The effect of beta-blockers on foetal birth weight in pregnancies in women with structural heart disease: a prospective cohort study

Johann Baard, Feriel Azibani, Ayesha Osman, Wentzel Dowling, Brian Rayner, Karen Sliwa

Abstract

Objective: To examine whether treatment with beta-blockers (BBs) in pregnant women with structural heart disease (SHD) resulted in a decrease in foetal birth weight (FBW) in a South African cohort.

Methods: This was a prospective cohort study conducted in a tertiary-level hospital in Cape Town from 2010 to 2016. Of the 178 pregnant women with SHD, 24.2% received BBs for a minimum of two weeks. Adverse foetal outcomes and mean FBW were compared between the BB groups and subgroups (congenital, valvular, cardiomyopathy and other). Adverse foetal outcome was defined as: low birth weight (LBW) < 2 500 g, Apgar score < 7, premature birth (< 37 weeks) and small for gestational age (SGA).

Results: BB exposure during pregnancy was found to be associated with a non-significant increased FBW (2 912 vs 2 807 g, p = 0.347). A significant decrease (p = 0.009) was noted in FBW for valvular SHD pregnancies using BBs, while a significant increase (p = 0.049) was observed for the same outcome in the cardiomyopathy subgroup using BBs. A significant increase was observed for SGA (p = 0.010) and LBW (p = 0.003) pregnancies within the valvular subgroup when exposed to BBs.

Conclusion: BB use in pregnant women with SHD in a South African cohort showed no association with a decrease in FBW or an increase in adverse foetal outcomes when compared to non-BB usage.

Keywords: beta-blockers, pregnancy, women, heart disease, foetal outcome

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Increasingly, pregnancies worldwide are complicated in women with pre-existing structural heart disease (SHD). Maternal congenital heart disease (CHD) dominates in high-income countries, while rheumatic valvular disease (RVD) represents the most frequent SHD in pregnancies in low- to medium-income countries. Pregnancies in women with SHD exhibit higher-than-average maternal mortality rates, necessitating increased monitoring and medication use during the antenatal period. The most commonly observed maternal complications during pregnancies affected by SHD are congestive heart failure and arrhythmias.

SHD also increases the rate of adverse foetal outcomes [preterm delivery, intra-uterine growth retardation (IUGR) and low birth weight (LBW)], with the strongest predictor of these outcomes being maternal cyanosis and reduced cardiac output. These adverse events set in motion a cascade of possible foetal neuro- and bronchopulmonary developmental abnormalities, resulting in increased healthcare costs and maladaptive programming in adult life.

Foetal outcomes, in part, are determined by maternal cardiovascular adaptation during pregnancy. Inadequate adaptation due to SHD leads to reduced utero-placental perfusion, resulting in impaired foetal growth and nutrition. This association is complicated by the use of beta-blockers (BBs) in pregnancies with SHD, as these drugs have been previously associated with small-for-gestational-age (SGA) infants and LBW, although some studies show contradictory results. BBs have also been associated with neonatal hypoglycaemia and bradycardia in the third trimester, with no increase in congenital defects shown.
Studies investigating the effect of BBs on SGA and LBW have focused more on hypertensive pregnancies than studies regarding SHD pregnancies. In addition to the effect on the foetus, BBs can also cause maternal bronchoconstriction, fatigue and sleep disturbances, which further signifies the importance of an interdisciplinary decision regarding the use of BBs in pregnancies with SHD. In this prospective study among patients recruited from a tertiary hospital in South Africa, we aimed to investigate the effect of treatment with oral BBs in women with SHD on the foetal birth weight (FBW).

Methods

A prospective cohort study was conducted from 2010 to 2016 at a tertiary multidisciplinary maternal care facility in Cape Town, South Africa. This is an analysis of an ongoing cohort for which data on methodology, overall patient characteristics and diagnosis, as well as six- and 12-month outcome has been published recently.

All patients gave written informed consent. All principles from the Declaration of Helsinki were adhered to. The study was approved by the ethics committee of the University of Cape Town (HEC ref: 173/2010).

Of 178 consecutive pregnant women with SHD, 24.2% received BBs (n = 43) in pregnancy. Data were manually extracted from both cardiology and obstetric clinical records, after screening for eligibility, and captured in a modified database. Data parameters recorded included gestational age, gender, mode of delivery, birth weight and Apgar scores for all patients. Data on type of BB used, treatment dosage, treatment duration in weeks and trimester of BB initiation were additionally recorded for the BB group. The type of BB available and prescribed in South African public service hospitals was recorded. Atenolol and carvedilol are the only BBs approved for provincial service in South Africa.

SHD pregnancies were sub-divided into congenital, valvular, cardiomyopathy and ‘other’ for extended analysis. The subgroup ‘other’ included infiltrative heart disease such as sarcoidosis, ischaemic heart disease and heart disease caused by arrhythmias. Patient exclusion criteria included: (1) essential information regarding birth weight, and gestational age not available, (2) pregnancies not exceeding 24 weeks of gestation, and (3) therapeutic abortions at any gestational period. Adverse foetal outcomes were defined as: perinatal death, LBW defined as birth weight < 2 500 g, Apgar scores < 7 and premature birth (< 37 weeks).

Statistical analysis

The descriptive statistics are stated as frequency, median and interquartile range or mean value and standard deviations where applicable. Comparison of continuous variables between case and control groups was performed using unpaired Student’s t-tests for data normally distributed. Otherwise the Mann–Whitney U-test was used. To compare categorical variables, the chi-squared or two-tailed Fisher’s exact test was used where appropriate; p < 0.05 was considered to be significant at the 95% confidence level.

Finally, we correlated the treatment duration of oral BBs with the relative deviation from expected FBW for the 24 patients for whom data were available. Data analysis was performed using SPSS 24 for Windows. Figures were created with GraphPad Prism 7 for Windows, Version 7.03.

Results

Baseline characteristics of all pregnancies are shown in Table 1. Pregnant women exposed to BBs were older than those who were not. No significant differences were noted between the groups for clinical and echocardiographic parameters. When dividing pregnancies into those with New York Heart

<table>
<thead>
<tr>
<th>Table 1. Baseline maternal characteristics of study population (n = 178)</th>
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<tbody>
<tr>
<td><strong>Clinical characteristic</strong></td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Parity, n (range)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
</tr>
<tr>
<td>I/II</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
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<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
</tr>
<tr>
<td>LVESD (mm)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
</tr>
<tr>
<td>General medical history (%)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Family history of CVD</td>
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<tr>
<td>Caesarean section, n (%)</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless otherwise specified. p-values based on unpaired t-tests, Mann–Whitney U-tests or chi-squared tests where appropriate.

Fig. 1. Distribution of BB groups among the SHD subgroups.
Association (NYHA) I–II and III–IV physical limitation, a significant increase \( (p = 0.001) \) was noted between the number of pregnancies exposed to BBs compared to those not exposed.

Of the 178 patients analysed in this study, 64 (36\%) presented with CHD, indicating predominance within this subgroup compared to valvular heart disease (33.1\%), cardiomyopathy (20.2\%) and ‘other’ (10.7\%) (Fig. 1). Dividing BB use among the four subgroups revealed higher BB usage within the valvular (32.6\%) and cardiomyopathy (41.9\%) subgroups.

BB exposure during pregnancy was found to be associated with a non-significant increased mean FBW (2 912 vs 2 807 g, \( p = 0.347 \)) and a similar mean gestational age of delivery (GAD) (37.4 vs 37.5 weeks, \( p = 0.841 \)) (Fig. 2A, B). The outcomes of mean GAD in weeks and mean FBW among the four subgroups are shown in Table 2. The highest mean GAD and FBW were found in the valvular (37.7 weeks) and cardiomyopathy (2 999 g) subgroups, respectively. Lowest mean FBW was in the ‘other’ group and lowest mean GAD occurred in the cardiomyopathy group. When comparing the different types of BBs used (atenolol versus carvedilol) with regard to the outcomes of mean GAD and FBW, we found a non-significant increase (2 728 vs 3 138 g, \( p = 0.094 \)) in FBW of 410 g and a similar GAD (37.5 vs 37.3 weeks, \( p = 0.51 \)) associated with the use of carvedilol (Fig. 3).

Data on BB treatment duration and dosage were available for all the treated patients. The median (range) dose used was 12.5 mg (6.25–50) for carvedilol and 50 mg (25–100) for atenolol. The median treatment duration was 98 days with a range of seven to 273 days. No difference in treatment duration was observed between carvedilol [122.5 days (7–273)] and atenolol [63 days (7–273)] \( (p = 0.97) \). The chi-squared test related to any effects on foetal outcome was not significant \( (p = 0.3796) \).

Apart from a significant decrease \( (p = 0.009) \) in FBW for valvular SHD pregnancies and an opposing significant increase \( (p = 0.049) \) in FBW in the cardiomyopathy subgroup when exposed to BBs, no differences were noted for FBW and GAD between the unexposed and BB-exposed groups in the remaining subgroups.

No significant differences were noted for any adverse foetal outcomes between the SHD pregnancies exposed to BB and those who were not exposed. Apgar scores < 7 occurred in 23 (17\%) pregnancies not exposed to BB compared to four (9\%) in the BB group \( (p = 0.33) \). Preterm births were noted in 32 (24\%) pregnancies not exposed to BBs, compared to 11 (26\%) pregnancies in the BB group \( (p = 0.80) \). LBWs were noted in 28 (21\%) pregnancies not exposed to BB, compared to nine (21\%) in the BB group \( (p = 0.87) \). SGA was documented in 41 (30\%) and 12 (28\%) pregnancies of the non-exposed and BB-exposed groups, respectively \( (p = 0.82) \). No significant foetal bradycardia was documented in the hospital records.

When comparing all adverse foetal outcomes between the BB groups for each SHD subgroup separately, we again found no significant differences except for SGA \( (p = 0.010) \) and LBW \( (p = 0.003) \) pregnancies within the valvular subgroup when exposed to BB (Table 2).

Severity of maternal SHD at presentation, together with HIV infection, can directly influence foetal outcome independent of BB treatment. We therefore compared women with severe cardiac conditions (NYHA III or IV at presentation) to women with NYHA I or II, for the occurrence of poor foetal events such as preterm birth (< 37 weeks), LBW and Apgar scores < 7. Results in Table 3 show no differences according to the severity of maternal cardiac condition.

In the same way, HIV impact on gestational period, birth weight and Apgar scores was analysed using contingency analyses (Table 3). Despite a trend towards a lower birth weight and abnormal Apgar scores in HIV-positive compared to HIV-negative women, none of the comparisons was statistically significant.
Correlating the duration of BB treatment with the relative deviation from expected FBW as a percentage, we found a non-significant direct correlation ($r = 0.20; p = 0.360; 95\% CI: 0.247–0.590$) for 24 patients, as seen in Fig. 4.

**Discussion**

This study, the first of its kind conducted within an African population, assessed whether the use of BBs in pregnant women with SHD decreased FBW and increased adverse foetal outcomes. Surprisingly, considering our status as a low- to middle-income country, the largest percentage of SHD pregnancies had CHD (36.0%) compared to RVD, which predominates in other low- to middle-income countries. This can be ascribed to an effective regional referral system, transferring both new and previously operated CHD cases.

Comparing outcomes between subgroups, we found the highest mean FBW (2 999 g) within the cardiomyopathy subgroup, despite registering the lowest gestational age at delivery in weeks (37.2). Matching these same outcomes to all subgroups combined, we established that SHD pregnancies exposed to BBs showed an increase in mean FBW, although this was not significant. Further analysis of foetal outcomes between BB-exposed and non-exposed groups within subgroups revealed significant outcomes for FBW in the cardiomyopathy and valvular subgroups.

BB usage in the valvular subgroup resulted in a significant decrease in FBW due, in part, to the predominant use of atenolol in this subgroup, and that the use of BB generally accompanies advanced cardiac disease. Conversely, BB usage in cardiomyopathy resulted in a non-significant increase in mean FBW, possibly due to the later mean gestational delivery age. A second potential causative factor could be the predominant use of carvedilol in this group.

Most pregnancies within the congenital and valvular subgroups were prescribed atenolol, which has previously been shown to decrease FBW. The largest proportion of BB use occurred within the valvular and cardiomyopathy subgroups with carvedilol predominantly used as a first-line BB. The variation in BB prescribing practice can be attributed to patients having treatment initiated at different sites, which follow different prescribing protocols. Atenolol is the only BB available in most primary healthcare facilities in South Africa and is, therefore, commonly used in patients with valvular heart disease. Conversely, cardiomyopathy patients are usually referred to a tertiary hospital for initiation of treatment where carvedilol is more readily available.

Further dividing the BB-exposed group ($n = 43$) between the different BBs used, we found an increase in mean FBW (2 999 g) within the cardiomyopathy subgroup, despite registering the lowest gestational age at delivery in weeks (37.2). Matching these same outcomes to all subgroups combined, we established that SHD pregnancies exposed to BBs showed an increase in mean FBW, although this was not significant. Further analysis of foetal outcomes between BB-exposed and non-exposed groups within subgroups revealed significant outcomes for FBW in the cardiomyopathy and valvular subgroups.

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**Table 3. Impact of maternal SHD severity and HIV on foetal outcome**

<table>
<thead>
<tr>
<th>Variables</th>
<th>NYHA III (n = 15)</th>
<th>NYHA II/III (n = 21)</th>
<th>HIV negative (n = 38)</th>
<th>HIV positive (n = 38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt; 37 weeks</td>
<td>19 (21)</td>
<td>17 (20)</td>
<td>38 (28)</td>
<td>38 (28)</td>
<td>0.609</td>
</tr>
<tr>
<td>Low birth weight &lt; 2 500 g</td>
<td>13 (13)</td>
<td>14 (14)</td>
<td>38 (28)</td>
<td>38 (28)</td>
<td>0.515</td>
</tr>
<tr>
<td>Apgar score at 1 min &lt; 7</td>
<td>15 (15)</td>
<td>12 (12)</td>
<td>38 (28)</td>
<td>38 (28)</td>
<td>0.217</td>
</tr>
</tbody>
</table>

Values are n (%). p-values based on Fisher’s exact tests. NYHA, New York Heart Association functional class.
causing vasodilation and α-receptor stimulation producing vasoconstriction, which in turn leads to foetal growth retardation. Although classified as a β1-selective blocker, atenolol usage at increased doses causes β2-receptor blockade and therefore vasoconstriction.\textsuperscript{13} Conversely, the vasoconstriction caused by carvedilol's non-selective β-blockade is opposed by its concomitant α-receptor stimulation and therefore reduces the possibility of foetal growth retardation.\textsuperscript{13} Interestingly, based on small reports, both drugs were shown to cross the placental barrier.\textsuperscript{17,20}

Additionally, higher NYHA functional classes, a clinical indicator of moderate/severe cardiac impairment, have been shown to increase adverse foetal outcomes, including SGA.\textsuperscript{21} This association, independent of BB usage, may similarly result from impaired placental perfusion. Atenolol was mostly used in the valvular subgroup while carvedilol was predominately used in the cardiomyopathy subgroup. Although underpowered, our results should encourage re-examination of BB prescribing practices within SHD pregnancies at Groote Schuur Hospital. Predominant use of a BB type within a subgroup prohibited analysis of BB subtype effects within each SHD subgroup.

Adverse foetal outcomes that were compared between the BB-exposed and non-exposed groups included Apgar score, preterm delivery (< 37 weeks), LBW (< 2 500 g) and SGA. SGA was defined as birth weight under 10% of expected weight for that gestational age. Variables such as the presence of IUGR and maternal parameters such as weight gain during pregnancy were not available for all pregnancies. They were therefore not incorporated in deciding whether to classify a delivery as SGA, as this may have affected interpretation of the results, especially when comparing them with other studies.

No significant differences were noted for all adverse foetal outcomes when comparing all SHD pregnancies exposed to BB and those not exposed to BB. Repeating the comparison between the different subgroups, we found a significant increase in SGA (p = 0.01) and LBW (p = 0.003) pregnancies in the BB-exposed group in the valvular subgroup only. As mentioned before, this most likely results from the predominant atenolol use within this subgroup, as well as the principle of confounding by indication. No bradycardia in foetuses or newborns was documented in the hospital records of women who had received BB therapy.

Previous studies have shown a significant inverse correlation between the duration of BB treatment (days) versus the relative deviation from expected FBW. We had detailed information regarding days of treatment with BB for 24 patients within our cohort. For these 24 pregnancies, we found a non-significant direct correlation (r = 0.20), showing that increased duration of treatment in pregnancy did not significantly correlate with an increase or decrease in deviation from expected FBW.

It has been previously described that HIV\textsuperscript{22} or severity of cardiac condition\textsuperscript{21} in pregnant women may influence foetal outcome. Despite some interesting tendencies towards an impact of HIV on LBW or abnormal Apgar scores, non-significant differences were observed in our cohort. It would appear that NYHA was not associated with poor foetal outcome.

Limitations and strengths

Limitations for this study include sample size, particularly in the BB group. Secondly, the principle of confounding by indication complicates interpretation of results, as pregnancies with more severe disease are more likely to receive BBs and thereby increase the probability of an adverse foetal outcome. Multivariate analysis was not performed and hence we could not delineate the contribution of several maternal variables to the outcome of FBW and adverse foetal outcomes. Comparison between studies is also limited due to the variation in inclusion criteria for the different SHD subgroups in different studies. Results concerning BB subtype are mainly applicable in low- to middle-income countries were atenolol is regularly used.

Despite these limitations, this study addresses a clinically relevant topic and the information could be very helpful to obstetricians and cardiology care providers. Indeed, the topic of BB use in pregnancy in these women deserves attention, and prospective data are required in this field. Furthermore, most data about pregnancy in structural heart disease come from high-income countries, while this is a relatively large cohort from an (upper) middle-income country.

Conclusion

Use of BBs in a South African cohort of pregnancies complicated with SHD was found to have no significant effect on the outcomes of mean FBW and adverse foetal outcomes. The use of carvedilol, an α- and β-receptor blocker resulted in a notable although not significant increase in mean FBW, compared to SHD pregnancies using atenolol. The results of this study reiterate the importance of making clinical decisions on an individual patient basis with careful consideration of both type of BB and subgroup of SHD being treated.

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