the no beta-blocker group was 9.5%, and similar to the expected proportion in the background population, whereas the proportion in the overall beta-blocker group was 19.8%, almost twice as high. This suggests that the type of heart disease is not likely to majorly influence the differences we found.

In this study, more than 86% of women using beta-blockers were treated with metoprolol, a beta-1-selective beta-blocker, and the recommended drug of choice for pregnant women with heart disease in Norway.\(^20\) None of the women were treated with bisoprolol, a very specific selective beta-1 blocker that is commonly used in other European countries. The beta-1-selective beta-blocker atenolol was prescribed for two women only, as it should be avoided in pregnancy due to high rates of fetal growth restriction.\(^3\) The unselective beta-blockers sotalol and nadolol were rarely used. Among all women, 8.6% were treated with the alpha/beta-blocker labetalol, mainly as treatment for pre-gestational or gestational hypertension. Labetalol is safe for the fetus.\(^22\) The proportion of women with hypertensive disorders in pregnancy was approximately doubled in the beta-blocker group. Preterm preeclampsia is closely associated with intrauterine growth restriction and SGA, so may be on the causal pathway.\(^23\) Some of these women did not change the overall results and we believe that adjusting for preeclampsia did not introduce significant bias. Another alpha/beta-blocker, carvedilol, often used in heart failure, was also rarely used.\(^14\)

Women in the beta-blocker group gave birth approximately 1 week earlier than the non-treated group, but although their infants were more often moved to the NICU, no difference in average Apgar scores was found. During the study period there was no routine screening for hypoglycemia in infants antenatally exposed to beta-blocker. This has since been implemented in national guidelines.

Based on our results, women with heart disease treated with low doses of beta-blocker are likely at lower risk of SGA, with an apparent dose–response relation. This information should be part of pre-pregnancy multidisciplinary counseling, in particular to promote compliance.\(^24\) Women on high doses, however, do need more careful monitoring to balance maternal and fetal needs. Further elucidation of the mechanisms for fetal growth restriction are needed for novel clinical approaches to prevent unfavorable fetal outcomes when caring for women with heart disease in need of beta-blocker treatment.

Our study design had some limitations. The cohort was not population-based due to in-referrals of high-risk women. Some women delivered multiple times, leading to dependency of data-bias which we tried to adjust for in the analyses. The majority of women were treated with metoprolol, and our findings cannot be extrapolated to other beta-blocker types. We did not have information on patient treatment compliance, which is known to be compromised in this group.\(^25\) Heart disease was classified based on the mWHO framework of maternal and not fetal risk, and alternative ways of classifying heart disease might yield different results. Among strengths, our cohort was large compared with previous studies, with complete inclusion. We had detailed and validated exposure information about type, dose, timing, and duration of beta-blocker use. Finally, patient treatment in the period was standardized by a single multidisciplinary team.

5  |  Conclusion

In women with heart disease, high doses of beta-blockers during pregnancy are associated with a reduced offspring birthweight and a five-fold increased risk of an SGA infant, compared with no beta-blocker use. Our study suggests a dose-dependent effect. Fetal growth monitoring is mandatory, especially among women requiring a high dose of beta-blocker medication. Women with heart disease treated with low doses of beta-blocker may have an increased risk to fetal growth, but more studies are needed.

Conflict of Interest

The authors report no conflicts of interest.

Author Contribution

This study was planned and designed by IKS, RH, HW, ASL, EL, and MEE. IKS, RH, and HW performed the statistical analyses and wrote
the manuscript. All authors contributed substantially to interpretation of results as well as to revisions of the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author (IKS) upon reasonable request.

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REFERENCES
1. Nyflot LT, Johansen M, Mulic-Lutvica A, et al. The impact of cardiovascular diseases on maternal deaths in the Nordic countries. Acta Obstet Gynecol Scand. 2021;100:1273-1279.
2. Schutte JM, Steegers EA, Schuitemaker NW, et al. Rise in maternal mortality in The Netherlands. BJOG. 2010;117:399-406.
3. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018;39:3165-3241.
4. Bottega N, Malhame I, Guo L, Ionescu-Ittu R, Therrien J, Marelli A. Secular trends in pregnancy rates, delivery outcomes, and related health care utilization among women with congenital heart disease. Congenit Heart Dis. 2019;14:735-744.
5. Gelson E, Curry R, Gatzoulis MA, et al. Effect of maternal heart disease on fetal growth. Obstet Gynecol. 2011;117:886-891.
6. Pieper PG, Balci A, Aarnoudse JG, et al. Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease. Circulation. 2013;128:2478-2487.
7. Pieper PG. Use of medication for cardiovascular disease during pregnancy. Nat Rev Cardiol. 2015;12:718-729.
8. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104:515-521.
9. 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;34:657-665.
10. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart. 2006;92:1520-1525.
11. KarihkeyanVJ, LipGY. Hypertension in pregnancy: pathophysiology and management strategies. Curr Pharm des. 2007;13:2567-2579.
12. Grandi E, Ripplinger CM. Antiarrhythmic mechanisms of beta blocker therapy. Pharmacol Res. 2019;146:104274.
13. Meidahl Petersen K, Jimenez-Solem E, Andersen JT, et al. Beta-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study. BMJ Open. 2012;2:e001185.
14. Tanaka K, Tanaka H, Kamiya C, et al. Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. Circ J. 2016;80:2221-2226.
15. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2003;3:CD002863.
16. Duan L, Ng A, Chen W, et al. Beta-blocker exposure in pregnancy and risk of fetal cardiac anomalies. JAMA Intern Med. 2017;177:885-887.
17. Ersboll AS, Hedegaard M, Sondergaard L, Ersboll M, Johansen M. Treatment with oral beta-blockers during pregnancy complicated by maternal heart disease increases the risk of fetal growth restriction. BJOG. 2014;121:618-626.
18. Balci A, Sollie-Szarynska KM, van der Bijl AG, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. Heart. 2014;100:1373-1381.
19. Skjaerven R, Gjessing HK, Bakkevig LS. Birthweight by gestational age in Norway. Acta Obstet Gynecol Scand. 2000;79:440-449.
20. Cardiac disease in pregnancy 2014. Norway: Norwegian Gynecological Association 2014; 2014 Available from: https://www.legeforeningen.no/foreningsled/fagmed/norsk-gynekologisk-forening/
21. Hameed A, Karaalp IS, Tummalap P, et al. The effect of valvular heart disease on maternal and fetal outcome of pregnancy. J Am Coll Cardiol. 2001;37:893-899.
22. Shekhar S, Gupta N, Kirubakaran R, Pareek P. Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis. BJOG. 2016;123:40-47.
23. Staff AC, Fjeldstad HE, Fosheim IK, et al. Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. Am J Obstet Gynecol. 2022;226:S895-S906.
24. Cauldwell M, Dos Santos F, Steer PJ, Swan L, Gatzoulis M, Johnson MR. Pregnancy in women with congenital heart disease. BMJ. 2018;360:k478.
25. Lupattelli A, Spigset O, Nordeng H. Adherence to medication for chronic disorders during pregnancy: results from a multinational study. Int J Clin Pharm. 2014;36:145-153.

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