Original Article

Neonatal effects of intrauterine metoprolol/bisoprolol exposure during the second and third trimester: a cohort study with two comparison groups

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Objectives: Our aim was to evaluate the effects of beta-blockers during the second and third trimester on fetal growth, length of gestation and postnatal symptoms in exposed infants.

Methods: The current prospective observational cohort study compares 294 neonates of hypertensive mothers on metoprolol or bisoprolol during the second and/or third trimester with 225 methyldopa-exposed infants and 588 infants of nonhypertensive mothers. The risks for reduced birth weight, prematurity, neonatal bradycardia, hypoglycaemia and respiratory disorders were analysed.

Results: The rate of small-for-gestational-age children was significantly higher in long-term beta-blocker exposed infants (24.1%) compared with the methyldopa cohort [10.2%, odds ratio $(OR)_{adj}$ 2.5, 95% confidence interval (CI) 1.2–5.2] and the nonhypertensive cohort (9.9%, OR_{adj} 4.3, 95% CI 2.6–7.1). The risk for preterm birth was significantly increased compared with nonhypertensive pregnancies (OR_{adj} 2.2, 95% CI 1.3–3.8) but not compared with the methyldopa cohort. Neonatal adverse outcomes occurred more frequently in the study cohort (11.5%) compared with the nonhypertensive comparison group (6.5%) and the methyldopa cohort (8.4%), but without statistical significance (OR_{adj} 1.5, 95% CI 0.7–3.0 and OR_{adj} 1.5, 95% CI 0.7–3.3, respectively).

Conclusion: Long-term intrauterine exposure to metoprolol or bisoprolol may increase the risk of being born small-for-gestational-age. It is still a matter of debate to which extent maternal hypertension contributes to the lower birth weight. Serious neonatal symptoms are rare. Altogether, metoprolol and bisoprolol are well tolerated treatment options, but a case-by-case decision on close neonatal monitoring is recommended.

Keywords: 'Bisoprolol'[Mesh], 'Cohort Studies'[Mesh], 'Fetal Growth Retardation'[Mesh], 'Hypertension'[Mesh], 'Metoprolol'[Mesh], 'Pregnancy Outcome'[Mesh]

Abbreviations: CI, confidence interval; DDD, defined daily dose; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HCP, healthcare professional; IQR, interquartile range; OR, odds ratio; SDS, SD score; SGA, small-for-gestational-age

INTRODUCTION

The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) have recently published guidelines for the management of arterial hypertension (AH) including hypertensive disorders in pregnancy [1,2]. They recommend methyldopa, labetalol and calcium-channel blockers as the drugs of choice for the treatment of hypertension in pregnancy. Due to evidenced fetotoxicity, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are contraindicated, particularly in the second half of pregnancy. Although recommended as antihypertensives during pregnancy, the ESC and the ESH point out that beta-blockers may induce fetal bradycardia, intrauterine growth retardation and hypoglycaemia in the neonate.

Results from a large nationwide prescription study on beta-blocker exposure at the time of delivery suggested that neonates are not only at increased risk for bradycardia but also for hypoglycaemia [3]. Exposure to beta-blockers during pregnancy may further be associated with fetal growth restriction and low birth weight, even if compared with methyldopa [4]. However, other studies discuss maternal hypertension as major risk factor for fetal growth restriction independent of maternal antihypertensive therapy [5–7].

Labetalol is not licensed in Germany, instead metoprolol and bisoprolol are the most frequently prescribed beta-blockers [8,9]. Due to the scarcity of published experience particularly with bisoprolol we wanted to evaluate the

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magnitude of beta-blocker-specific adverse effects in an observational prospective cohort study.

The primary objective is to compare frequencies of neonatal bradycardia, hypoglycaemia and respiratory disorders as well as birth weights and occurrence of preterm delivery in second and/or third trimester exposed infants of mothers with chronic or gestational hypertension, who did not exhibit preeclampsia. The clinical implications of these potential effects are quite different: neonatal adverse symptoms are transient and might lead to the recommendation of closer postnatal surveillance, whereas small-for-gestational-age (SGA) infants are at increased risk for developmental delay and chronic diseases in later life [10].

METHODS

Data collection

The German Embryotox Pharmacovigilance Centre in Berlin is a well established publicly funded nonprofit institution that offers risk assessment on drug use in pregnancy to healthcare professionals (HCPs) and pregnant women [11]. Out of approximately 14 000 annual requests, more than 4000 exposed pregnancies per year are documented as to their outcome. In addition, Embryotox serves as a national clearinghouse for suspected adverse drug reactions in pregnancy and receives case reports for evaluation from HCPs, patients, pharmaceutical industry and the Drug commission of the German Medical Association.

Using a structured questionnaire at the first contact, all relevant data with respect to medication (including duration, time, dosage), exposure to other agents, maternal characteristics and comorbidities are documented. In the majority of cases outcome of pregnancy is prospectively ascertained, which means that neither pregnancy outcome nor prenatal abnormalities are known at the time our institute is contacted. Approximately 8 weeks after the expected date of delivery, follow-up data are obtained with a second questionnaire. Follow-up includes data on maternal complications during pregnancy and delivery, gestational age at birth, sex, birth weight, length, head circumference, umbilical cord artery pH, Apgar score and, if applicable, details of congenital anomalies and postnatal disorders. If necessary, hospital discharge letters and additional medical reports are requested.

This standardized procedure results in a high response rate of nearly 75% of initiated follow-ups. The way of data collection and analysis of our centre is similar to that of other European and International Teratology Information Services. In this way, postmarketing surveillance and pharmacoepidemiological studies on drug use during pregnancy are made possible [12].

Study design (inclusion and exclusion criteria) and definitions

The current prospective observational cohort study consists of a beta-blocker exposed cohort, a hypertensive reference cohort and a nonhypertensive comparison cohort. Only those pregnancies were considered that lasted longer than $24+0$ gestational weeks. All cases were enrolled between 1 January 2001 and 31 December 2015. The study cohort consisted of hypertensive women treated with metoprolol and/or bisoprolol after the first trimester, but not with methyldopa at any time during pregnancy. The hypertensive reference group was composed of pregnant women on methyldopa after the first trimester, but not on beta-blockers at any time during pregnancy. Pregnant women without hypertension and without any antihypertensive therapy at any time during pregnancy represented the nonhypertensive comparison cohort, which was matched by year of ascertainment using a ratio 1 : 2. Metoprolol/bisoprolol or methyldopa exposure may have started before the second trimester. Only cases receiving the study drug for AH were included. The following exclusion criteria were applied to all three groups: maternal concomitant medications considered as potent teratogens or fetotoxins (acenocoumarol, carbamazepine, lenalidomide, methotrexate, mycophenolate, phenobarbital, phenprocoumon, phenytoin, retinoids (acitretin, adapalen, isotretinoin, tazaroten, tretinoin), thalidomide, topiramate, valproic acid, warfarin, angiotensin-converting-enzyme inhibitors and angiotensin II receptor antagonists), women with acute malignancies, preeclampsia or HELLP-syndrome.

Weeks of gestation were calculated either based on ultrasound measurements during the first trimester or, if not available, using the first day of last menstrual period. The start of the second trimester was set at gestational week $13+0$. In cases of a multiple pregnancy, all neonates were considered separately and in cases of early fetal death, the surviving fetus was considered as a singleton.

According to international standards, SGA was defined as a birth weight below the 10th percentile for gestational age and sex [13]. For comparing frequencies of SGA infants by cohort, exposure had to comprise at least 2 months (>60 days) after the first trimester. For evaluating postnatal adverse symptoms, the therapy should have lasted at least until 24 h before delivery.

Preterm delivery was defined as delivery before 37 completed gestational weeks ($<37+0$ weeks). Stillbirth was defined as death of a fetus of at least 500 g weight or that occurred after 24 completed gestational weeks ($\geq 24+0$) in cases where fetal weight was not available.

A neonate was considered hypoglycaemic, if blood glucose levels were less than 35 mg/dl at the first day of life or less than 45 mg/dl after the first day of life [14,15]. The diagnosis of bradycardia and postnatal respiratory disorder was retrieved from medical reports.

Statistical analysis

Logistic regression was used to evaluate the risk of the primary endpoints, that is SGA and a composite endpoint for the presence of one of the three neonatal complications bradycardia, hypoglycaemia or respiratory problems. Logistic regression was applied to assess the effect of prematurity on pregnancy outcome.

In addition, birth weight and head circumference were evaluated as continuous variables. For the comparison between cohorts, birth weight was adjusted to gestational age at birth and infant's sex and classified according to percentile values derived from the German perinatal survey [13]. A score was determined through standardization [SD score (SDS)] and included in a linear model as dependent variable. Head circumference was evaluated correspondingly.

All analyses involved propensity score adjustment for bias reduction, classifying pregnant women into five strata defined by the quintiles of the propensity score [16]. The propensity score was estimated using boosted regression trees based on maternal age, BMI, alcohol consumption, smoking habits and number of previous deliveries as covariates [17]. Missing data in the covariates were estimated by multiple imputation using chained equations, assuming that the data were missing at random [18]. Twenty imputed data sets were generated per outcome, including the respective outcomes and the covariates used for propensity score estimation. For each imputed data set, analyses were performed as described above. Results were then combined using Rubin's rule [19]. To avoid suppression of potential signals, no adjustment for multiple testing was performed. All analyses were performed with R version 3.3 (R Development Core Team, Vienna, Austria).

To compare dosages of the three substances, median doses per substance were contrasted with the defined daily dose (DDD) [20]. A value of 1 means that the median dose of our sample corresponds to the DDD.

The methodology and the recommendations of the Strengthening the Reporting of Observational Cohort Studies in Epidemiology (STROBE) statement were adapted to the needs of pregnancy outcome studies [21,22].

Retrospective reports

Retrospectively collected adverse drug reports after maternal therapy with metoprolol or bisoprolol after the first trimester were evaluated separately to look for specific pattern of neonatal adverse effects.

Ethics approval was obtained from the ethics committee of the Charité Universitätsmedizin Berlin, Germany (EA4/065/17). The study was registered in the German Clinical Trials Register (DRKS00012418).

RESULTS

During the study period between 2001 and 2015, the German Embryotox Pharmacovigilance Centre received 4295 requests on metoprolol or bisoprolol medication. After excluding requests concerning paternal exposure, lactation, planning pregnancy or duplicate requests, 1134 prospectively reported pregnancies with completed follow-up were identified. According to the study protocol, 291 pregnancy courses (including six pairs of twins) with 297 fetuses fulfilled the inclusion criteria (refer to Fig. S1, Supplemental Digital Content 1, http://links.lww.com/HJH/B149, which shows the flowchart of prospective requests). Accordingly, 221 pregnancies were identified for the methyldopa reference group and 580 pregnancies constituted the nonhypertensive comparison cohort including four and 10 pairs of twins, respectively. Three pregnancies of the beta-blocker cohort resulted in stillbirths, none of the methyldopa cohort and two of the comparison cohort (Table 1).

TABLE 1. Pregnancy outcome by cohort

	Beta-blocker	Methyldopa	Comparison
Pregnancies, *n*	291	221	580
Stillbirth, *n* (%)	3 (1)	–	2 (0.3)
Live birth, *n* (%)	288 (99)	221 (100)	578 (99.7)
Twin-pregnancies, *n*	6	4	10
Live born infants, *n*	**294**	**225**	**588**

Bold indicates data for sum of live-born infants.

Maternal characteristics

Maternal characteristics by cohort are shown in Table 2. The median maternal BMI was 27 kg/m^2 in both hypertensive groups, but only 23 kg/m^2 in the nonhypertensive comparison group. Women of the nonhypertensive comparison group were less often affected by gestational diabetes. Methyldopa exposed women contacted our institute later during the 1st trimester than women of the other two groups. Although chronic hypertension predominated in both hypertensive cohorts, 28.1% of patients in the methyldopa reference group and 5.8% in the beta-blocker group received the antihypertensive medication for pregnancy-induced hypertension. There were no differences between the cohorts in smoking or alcohol habits, educational level and attitude towards pregnancy. Mothers of the methyldopa reference group were more often cotreated for other chronic diseases, especially for bronchial asthma (20 vs. 9 women), in comparison with mothers of the beta-blocker cohort (data not shown). The analysis of comorbidities and corresponding pharmacotherapy showed no relevant differences in both hypertensive cohorts. The most frequent comorbidities were psychiatric and autoimmune diseases.

The median DDD quotient in the beta-blocker exposed as well as in the methyldopa exposed cohort was 0.5. 20 mothers of the beta-blocker cohort were initially treated with other beta-blockers (atenolol $n = 8$, carvedilol $n = 4$, nebivolol $n = 4$, penbutolol $n = 1$, pindolol $n = 1$, propranolol $n = 2$) before being switched to metoprolol/ bisoprolol.

Analysis of the exposure time in both hypertensive cohorts revealed that 85.6% of the women on beta-blockers were treated from the beginning of pregnancy whereas only 36.4% of the methyldopa treated were. Median duration of treatment with beta-blockers was 38.3 weeks [interquartile range (IQR) 34, 39.9] and 25.6 weeks in methyldopa treated (IQR: 6.0, 37.4) women.

Neonatal outcome and characteristics

For neonatal outcome, see Table 3. The median birth weight of the beta-blocker exposed infants was in normal range, but lower than in both other groups.

To focus explicitly on long-term exposure effects on birth weight, comparison was limited to infants prenatally exposed for more than 60 days (Table 4). Median maternal treatment duration in these subgroups was 38.6 weeks (IQR: 36.3, 40) for the 274 beta-blocker exposed and 34.2 weeks (IQR: 23.9, 38.7) for the 147 methyldopa exposed. Of note, 24.1% of these long-term beta-blocker exposed infants were born SGA, but only 10.2% of the methyldopa exposed infants [odds ratio $(OR)_{adj.}$ 2.5, 95% confidence interval (CI) 1.2–5.2] and 9.9% of the nonhypertensive cohort (OR_{adj} 4.3, 95% CI 2.6–7.1). The propensity score adjusted SDS for birth weights of the beta-blocker exposed infants ($n = 274$) compared with the methyldopa infants ($n = 147$) was significant (SDS difference −0.4, 95%

TABLE 2. Maternal characteristics by cohort

	Beta-blocker	Methyldopa	Comparison
N	291	221	580
Age, *n*	291	221	577
Age (years)	33 (29–36) (17–49)	33 (29–36) (20–49)	32 (28–35) (14–46)
BMI, *n*	244	204	451
BMI (kg/m^2)	27.3 (22.7–33.5) (17.4–50.7)	27.4 (23.5–34.5) (17.7–51.9)	22.6 (20.6–25.8) (14.8–59.1)
Drug treatment indication, *n*	291	221	N/A
Chronic hypertension, *n* (%)	274 (94.2)	159 (71.9)	N/A
Pregnancy-induced hypertension, *n* (%)	17 (5.8)	62 (28.1)	N/A
Dose, *n*	M 198/ B 79	189	N/A
Daily dose (mg)	M 50 (47.5–100)	500 (250–750)	N/A
	(12–400)	(125–2000)	
	B 5 (2.5–5) (1.25–10)		
Gestational diabetes, *n*	176	180	317
Gestational diabetes, *n* (%)	42 (23.9)	31 (17.2)	35 (11.0)
Smoking, *n*	290	221	574
No, *n* (%)	248 (85.5)	197 (89.1)	491 (85.5)
≤5 cig/day	10 (3.4)	7 (3.2)	20 (3.5)
>5 cig/day	32 (11)	17 (7.7)	63 (11)
Alcohol, *n*	289	220	573
No, *n* (%)	275 (95.2)	211 (95.9)	538 (93.9)
≤1 drink/day	7 (2.4)	4 (1.8)	24 (4.2)
>1 drink/day	7 (2.4)	5 (2.3)	11 (1.9)
Pregnancy wanted, *n*	239	176	485
Yes, *n* (%)	230 (96.2)	168 (95.5)	450 (92.8)
Indifferent, *n* (%)	6 (2.5)	8 (4.5)	20 (4.1)
No, *n* (%)	3 (1.3)	0 (0)	15 (3.1)
Previous deliveries, *n*	291	219	574
0, *n* (%)	141 (48.5)	128 (58.4)	310 (54)
1, *n* (%)	108 (37.1)	63 (28.8)	185 (32.2)
2, *n* (%)	27 (9.3)	15 (6.8)	67 (11.7)
3 or more, *n* (%)	15 (5.2)	13 (5.9)	12 (2.1)
Gestational week at first TIS contact, *n*	291	221	580
Week at first TIS contact	9.7 (6.5–16.4) (3–40.6)	11.6 (7.1–21.4) (4–39.1)	9 (6.1–15.4) (3.6–40)

For age, BMI, dose and week at first TIS contact, median, interquartile range and min/max are presented. B, bisoprolol; M, metoprolol; N/A, not available; TIS, teratology information service.

CI −0.7 to −0.2). Limited to singleton pregnancies results were similar (data not shown). Figure 1 illustrates infants' birth weight by cohorts according to percentile categories and sex.

The rate of preterm infants was higher in both hypertensive groups (15.3 and 16.0%) compared with the nonhypertensive comparison cohort (9.5%) (Table 3). The difference between beta-blocker exposed pregnancies and nonhypertensive pregnancies was statistically significant (OR_{adj} 2.2, 95% CI 1.3–3.8). This was not the case in comparing beta-blocker exposed to methyldopa exposed pregnancies (OR_{adj} 1.2, 95% CI 0.7–2.3).

TABLE 3. Neonatal characteristics of live born infants by cohort

	Beta-blocker	Methyldopa	Comparison
N	294	225	588
Gestational week, *n*	294	225	588
Gestational week at birth	39 (38–40) (27.6–42)	38.7 (37.7–40) (28–42)	39.3 (38–40.4) (25.3–42)
Preterm Birth, *n*	294	225	588
Preterm, *n* (%)	45 (15.3)	36 (16)	56 (9.5)
Term, *n* (%)	249 (84.7)	189 (84)	532 (90.5)
Child's sex, *n*	294	225	588
Female, *n* (%)	141 (48)	104 (46.2)	279 (47.4)
Male, *n* (%)	153 (52)	121 (53.8)	309 (52.6)
Weight, *n*	294	223	587
Child weight (g)	3100 (2700–3460) (730–4550)	3260 (2890–3600) (840–4640)	3330 (3000–3680) (820–5250)
Length, *n*	290	220	583
Child length (cm)	50 (48–52) (30–57)	51 (49–52) (30.5–59)	51 (49–53) (31–60)
Head circumference, *n*	275	216	532
Head circumference (cm)	34 (33–35) (21.8–40)	34.5 (33.5–35.6) (23.5–38)	35 (34–36) (23–39)

For gestational week at birth, weight and length of the baby, median, interquartile range and min/max are presented.

TABLE 4. Comparison of birth weights of infants with at least 60 days beta-blocker or methyldopa exposure

	Beta-blocker, $n = 274$[a]	Methyldopa, $n = 147$[a]	OR (95% CI)	OR adjusted (95% CI)
SGA, *n* (%)	66 (24.1)	15 (10.2)	2.8 (1.5–5.1)	2.5 (1.2–5.2)
	Beta-blocker, $n = 274$[a]	**Comparison, $n = 587$[a]**	**OR (95% CI)**	**OR adjusted (95% CI)**
SGA, *n* (%)	66 (24.1)	58 (9.9)	2.9 (2.0–4.3)	4.3 (2.6–7.1)

CI, confidence interval; OR, odds ratio; SGA, small-for-gestational-age.
[a]Live born infants with complete data (birth weight, sex, gestational age at birth).

Frequencies of neonatal adverse effects in at least until 24 h before delivery-exposed infants are presented in Table 5. Hypoglycaemia occurred more often in beta-blocker exposed infants (2.8%) compared with methyldopa exposed (1.5%), but was not significantly different from the nonhypertensive comparison cohort (2.2%). Bradycardia was least present in the nonhypertensive cohort (0.8%) in contrast to 2.0% of beta-blocker exposed and 2.5% of methyldopa exposed infants. Results for respiratory symptoms showed a similar tendency with 8.7% in beta-blocker exposed, 8.0% in methyldopa exposed and 5.4% in the nonhypertensive cohort. However, none of these differences reached statistical significance.

Retrospectively reported cases

Twenty-six retrospectively reported cases on beta-blockers were recorded following the same study criteria as the prospectively ascertained cases. Among these, two stillbirths and one sudden infant death (5-h postpartum), as well as five SGA newborns were reported. None of the five infants with transient neonatal adverse symptoms (four with respiratory disorders, one of these also with bradycardia, and one with hypoglycaemia) exhibited symptoms of longer duration or severity. In two of these cases, symptoms were possibly attributable to psychiatric comedication.

DISCUSSION

Birth weight

The prospective observational cohort study reports the outcome of 294 live-born infants exposed to metoprolol/bisoprolol after the first trimester. The median birth weight in beta-blocker exposed infants was lower than in methyldopa exposed and unexposed infants. In restricting the analysis to pregnancies with long-term antihypertensive exposure (>2 months), we found a significantly increased rate of SGA (24.1 vs. 10.2 vs. 9.9%). Figure 1 illustrates that boys and girls of the beta-blocker exposed cohort were overrepresented in the lower percentile sector, and mostly underrepresented in the ranges from 50% and higher.

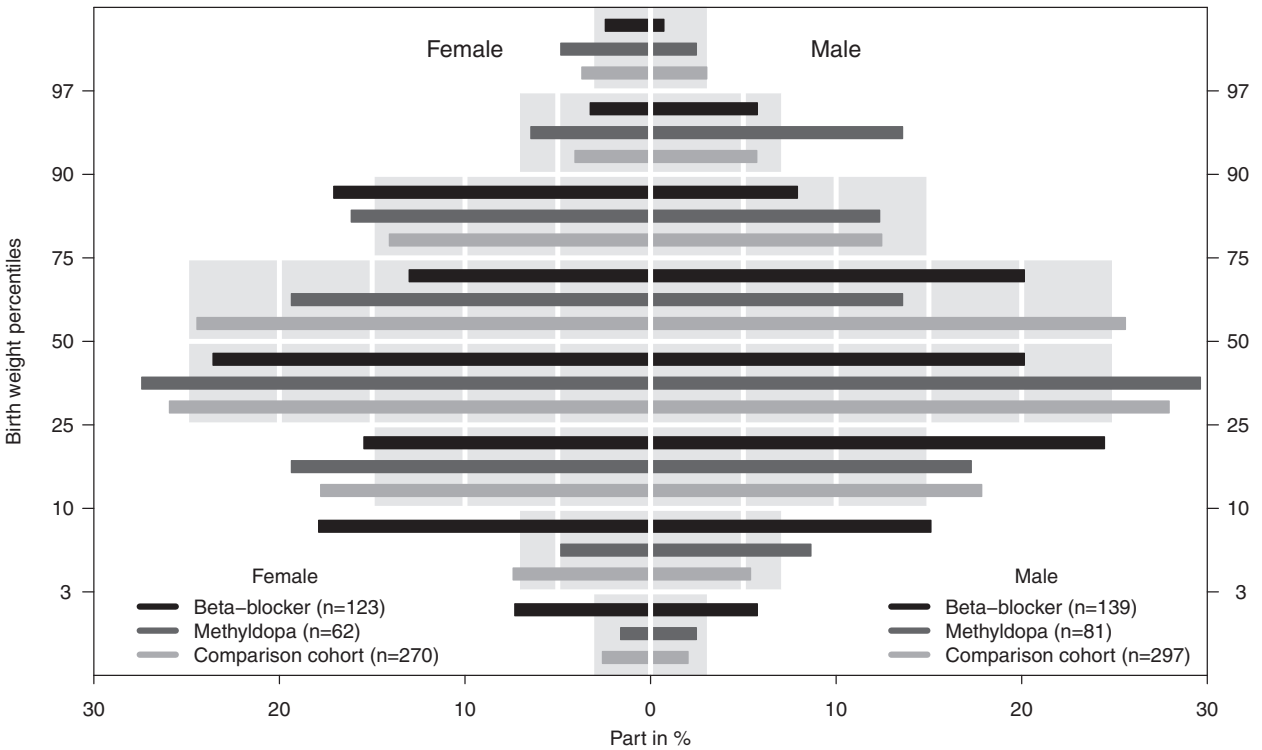

FIGURE 1 Birth weight according to percentile categories and sex by cohort. Coloured bars give the proportions of infants with at least 60 days beta-blocker or methyldopa exposure and nonexposed children (excluding multiples) according to percentile categories. Grey bars represent the proportion of newborns of the German perinatal survey.

TABLE 5. Postnatal symptoms of infants with beta-blocker or methyldopa exposure at least 24 h before delivery

	Beta-blocker, $n = 252$[a]	Methyldopa, $n = 199$[a]	OR (95% CI)	OR adjusted (95% CI)
Bradycardia, *n* (%)	5 (2.0)	5 (2.5)	0.8 (0.2–2.8)	0.9 (0.2–3.4)
Hypoglycaemia, *n* (%)	7 (2.8)	3 (1.5)	1.9 (0.5–7.3)	1.8 (0.4–7.1)
Respiratory, *n* (%)	22 (8.7)	16 (8.0)	1.1 (0.6–2.1)	1.1 (0.5–2.9)
Any of these, *n* (%)	29 (11.5)	19 (8.4)	1.2 (0.7–2.3)	1.5 (0.7–3.3)
	Beta-blocker, $n = 252$[a]	**Comparison, $n = 588$[a]**	**OR (95% CI)**	**OR adjusted (95% CI)**
Bradycardia, *n* (%)	5 (2.0)	5 (0.8)	2.4 (0.7–8.2)	1.8 (0.5–7.2)
Hypoglycaemia, *n* (%)	7 (2.8)	13 (2.2)	1.3 (0.5–3.2)	1.0 (0.4–2.8)
Respiratory, *n* (%)	22 (8.7)	32 (5.4)	1.7 (0.9–2.9)	1.5 (0.7–3.3)
Any of these, *n* (%)	29 (11.5)	38 (6.5)	1.5 (0.9–2.6)	1.5 (0.7–3.0)

CI, confidence interval; OR, odds ratio.
[a]Live born infants exposed at least 24 h before delivery

The challenging question is whether this finding is due to mother's medication or her hypertension which might differ between beta-blocker and methyldopa exposed. A total of 85.6% of the beta-blocker women but only 36.4% in the methyldopa group had started their treatment already before conception. Furthermore, 5.8 and 28.1%, respectively, were explicitly treated for pregnancy-induced hypertension. With other words, compared with methyldopa, beta-blocker exposed mothers were more often affected by chronic hypertension with a negative impact on placental function.

To date, there is no evidence that an isolated high maternal BMI increases the risk of SGA in children. A large multicentre study [23] found that high maternal prepregnancy BMI was even associated with a reduced risk of SGA.

Sixty-one of the 66 SGA children in the long-term exposed beta-blocker group had been exposed from the very beginning of pregnancy. Relations were less pronounced among long-term exposed methyldopa pregnancies: nine out of 15 SGA children had already been exposed from preconception. This might point to preexisting hypertension as an important factor for SGA but still does not exclude stronger toxicity of beta-blockers compared with methyldopa. Subgroup analyses of preexistent hypertension and pregnancy-induced hypertension were not reasonable because the resulting subgroups became too small. In the long-term exposed groups, only 2% of the beta-blocker exposed and 9% of the methyldopa exposed were treated due to pregnancy-induced hypertension. We could not compare severity of hypertension between groups, as information on mother's blood pressure (BP) was not available. Drug dosage might be interpreted as a proxy for severity of hypertension. However, in both hypertensive cohorts the median doses were below the DDD [20] which may indicate less severe hypertension, insufficient treatment or a less strict BP control during pregnancy as recommended in guidelines [2].

Several previous studies also found lower birth weights in infants of mothers on beta-blockers. Meidahl Petersen *et al.* [24] compared infants of women with beta-blocker prescriptions before gestational week 20 with the general population and found a significant increase in SGA infants (OR_{adj} 1.97, 95% CI 1.75–2.23). Another retrospective prescription study [4] calculated an increased risk of reduced birth weight for infants prenatally exposed to beta-blockers (OR_{adj} 1.95, 95% CI 1.21–3.15) in contrast to infants exposed to methyldopa only. However, exposure interval during pregnancy is not well defined in this study and likewise, there is no information on maternal BP. In none of these studies, the influence of hypertension and antihypertensive medication could be disentangled.

Severity of maternal hypertension is a well known risk factor for fetal or neonatal complications, such as intrauterine growth restriction or prematurity [25]. This was also shown by Nzelu *et al.* [26], who analysed the rate of SGA infants in four cohorts of mothers with chronic hypertension of different severity. With increasing severity, SGA rates increased from 18.6% (no antihypertensive medication during the first trimester) to 31.8%. Patients developing preeclampsia were not excluded from this study. Thus, the 24% of SGA infants in our beta-blocker cohort are quite comparable considering that patients with preeclampsia were excluded.

Preterm birth

As observed in other studies on chronic hypertension, we also found a higher risk for preterm birth [4,24]. This effect is statistically significant compared with the nonhypertensive comparison cohort (OR_{adj} 2.2, 95% CI 1.3–3.8) but not with methyldopa exposed pregnancies. Again, it cannot be ruled out that the underlying disease is the main risk factor, as mentioned in other studies [27–29]. Meidahl Petersen *et al.* [24] found 42% preterm births in pregnancies exposed to methyldopa and 28% in those exposed to beta-blockers. In contrast to our study, these authors did not exclude pregnancies complicated by preeclampsia.

Postnatal symptoms

Unexpectedly, the risks for hypoglycaemia, bradycardia or respiratory problems were not significantly increased among beta-blocker exposed neonates compared with the methyldopa and the unexposed cohort.

The risk of neonatal hypoglycaemia in our cohort study was 2.8% among beta-blocker exposed neonates (Table 5) in contrast to the unexposed infants (2.2%). Bateman *et al.* [3] found a risk of 4.3% for hypoglycaemia in beta-blocker exposed neonates versus 0.5% in the unexposed. His definition of hypoglycaemia was based on International

Statistical Classification of Diseases and Related Health Problems (ICD) codes during the first month of life (blood sugar concentration ≤45 mg/dl and/or intravenous administration of glucose), whereas our interpretation is based on definitions of the German Neonatal Society (blood sugar concentration <35 mg/dl on the first day of life or <45 mg/dl after the first day of life) [15]. Although neonatologists are well aware about the metabolic risk of maternal beta-blocker therapy, the rate of coded hypoglycaemia in our cohort is still low – even in the light of 24% of patients suffering from gestational diabetes. This underlines the overall low risk after prenatal exposure to beta-blockers.

The risk for bradycardia in our cohort was 2.0% in the exposed versus 0.8% in the unexposed group which corresponds to the results of the Bateman *et al.*'s study [3] with 1.6% in the exposed versus 0.5% in the unexposed cohort. Bradycardia and respiratory symptoms are less well defined than hypoglycaemia. However, since both require attention to decide upon immediate intervention coded diagnoses appear to be a reliable basis to compare cohort-specific risks.

In our study, neonatal head circumferences did not differ between cohorts. This is in contrast to other studies, which observed a smaller head circumference in boys exposed to methyldopa [30,31].

Strength and limitation

Strengths and limitations of observational pregnancy outcome studies have been discussed in detail elsewhere [12,21].

One important limitation of our study is the lack of information on the severity of maternal hypertension. Our reassuring findings regarding the low risk of neonatal adverse effects may not be applicable to higher doses of beta-blockers.

Our study is based on patients who or whose HCP contacted our institute for risk counselling. Therefore, the Embryotox cohort may not be representative of the general pregnant population in Germany. Educational achievement is usually higher in women seeking advice at Embryotox [32]. However, possible selection bias was reduced by using matched comparison cohorts from the same data pool with similar procedures of case ascertainment.

As far as we know, this is the largest prospective cohort study focusing on postnatal outcome after second and/or third trimester exposure to beta-blockers. Most other studies have a retrospective point of view [5,33] or are based on prescription data [3,4,24]. In contrast to studies analysing healthcare databases, Embryotox exposure and outcome data underwent a case-by-case plausibility check followed by callbacks to the attending HCPs if necessary. Follow-up procedures after birth are similar across exposed and comparison cohorts and therefore minimize exposure dependent biases. One further strength of our study is the detailed information on drug doses and treatment duration.

In conclusion, as with other beta-blockers, infants long-term exposed to maternal metoprolol or bisoprolol are at increased risk of being born SGA. It is still a matter of debate to which extent maternal hypertension contributes to the lower birth weight. The risk of neonatal bradycardia, hypoglycaemia and respiratory symptoms seems to be modest compared with nonexposed infants. Overall, antihypertensive therapy with metoprolol and bisoprolol is a well tolerated treatment option during pregnancy. A case-by-case decision on close monitoring of the neonate is recommended.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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