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Beta-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study

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ABSTRACT

Objective: To investigate the association between exposure to beta-blockers during pregnancy and the risk of being born small for gestational age (SGA), preterm birth, and perinatal mortality in a nationwide cohort.

Design: A population-based retrospective cohort study, using the Danish Fertility Database. We identified all pregnant women redeeming a prescription for beta-blockers using the National Prescription Registry. Multivariate logistic regression models were used to assess the association between exposure and our outcomes.

Setting: Register based survey.

Participants: 911685 births between 1995 and 2008 obtained from the Danish Fertility Database.

Outcome measures: Being born SGA was defined as having a birth weight below the tenth percentile for the corresponding gestational week. Preterm birth was defined as birth before the 37th gestational week. Perinatal mortality was defined as either death occurring within the first 28 days of life, or stillbirth. Before 2004, foetal deaths were recorded as stillbirths if they occurred after 28 weeks of gestation, but since then stillbirth is recorded for deaths after 22 gestational weeks.

Results: We identified 2459 pregnancies exposed to beta-blockers. Beta-blocker exposure during pregnancy was found to be associated with increased risk of SGA; adjusted OR=1.97 (95% CI, 1.75–2.23), preterm birth; adjusted OR=2.26 (95% CI, 2.03–2.52) and perinatal mortality; adjusted OR=1.89 (95 % CI, 1.25–2.84). Analyses were adjusted for socio-economic and maternal variables. We found similar risk profiles for pregnancies exposed to labetalol and for pregnancies exposed to other beta-blockers.

Conclusion: We found that exposure to beta-blockers during pregnancy was associated with being born SGA, preterm birth and perinatal mortality. Our findings show that labetalol is not safer than

other beta-blockers during pregnancy, and future treatment of pregnant women with beta-blockers should therefore be based primarily on the individual needs of the mother and not the unborn child.

ARTICLE SUMMARY

Article focus

- There is contradictory evidence concerning the consequences of beta-blocker treatment during pregnancy.
- This survey explores the effects of beta-blocker exposure during pregnancy in a Danish birth cohort comprising all births in Denmark between 1995 and 2008. In addition we compared risks associated with exposure to labetalol with exposure to other beta-blockers.

Key messages

- Redeeming prescriptions of beta-blockers was found to be significantly associated with increased risk of being born SGA, preterm birth, and perinatal mortality.
- We found comparable risk profiles in labetalol-exposed pregnancies and in pregnancies exposed to any other beta-blocker.

Strengths and limitations of this study

- This study is the largest of its kind to date, and covers an entire nation which minimises risk of selection bias.
- Given the study design, we were not able to adjust for treatment indication and severity of maternal disease, nor were we able to rule out confounding by indication, the underlying maternal disease, as a possible explanation for our findings.

INTRODUCTION

Beta-blockers are widely used in the treatment of chronic hypertension,[1-4] migraine,[5] essential tremor[6], and various other conditions. There is contradictory evidence concerning the consequences of beta-blocker treatment during pregnancy. Some studies report an association between beta-blocker treatment and small for gestational age (SGA) newborns, and preterm birth,[4,7-10] while others do not.[2,11] Preterm birth and being born SGA are both associated with increased risk of perinatal mortality.[12,13] We set out to investigate whether the use of beta-blockers during pregnancy was associated with being born SGA, preterm birth and perinatal mortality in a nationwide survey between 1995 and 2008.

METHOD

Study population

We used data obtained from three nationwide registries: the Danish Fertility Database,[14] the Danish National Hospital Register[15], and the National Prescription Register.[16] Data concerning income and educational level were obtained respectively from the Income Statistics Register[17] and the Danish Education register,[18] both of which are provided by Statistics Denmark. In Denmark all citizens are given a unique ten-digit identification number at birth.[19] This number can be used to link information between nationwide registers.

Using the Danish Fertility Database we identified 974 805 births between 1995 and 2008. We removed 52 603 records lacking information on pregnancy duration and 7681 records with coding errors. In addition, we excluded 2836 records with pregnancy-induced hypertension, defined as having redeemed an antihypertensive drug prescription after the twentieth week of gestation, but never before. The final study population thus comprised 911 685 births.

The Danish Fertility Database contains information on maternal age, date of birth, and previous births, as well as on each child's sex, gestational age, weight, and mortality.[14]

Time of conception is based on ultrasound estimates in early pregnancy, or information on last menstrual period.

Information on redeemed prescriptions was retrieved from the National Prescription Register, which holds information on date of redemption, quantity, strength, and form.[16] Drugs are coded in accordance with the Anatomical Therapeutic Chemical (ATC) classification.

The Danish National Hospital Register contains information on diagnoses of somatic admissions and outpatients at all Danish hospitals since 1977[15] in accordance with the Danish revision of the 10th International Classification of Diseases (ICD)-system. Pre-eclampsia and eclampsia were defined as women diagnosed with O13, O14, or O15. Migraine was defined as G43 or G44, essential tremor as G250 and arrhythmias as I47, I48, and I49. Maternal smoking was defined as women diagnosed with UT00, UT20, UT21, UT22, and UT23.

Identification of Exposure

We defined exposure to beta-blockers as the redemption of at least two prescriptions between six months before conception and the twentieth week of gestation. At least one of these prescriptions had to be redeemed between conception and the twentieth week of gestation.

We assessed exposure to beta-blockers by identifying redeemed prescriptions with ATC code C07. Furthermore, we identified the most frequently redeemed beta-blockers in Denmark: labetalol (C07AG01), metoprolol (C07AB02), atenolol (C07AB03), propranolol (C07AA05), pindolol (C07AA03), and sotalol (C07AA07). Fewer than 50 pregnancies were exposed to any of the remaining beta-blockers.

We divided beta-blocker exposure into exposure to labetalol and exposure to other beta-blockers. The latter group was formed because there were few redeemed prescriptions of individual beta-blockers other than labetalol. We compared risks associated with exposure to beta-blockers

with exposure to methyldopa (C02AB01, C02AB02), calcium channel blockers (C08C), and ACE inhibitors (C09A) to assess possible confounding by indication.

Maternal diabetes mellitus was defined as redeeming a prescription for insulin or an insulin analogue (ATC code A10A). Furthermore, we assessed co-medication with statins (ATC code C10) and antiobesity drugs (ATC code A08A). We identified pregnant women redeeming prescriptions with these drugs in order to adjust for diabetes mellitus, obesity, and statin use since these women have different risk profiles for the defined outcomes.

Definition of Outcomes

Being born SGA was defined as having a birth weight below the tenth percentile for the corresponding gestational week. Preterm birth was defined as birth before the 37th gestational week. Perinatal mortality was defined as either death occurring within the first 28 days of life, or stillbirth. Before 2004, foetal deaths were recorded as stillbirths if they occurred after 28 weeks of gestation, but since then stillbirth is recorded for deaths after 22 gestational weeks.[20]

Statistical analyses

Data were managed and analysed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Logistic regression models were developed for dichotomous variables adjusted for maternal age, year of conception, annual household income, parity, and educational level (model 1). Maternal age was divided into five groups: <20, 21-25, 26-30, 31-35, >35 years (no missing values). Annual household income at year of birth was divided into quartiles (1266 missing values). Subjects were divided into quartiles according to the number of previous births, including stillbirths (37 missing values): 0, 1, 2, ≥3 births. Year of conception was ordered into three categories (1994-1998, 1999-2003, and 2004-2008). Educational level was divided into tertiles by highest level of education

achieved at the year of birth. For missing information we used information from the following calendar year (32 745 missing values).

We constructed a separate logistic regression model (model 2) including the socio-economic variables in model 1 and additional confounding variables: smoking status, co-medication (yes/no) with statins, antiobesity drugs, insulin and insulin analogues, and diagnoses of pre-eclampsia/eclampsia. These confounders were included in model 2 due to the high frequency of missing data, because information on smoking and diagnoses of pre-eclampsia/eclampsia were not available for the years 1995 and 2008. Maternal smoking was divided into four categories according to the number of cigarettes smoked daily (0, 1-10, 11-20, >20).

When estimating the risk of perinatal mortality, analyses were further adjusted for previous stillbirths. Odds ratios are presented with 95% confidence intervals (95% CIs). For description of basic characteristics we used frequencies with percentages. We used Chi-square tests to analyse differences in the proportions of the different classes of categorical baseline characteristics. Statistical significance was defined as $p<0.05$. All tests were two-sided.

In addition, we carried out a propensity score-matched regression analysis to consolidate our findings. We calculated a propensity score for the likelihood of redeeming a beta-blocker during pregnancy by multivariate logistic regression conditional on baseline covariates. Using the Greedy matching macro (http://mayoresearch.mayo.edu/mayo/research/biostat/upload/gmatch.sas), we matched each case to four controls on the basis of the propensity score (table 1). We did not match on diagnoses of pre-eclampsia/eclampsia since a large fraction of these cases redeemed beta-blocker prescriptions.

RESULTS

Table 1 presents maternal characteristics in beta-blocker-exposed and unexposed women (number and percentage of pregnancies). We identified 2381 pregnancies exposed to only one beta-blocker, 1452 exposed to labetalol only, and 929 exposed to other beta-blockers. 98 pregnancies were exposed to more than one beta-blocker. We found 515 pregnancies exposed to methyldopa, 86 pregnancies to calcium channel blockers (CCBs), and 48 pregnancies exposed to ACE inhibitors. Women exposed to beta-blockers during pregnancy were older, had higher income, and higher parity than unexposed women. The proportions of women redeeming prescriptions for statins, antiobesity preparations, and insulins were higher among the beta-blocker-exposed group. The proportion of pregnancies complicated by pre-eclampsia was higher among beta-blocker-exposed pregnancies. There was no difference in smoking prevalence between beta-blocker-exposed and unexposed women (table 1).

	Beta-blocker-exposed (n=2459)	Beta-blocker-unexposed (n=909228)	Propensity matched (n=9662)

Table 1. Basic characteristics for pregnancies exposed to beta-blockers, compared with unexposed pregnancies and propensity score-matched pregnancies.

Characteristics	n (%)	n (%)	p-value[a]	n (%)	p-value[a]
Educational level			<0.001		0.991
Low	739 (30.05)	311 600 (35.45)		2965 (30.69)	
Medium	972 (39.53)	285 450 (32.47)		3883 (40.19)	
High	707 (28.75)	279 431 (31.79)		2814 (29.12)	
Annual household income (GBP)			<0.001		0.989
0- 36 770	509 (23.99)	226 228 (24.84)		1924 (19.91)	
36 771 – 52 703	594 (24.16)	227 195 (24.96)		2337 (24.19)	
52 704 – 74 699	662 (26.92)	227 089 (24.94)		2631 (27.23)	
≥ 74 700	693 (28.18)	227 448 (24.98)		2770 (28.67)	
Parity			<0.001		0.998
1	900 (36.60)	394 661 (43.29)		3487 (28.87)	
2	918 (37.33)	338 989 (37.18)		3658 (30.28)	
3	455 (18.50)	129 482 (14.20)		1788 (14.80)	
>3	186 (7.56)	46 057 (5.05)		729 (6.04)	
Age (years)			<0.001		1.000
<20	18 (0.73)	26 321 (2.89)		68 (0.56)	
21-25	174 (7.07)	147 298 (16.16)		699 (5.79)	
26-30	700 (28.47)	350 105 (38.40)		2757 (22.82)	
31-35	930 (37.82)	281 154 (30.84)		3665 (30.34)	
>35	637 (24.90)	104 339 (11.44)		2473 (20.47)	
Daily cigarettes[b]			0.427		0.385
0	1548 (80.29)	572 642 (81.15)		6140 (81.81)	
1-10	251 (13.02)	90 033 (12.76)		913 (12.16)	
11-20	114 (5.19)	36201 (5.13)		394 (5.25)	
>20	15 (0.78)	4849 (0.69)		59 (0.79)	
Statins			<0.001		0.492
Used	5 (0.20)	111 (0.01)		14 (0.14)	
Not used	2454 (99.8)	909 115 (99.99)		9648 (99.86)	
Antiobesity preparations (A10)			0.018		0.251
Used	9 (0.40)	1539 (0.17)		23 (0.24)	
Not used	2450 (99.6)	907 687 (99.83)		9639 (99.76)	
Insulins and analogues			<0.001		0.782
Used	101 (4.11)	4208 (0.46)		412 (4.14)	
Not used	2358 (95.89)	905 018 (99.53)		9250 (95.74)	
Pre-eclampsia (O13-O15)			<0.001		
Yes	99 (4.03)	7806 (0.86)		-	
No	2360 (95.97)	901 420 (99.14)		-	

[a]Chi-square tests were used to assess the overall p value for the group comparison.

[b]Information on smoking was only available for 1996-2007.

Women redeeming labetalol prescriptions were older, had a higher education level, and a higher prevalence of preeclampsia and smoking than women exposed to other beta-blockers (table 2). The proportion of women redeeming prescriptions for insulin was larger among the labetalol-exposed group. There was no difference in income or co-medication with statins and antiobesity preparations between the two groups. Diagnoses of migraine and arrhythmias were more common among women exposed to any other beta-blocker. Women exposed to other beta-blockers had higher parity than those exposed to labetalol.

Table 2. Basic characteristics for pregnancies exposed to labetalol, compared with pregnancies exposed to other beta-blockers.

Characteristics	Labetalol (n=1452) n (%)	Other beta-blockers (n=929) n (%)	p-value[a]
Educational level			<0.001
Low	391 (26.93)	321 (34.55)	
Medium	571 (39.33)	369 (39.72)	
High	462 (31.82)	226 (24.33)	
Annual household income (GBP)			0.138
0 – 36 770	202 (13.91)	289 (31.11)	
36 771 – 52 703	223 (15.36)	357 (38.43)	
52 704 – 74 699	228 (15.70)	413 (44.46)	
≥74 700	275 (19.94)	393 (42.30)	
Parity			0.004
0	512 (35.26)	363 (39.07)	
1	586 (40.36)	308 (33.15)	
2	256 (17.63)	179 (19.27)	
≥3	98 (6.75)	79 (8.50)	
Age (years)			<0.001
<20	7 (0.58)	10 (1.08)	
21-25	69 (4.75)	97 (10.44)	
26-30	406 (27.96)	275 (29.60)	
31-35	586 (40.36)	314 (33.79)	
>35	384 (26.45)	233 (25.08)	
Daily cigarettes[b]			<0.001
0	933 (64.26)	565 (60.82)	
1-10	130 (8.95)	112 (12.06)	
11-20	44 (3.03)	62 (6.67)	

>20	9 (6.19)	6 (0.65)	
Antiobesity drugs			0.052
Yes	5 (0.34)	9 (0.97)	
No	1447 (99.66)	920 (99.03)	
Statins			0.261
Yes	5 (0.34)	1 (0.10)	
No	1447 (99.66)	928 (99.90)	
Insulins and analogues			<0.001
Yes	1369 (5.72)	16 (1.72)	
No	83 (94.28)	913 (92.28)	
Migraine			<0.001
Yes	26 (1.79)	46 (4.95)	
No	1426 (98.21)	883 (95.05)	
Pre-eclampsia			0.001
Yes	1378 (94.90)	908 (97.84)	
No	74 (5.10)	21 (2.26)	
Arrhythmia			<0.001
Yes	23 (1.58)	82 (8.83)	
No	1429 (98.42)	847 (91.17)	
Essential tremor			0.030
Yes	-	3 (0.33)	
No	1452 (100)	926 (99.67)	

[a]Chi square tests were used to assess the overall p value for the group comparison.

[b]Information on smoking was only available for 1996-2007.

Table 3 presents ORs with 95% CIs for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

SGA

We found 93 662 children born SGA in the unexposed population (table 3). There were 446 children born SGA among pregnancies exposed to some kind of beta-blocker. We found a higher proportion of SGA among women exposed to beta-blockers compared with unexposed women.

Women exposed to labetalol or to other beta-blockers had similarly higher odds ratios than unexposed women (table 3).

Preterm birth

We identified 109 163 preterm births in the unexposed population (table 3). There were 697 preterm births among pregnancies exposed to beta-blockers. We found an association between preterm birth and beta-blocker exposure compared with unexposed women. Those exposed to labetalol or to other beta-blockers had similarly higher odds ratios than unexposed women (table 3).

Perinatal mortality

We identified 6048 perinatal deaths in the unexposed population (table 3). There were 44 perinatal deaths among infants exposed to beta-blockers. We found a higher rate of perinatal mortality amongst women exposed to beta-blockers (table 3).

When stratifying for different beta-blockers we found 30 perinatal deaths among labetalol-exposed pregnancies. Labetalol exposure was associated with increased risk of perinatal mortality (table 3).

We identified 13 perinatal deaths among pregnancies exposed to other beta-blockers. Exposure to other beta-blockers was found to be significantly associated with perinatal mortality in the unadjusted model and model 1. However, adjusting our analysis for additional confounding variables (Model 2) rendered the association statistically insignificant (table 3).

Other analyses

We identified 515 pregnancies exposed to methyldopa (table 3). We found 61 children born SGA, 216 preterm births and 4 perinatal deaths among these pregnancies. We found a positive association

between children born SGA and exposure to methyldopa, and between methyldopa exposure and increased risk of preterm birth. Exposure to methyldopa during pregnancy was not significantly associated with perinatal mortality (table 3).

Table 3. ORs with 95% CIs for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

Exposure	N (%)	Crude OR (95% CI)	Adjusted (model 1) OR (95% CI)	Adjusted (model 2) OR (95% CI)
		SGA		
Unexposed (n=909 226)	93 662 (10.30)	Reference	Reference	Reference
All beta-blockers (n=2459)	446 (18.14)	1.93 (1.74-2.14)	1.99 (1.79-2.21)	1.97 (1.75-2.23)
Labetalol only (n=1452)	258 (17.77)	1.88 (1.64-2.15)	1.95 (1.70-2.24)	2.02 (1.72-2.37)
Other beta-blockers (n=929)	179 (19.27)	2.08 (1.76-2.44)	2.11 (1.79-2.49)	2.01 (1.66-2.43)
Methyldopa (n= 515)	61 (11.84)	1.17 (0.89-1.53)	1.32 (1.01-1.73)	1.43 (1.04-1.96)
CCBs (n=86)	21 (24.42)	2.30 (1.42-3.73)	2.24 (1.36-3.67)	1.88 (1.02-3.49)
		Preterm birth		
Unexposed (n=909 226)	109 163 (12.01)	Reference	Reference	Reference
All beta-blockers (n=2459)	697 (28.34)	2.9 (2.66-3.14)	2.71 (2.48-2.97)	2.26 (2.03-2.52)
Labetalol only (n=1452)	473 (32.58)	3.54 (3.17-3.95)	3.33 (2.98-3.72)	2.74 (2.39-3.13)
Other beta-blockers (n=929)	206 (22.17)	2.08 (1.78-2.43)	1.93 (1.65-2.26)	1.69 (1.41-2.03)
Methyldopa (n= 515)	216 (41.94)	5.29 (4.44-6.31)	5.03 (4.21-6.01)	4.21 (3.38-5.23)
CCBs (n=86)	26 (30.23)	2.55 (1.63-3.99)	2.50 (1.60-3.89)	2.15 (1.26-3.67)
		Perinatal mortality		
Unexposed (n=909 226)	6048 (0.67)	Reference	Reference	Reference
All beta-blockers (n=2459)	44 (1.79)	2.72 (2.02-3.67)	2.69 (1.98-3.65)	1.89 (1.25-2.84)
Labetalol only (n=1452)	30 (2.07)	3.15 (2.19-4.52)	3.24 (2.25-4.67)	2.08 (1.26-3.44)
Other beta-blockers (n=929)	13 (1.39)	2.12 (1.22-3.66)	1.92 (1.08-3.40)	1.72 (0.85-3.48)
Methyldopa (n= 515)	4 (0.78)	1.15 (0.43-3.07)	1.16 (0.43-3.12)	0.35 (0.05-2.50)
CCBs (n=86)	1 (1.16)	1.78 (0.25-12.57)	2.00 (0.28-14.83)	3.26 (0.45-23.77)

Analyses are adjusted for maternal age, household income, educational level, parity, birth year and prior stillbirths. [a]Model 2 is furthermore adjusted for smoking and comedication with statins, antiobesity preparations, insulins and diagnoses of pre-eclampsia/eclampsia. The cohort in model 2 comprises all births between 1996 and 2007 (n=778 394).

We found 86 pregnancies exposed to calcium channel blockers (table 3). These included 17 children born SGA, 18 preterm births and 1 perinatal death. We found an association between exposure to calcium channel blockers and children born SGA in all models.

Additionally, we found an association between exposure to calcium channel blockers and increased risk of preterm birth in all models. As with methyldopa, exposure to calcium channel blockers during pregnancy was not found to be associated with perinatal mortality (table 3). Analyses for exposure to ACE inhibitors were not performed since we identified only 48 pregnancies exposed to them.

Post hoc we analysed the effect of exposure to all beta-blockers using a propensity score-matched control group (Table 1) and found similar results to those of the primary analyses: SGA, OR=1.93 (95% CI, 1.71–2.19); preterm birth, OR=2.40 (95% CI, 2.16–2.67); perinatal mortality, OR=3.22 (95% CI, 2.15–4.82).

DISCUSSION

In the present study, which we believe to be the largest of its kind to date, we found an association between redeeming prescriptions of beta-blockers during pregnancy and being born SGA, preterm birth, and perinatal mortality. In addition, we found an association between redeeming prescriptions of methyldopa and calcium channel blockers, being born SGA, and preterm birth. Methyldopa and calcium channel blockers were not found to be associated with perinatal mortality.

We found exposure to any beta-blocker to be associated with being born SGA. Our results are in accordance with a recent study reporting increased risk of being born SGA among pregnancies exposed to selective beta-blockers (OR=6.00; 95% CI, 1.06–33.87) and labetalol (OR=2.26; 95% CI, 1.04–4.88).[9] Labetalol is generally considered safe for use during pregnancy.[1,8,21]

Exposure to beta-blockers was found to be associated with preterm birth. When stratifying for different beta-blockers we found an increased risk of preterm birth after exposure to labetalol, and all other beta-blockers, respectively.

We found an association between exposure to beta-blockers and perinatal mortality. When stratifying for different beta-blockers we found this association to be statistically significant for exposure to labetalol and other beta-blockers**.** When adjusting our analysis for maternal co-morbidity, co-medication, and smoking, only labetalol was found to be associated with perinatal mortality.

Methyldopa is mainly used to treat chronic hypertension during pregnancy as first-line therapy.[1] Previous studies did not find any associations between methyldopa exposure and being born SGA or preterm birth.[1,3] Methyldopa has not been found to have effects on placental haemodynamics.[1] However, a recent case-control study reported an increased risk of being born SGA among pregnancies exposed to centrally acting adrenergic agents during the second and third trimesters[9]: OR=1.70 (95% CI, 1.00–2.89). We found that methyldopa exposure was associated with being born SGA and preterm birth. This could be due to indicative antihypertensive treatment with methyldopa in pregnant women with diabetes or pregnancy related diabetes. The prevalence of diabetes among methyldopa-exposed pregnancies was found to be higher: 11.1% compared with 3.9% among beta-blocker-exposed pregnancies. Increased risk of preterm birth was still seen after adjusting our analyses for additional confounding variables in model 2. We found no association between exposure to methyldopa and perinatal mortality. These findings are consistent with those of a previous study.[3]

Calcium channel blockers are considered to be safe during pregnancy.[3,22] We found that exposure to calcium channel blockers was associated with being born SGA and with preterm birth. The risk of being born SGA and preterm of birth remained after adjusting our analyses for

additional confounding variables in model 2. We found no statistically significant association between calcium channel blocker exposure during pregnancy and perinatal mortality.

We chose to analyse two outcomes previously reported to be associated with beta-blocker exposure during pregnancy —SGA and preterm birth[1,10,23] — that have been associated with increased perinatal mortality in previous studies.[12,13] Therefore we investigated the risk of perinatal mortality among beta-blocker-exposed pregnancies. We compared risks associated with exposure to beta-blockers with exposure to methyldopa and calcium channel blockers to assess possible confounding by indication. Our analyses show a similar risk of being born SGA and an increased risk of preterm birth for all recommended agents during pregnancy. There are various possible explanations for this finding. It is possible that the underlying indication for treatment, maternal disease, is the true risk factor. Possible maternal diseases include hypertension, either predating or complicating pregnancy. Accordingly, we were not able to rule out a potential effect of maternal disease on perinatal outcomes.

We found an association between exposure to beta-blockers during pregnancy and perinatal mortality. This association was not found for exposure to methyldopa and calcium channel blockers, which might be due to the small number of cases.

We believe that the similar risks found for exposure to the various beta-blockers and SGA, preterm birth, and perinatal mortality are a class effect. This seems to be true in spite of statistically significant differences in the basic characteristics of women exposed to labetalol and those exposed to other beta-blockers (table 2). After adjustments were made for these variables, we found comparable risk profiles for labetalol-exposed pregnancies and pregnancies exposed to other beta-blockers. Most beta-blockers are known to cross the placenta,[21,24] and effects on placental haemodynamics have been observed in both human and animal studies. A mechanism has been proposed of diminished placental blood flow due to the selective vasoconstriction of placental

vessels by beta-blockers without intrinsic sympathomimetic activity.[24] This effect on placental haemodynamics could explain growth retardation of foetuses exposed to beta-blockers during pregnancy and might result in children being born SGA and preterm.

We defined exposure as redemption of at least two prescriptions between six months before conception and the twentieth week of gestation. At least one of these prescriptions had to be redeemed between conception and twentieth week of gestation. We believe that this model increases the probability of identifying continuous use that extends into pregnancy.

The rate of perinatal mortality in Denmark is low (table 3).[25] A large number of women exposed to beta-blockers, methyldopa, and calcium channel blockers are therefore needed to identify a possible risk increase associated with these outcomes. Our cohort comprises all births in Denmark between 1995 and 2008. This minimises confounding due to race, educational level, and other socio-economic factors. The national Danish registers cover the entire nation and are considered valid. As part of the national health care reimbursement scheme, Danish pharmacies are required by law to register all redeemed prescriptions. Approximately 97.5% of all redeemed prescriptions are registered in the Danish Prescription register.[16] Our study includes data on exposure to beta-blockers based on information on prescriptions paid for at the pharmacy, and not only prescribed by the physician, thereby increasing the probability of exposure. Furthermore, our study was not confounded by recall bias since information was recorded prospectively. The Danish Fertility Database contains more than 99% of all births during the study period.[14]

Limitations of our study include missing information on maternal weight and alcohol consumption. We were unable to adjust for treatment indication and severity of maternal disease. Given the study design, we were not able to address this issue further, nor were we able to rule out confounding by indication, the underlying maternal disease, as a possible explanation for our findings.

We estimated exposure from National Prescription Registry data, which contains information on all redeemed prescriptions.[16] Overestimation of exposure is therefore a possibility, since we cannot adjust for a potential lack of compliance. However, in a study by Olesen et al. conducted in a cohort of pregnant Danish women in the county of North Jutland,[26] compliance with prescribed beta-blockers was estimated to be complete, strengthening the validity of our analyses. Furthermore, overestimation of exposure would bias the estimates towards unity.

There is a general consensus that labetalol is safer than other beta-blockers during pregnancy and this drug is rapidly becoming the first-line choice in conditions such as chronic hypertension during pregnancy.[21,23] We found an association between redeeming prescriptions for beta-blockers and being born SGA, preterm birth, and perinatal mortality. Risk profiles for pregnancies exposed to labetalol and to other beta-blockers were similar. Our findings therefore suggest that future treatment of pregnant women with beta-blockers should be based primarily on the individual needs of the mother and not of the unborn child. The increasing use and uncertainty of effects and possible side effects of treatment with beta-blockers during pregnancy call for further studies.

Conflicts of interests

The authors have no relevant conflict of interests.

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Contributorship Statement

KMP, EJS, JTA, MP, KB, LK, CTP, HEP
KMP, EJS, JTA and HEP conceptualized the study. MP, KB, LK and CTP assisted with the study design. KMP preformed the analyses assisted by EJS and JTA, MP, KB, LK, CTP and HEP assisted in the interpretation. KMP, EJS, JTA, MP, KB, LK, CTP and HEP wrote and revised the final manuscript. Figure design was done by KMP, EJS, JTA, MP, KB, LK, CTP and HEP. All authors approved the final version to be published.

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Beta-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population based cohort study

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Beta-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study

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ABSTRACT

Objective: To investigate the association between exposure to beta-blockers during pregnancy and the risk of being born small for gestational age (SGA), preterm birth, and perinatal mortality in a nationwide cohort.

Design: A population-based retrospective cohort study, using the Danish Fertility Database. We identified all pregnant women redeeming a prescription for beta-blockers using the National Prescription Registry. Multivariate logistic regression models were used to assess the association between exposure and our outcomes.

Setting: Register based survey.

Participants: 911685 births between 1995 and 2008 obtained from the Danish Fertility Database.

Outcome measures: Being born SGA was defined as having a birth weight below the tenth percentile for the corresponding gestational week. Preterm birth was defined as birth before the 37th gestational week. Perinatal mortality was defined as either death occurring within the first 28 days of life, or stillbirth. Before 2004, foetal deaths were recorded as stillbirths if they occurred after 28 weeks of gestation, but since then stillbirth is recorded for deaths after 22 gestational weeks.

Results: We identified 2459 pregnancies exposed to beta-blockers. Beta-blocker exposure during pregnancy was found to be associated with increased risk of SGA; adjusted OR=1.97 (95% CI, 1.75–2.23), preterm birth; adjusted OR=2.26 (95% CI, 2.03–2.52) and perinatal mortality; adjusted OR=1.89 (95 % CI, 1.25–2.84). Analyses were adjusted for socio-economic and maternal variables. We found similar risk profiles for pregnancies exposed to labetalol and for pregnancies exposed to other beta-blockers.

Conclusion: We found that exposure to beta-blockers during pregnancy was associated with being born SGA, preterm birth and perinatal mortality. Our findings show that labetalol is not safer than other beta-blockers during pregnancy..

ARTICLE SUMMARY

Article focus

- There is contradictory evidence concerning the consequences of beta-blocker treatment during pregnancy.
- This survey explores the effects of beta-blocker exposure during pregnancy in a Danish birth cohort comprising all births in Denmark between 1995 and 2008. In addition we compared risks associated with exposure to labetalol with exposure to other beta-blockers.

Key messages

- Redeeming prescriptions of beta-blockers was found to be significantly associated with increased risk of being born SGA, preterm birth, and perinatal mortality.
- We found comparable risk profiles in labetalol-exposed pregnancies and in pregnancies exposed to any other beta-blocker.

Strengths and limitations of this study

- This study is the largest of its kind to date, and covers an entire nation which minimises risk of selection bias.
- Given the study design, we were not able to adjust for treatment indication and severity of maternal disease, nor were we able to rule out confounding by indication, the underlying maternal disease, as a possible explanation for our findings.

INTRODUCTION

Beta-blockers are widely used in the treatment of chronic hypertension,[1-4] migraine,[5] essential tremor[6], and various other conditions. There is contradictory evidence concerning the consequences of beta-blocker treatment during pregnancy. Some studies report an association between beta-blocker treatment and small for gestational age (SGA) newborns, and preterm birth,[4,7-10] while others do not.[2,11] Preterm birth and being born SGA are both associated with increased risk of perinatal mortality.[12,13] We set out to investigate whether the use of beta-blockers during pregnancy was associated with being born SGA, preterm birth and perinatal mortality in a nationwide survey between 1995 and 2008.

METHOD

Study population

We used data obtained from three nationwide registries: the Danish Fertility Database,[14] the Danish National Hospital Register[15], and the National Prescription Register.[16] Data concerning income and educational level were obtained respectively from the Income Statistics Register[17] and the Danish Education register,[18] both of which are provided by Statistics Denmark. In Denmark all citizens are given a unique ten-digit identification number at birth.[19] This number can be used to link information between nationwide registers.

Using the Danish Fertility Database we identified 974 805 births between 1995 and 2008. We removed 52 603 records lacking information on pregnancy duration and 7681 records with coding errors. In addition, we excluded 2836 records with pregnancy-induced hypertension, defined as having redeemed an antihypertensive drug prescription after the twentieth week of gestation, but never before. The final study population thus comprised 911 685 births.

The Danish Fertility Database contains information on maternal age, date of birth, and previous births, as well as on each child's sex, gestational age, weight, and mortality.[14]

Time of conception is based on ultrasound estimates in early pregnancy, or information on last menstrual period.

Information on redeemed prescriptions was retrieved from the National Prescription Register, which holds information on date of redemption, quantity, strength, and form.[16] Drugs are coded in accordance with the Anatomical Therapeutic Chemical (ATC) classification.

The Danish National Hospital Register contains information on diagnoses of somatic admissions and outpatients at all Danish hospitals since 1977[15] in accordance with the Danish revision of the 10th International Classification of Diseases (ICD)-system. We used primary discharge diagnoses and disregarded secondary diagnoses, because secondary diagnoses in general are not validated. We identified diagnoses of pre-eclampsia and eclampsia, migraine, essential tremor, arrhythmias and maternal smoking. Pre-eclampsia and eclampsia were defined as women diagnosed with O13, O14, or O15. Migraine was defined as G43 or G44, essential tremor as G250 and arrhythmias as I47, I48, and I49. Maternal smoking was defined as women diagnosed with UT00, UT20, UT21, UT22, and UT23.

Identification of Exposure

We defined exposure to beta-blockers as the redemption of at least two prescriptions between six months before conception and the twentieth week of gestation. At least one of these prescriptions had to be redeemed between conception and the twentieth week of gestation.

We assessed exposure to beta-blockers by identifying redeemed prescriptions with ATC code C07. Furthermore, we identified the most frequently redeemed beta-blockers in Denmark: labetalol (C07AG01), metoprolol (C07AB02), atenolol (C07AB03), propranolol (C07AA05), pindolol (C07AA03), and sotalol (C07AA07). Fewer than 50 pregnancies were exposed to any of the remaining beta-blockers.

We divided beta-blocker exposure into exposure to labetalol and exposure to other beta-blockers. The latter group was formed because there were few redeemed prescriptions of individual beta-blockers other than labetalol. We compared risks associated with exposure to beta-blockers with exposure to methyldopa (C02AB01, C02AB02), calcium channel blockers (C08C), and ACE inhibitors (C09A) to assess possible confounding by indication.

Maternal diabetes mellitus was defined as redeeming a prescription for insulin or an insulin analogue (ATC code A10A). Furthermore, we assessed co-medication with statins (ATC code C10) and antiobesity drugs (ATC code A08A). We identified pregnant women redeeming prescriptions with these drugs in order to adjust for diabetes mellitus, obesity, and statin use since these women have different risk profiles for the defined outcomes.

Definition of Outcomes

Being born SGA was defined as having a birth weight below the tenth percentile for the corresponding gestational week. Preterm birth was defined as birth before the 37th gestational week. Perinatal mortality was defined as either death occurring within the first 28 days of life, or stillbirth. Before 2004, foetal deaths were recorded as stillbirths if they occurred after 28 weeks of gestation, but since then stillbirth is recorded for deaths after 22 gestational weeks.[20]

Statistical analyses

Data were managed and analysed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Logistic regression models were developed for dichotomous variables adjusted for maternal age, year of conception, annual household income, parity, and educational level (model 1). Maternal age was divided into five groups: <20, 21-25, 26-30, 31-35, >35 years (no missing values). Annual household income at year of birth was divided into quartiles (1266 missing values). Subjects were

divided into quartiles according to the number of previous births, including stillbirths (37 missing values): 0, 1, 2, ≥3 births. Year of conception was ordered into three categories (1994-1998, 1999-2003, and 2004-2008). Educational level was divided into tertiles by highest level of education achieved at the year of birth. For missing information we used information from the following calendar year (32 745 missing values).

We constructed a separate logistic regression model (model 2) including the socio-economic variables in model 1 and additional confounding variables: smoking status, co-medication (yes/no) with statins, antiobesity drugs, insulin and insulin analogues, and diagnoses of pre-eclampsia/eclampsia. These confounders were included in model 2 due to the high frequency of missing data, because information on smoking and diagnoses of pre-eclampsia/eclampsia were not available for the years 1995 and 2008. Maternal smoking was divided into four categories according to the number of cigarettes smoked daily (0, 1-10, 11-20, >20).

When estimating the risk of perinatal mortality, analyses were further adjusted for previous stillbirths. Odds ratios are presented with 95% confidence intervals (95% CIs). For description of basic characteristics we used frequencies with percentages. We used Chi-square tests to analyse differences in the proportions of the different classes of categorical baseline characteristics. Statistical significance was defined as $p<0.05$. All tests were two-sided.

In addition, we carried out a propensity score-matched regression analysis to consolidate our findings. We calculated a propensity score for the likelihood of redeeming a beta-blocker during pregnancy by multivariate logistic regression conditional on baseline covariates. Using the Greedy matching macro (http://mayoresearch.mayo.edu/mayo/research/biostat/upload/gmatch.sas), we matched each case to four controls on the basis of the propensity score (table 1). We did not match on diagnoses of pre-eclampsia/eclampsia since a large fraction of these cases redeemed beta-blocker prescriptions.

RESULTS

Table 1 presents maternal characteristics in beta-blocker-exposed and unexposed women (number and percentage of pregnancies). We identified 2381 pregnancies exposed to only one beta-blocker, 1452 exposed to labetalol only, and 929 exposed to other beta-blockers. 98 pregnancies were exposed to more than one beta-blocker. We found 515 pregnancies exposed to methyldopa, 86 pregnancies to calcium channel blockers (CCBs), and 48 pregnancies exposed to ACE inhibitors. Women exposed to beta-blockers during pregnancy were older, had higher income, and higher parity than unexposed women. The proportions of women redeeming prescriptions for statins, antiobesity preparations, and insulins were higher among the beta-blocker-exposed group. The proportion of pregnancies complicated by pre-eclampsia was higher among beta-blocker-exposed pregnancies. There was no difference in smoking prevalence between beta-blocker-exposed and unexposed women (table 1).

	Beta-blocker-exposed	Beta-blocker-unexposed		Propensity matched	
Table 1. Basic characteristics for pregnancies exposed to beta-blockers, compared with unexposed pregnancies and propensity score-matched pregnancies.					
Characteristics	**(n=2459) n (%)**	**(n=909228) n (%)**	**p-value[a]**	**(n=9662) n (%)**	**p-value[a]**
Educational level			<0.001		0.991
Low	739 (30.05)	311 600 (35.45)		2965 (30.69)	
Medium	972 (39.53)	285 450 (32.47)		3883 (40.19)	
High	707 (28.75)	279 431 (31.79)		2814 (29.12)	
Annual household income (GBP)			<0.001		0.989
0- 36 770	509 (23.99)	226 228 (24.84)		1924 (19.91)	
36 771 – 52 703	594 (24.16)	227 195 (24.96)		2337 (24.19)	
52 704 – 74 699	662 (26.92)	227 089 (24.94)		2631 (27.23)	
≥ 74 700	693 (28.18)	227 448 (24.98)		2770 (28.67)	
Parity			<0.001		0.998
1	900 (36.60)	394 661 (43.29)		3487 (28.87)	
2	918 (37.33)	338 989 (37.18)		3658 (30.28)	
3	455 (18.50)	129 482 (14.20)		1788 (14.80)	
>3	186 (7.56)	46 057 (5.05)		729 (6.04)	
Age (years)			<0.001		1.000
<20	18 (0.73)	26 321 (2.89)		68 (0.56)	
21-25	174 (7.07)	147 298 (16.16)		699 (5.79)	
26-30	700 (28.47)	350 105 (38.40)		2757 (22.82)	
31-35	930 (37.82)	281 154 (30.84)		3665 (30.34)	
>35	637 (24.90)	104 339 (11.44)		2473 (20.47)	
Daily cigarettes[b]			0.427		0.385
0	1548 (80.29)	572 642 (81.15)		6140 (81.81)	
1-10	251 (13.02)	90 033 (12.76)		913 (12.16)	
11-20	114 (5.19)	36201 (5.13)		394 (5.25)	
>20	15 (0.78)	4849 (0.69)		59 (0.79)	
Statins			<0.001		0.492
Used	5 (0.20)	111 (0.01)		14 (0.14)	
Not used	2454 (99.8)	909 115 (99.99)		9648 (99.86)	
Antiobesity preparations (A10)			0.018		0.251
Used	9 (0.40)	1539 (0.17)		23 (0.24)	
Not used	2450 (99.6)	907 687 (99.83)		9639 (99.76)	
Insulins and analogues			<0.001		0.782
Used	101 (4.11)	4208 (0.46)		412 (4.14)	
Not used	2358 (95.89)	905 018 (99.53)		9250 (95.74)	
Pre-eclampsia diagnosis(O13-O15)			<0.001		

Yes	99 (4.03)	7806 (0.86)	-
No	2360 (95.97)	901 420 (99.14)	-

[a]Chi-square tests were used to assess the overall p value for the group comparison.

[b]Information on smoking was only available for 1996-2007.

Women redeeming labetalol prescriptions were older, had a higher education level, and a higher prevalence of preeclampsia and smoking than women exposed to other beta-blockers (table 2). The proportion of women redeeming prescriptions for insulin was larger among the labetalol-exposed group. There was no difference in income or co-medication with statins and antiobesity preparations between the two groups. Diagnoses of migraine and arrhythmias were more common among women exposed to any other beta-blocker. Women exposed to other beta-blockers had higher parity than those exposed to labetalol.

Table 2. Basic characteristics for pregnancies exposed to labetalol, compared with pregnancies exposed to other beta-blockers.

Characteristics	Labetalol (n=1452) n (%)	Other beta-blockers (n=929) n (%)	p-value[a]
Educational level			<0.001
Low	391 (26.93)	321 (34.55)	
Medium	571 (39.33)	369 (39.72)	
High	462 (31.82)	226 (24.33)	
Annual household income (GBP)			0.138
0 – 36 770	202 (13.91)	289 (31.11)	
36 771 – 52 703	223 (15.36)	357 (38.43)	
52 704 – 74 699	228 (15.70)	413 (44.46)	
≥74 700	275 (19.94)	393 (42.30)	
Parity			0.004
0	512 (35.26)	363 (39.07)	
1	586 (40.36)	308 (33.15)	
2	256 (17.63)	179 (19.27)	
≥3	98 (6.75)	79 (8.50)	
Age (years)			<0.001
<20	7 (0.58)	10 (1.08)	

21-25	69 (4.75)	97 (10.44)	
26-30	406 (27.96)	275 (29.60)	
31-35	586 (40.36)	314 (33.79)	
>35	384 (26.45)	233 (25.08)	
Daily cigarettes[b]			<0.001
0	933 (64.26)	565 (60.82)	
1-10	130 (8.95)	112 (12.06)	
11-20	44 (3.03)	62 (6.67)	
>20	9 (6.19)	6 (0.65)	
Antiobesity drugs			0.052
Yes	5 (0.34)	9 (0.97)	
No	1447 (99.66)	920 (99.03)	
Statins			0.261
Yes	5 (0.34)	1 (0.10)	
No	1447 (99.66)	928 (99.90)	
Insulins and analogues			<0.001
Yes	83 (5.72)	16 (1.72)	
No	1369 (94.28)	913 (92.28)	
Migraine			<0.001
Yes	26 (1.79)	46 (4.95)	
No	1426 (98.21)	883 (95.05)	
Pre-eclampsia diagnosis			0.001
Yes	74 (5.10)	21 (2.26)	
No	1378 (94.90)	908 (97.84)	
Arrhythmia			<0.001
Yes	23 (1.58)	82 (8.83)	
No	1429 (98.42)	847 (91.17)	
Essential tremor			0.030
Yes	-	3 (0.33)	
No	1452 (100)	926 (99.67)	

[a]Chi square tests were used to assess the overall p value for the group comparison.

[b]Information on smoking was only available for 1996-2007.

Table 3 presents ORs with 95% CIs for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

SGA

We found 93 662 children born SGA in the unexposed population (table 3). There were 446 children born SGA among pregnancies exposed to some kind of beta-blocker. We found a higher proportion of SGA among women exposed to beta-blockers compared with unexposed women. Women exposed to labetalol or to other beta-blockers had similarly higher odds ratios than unexposed women (table 3).

Preterm birth

We identified 109 163 preterm births in the unexposed population (table 3). There were 697 preterm births among pregnancies exposed to beta-blockers. We found an association between preterm birth and beta-blocker exposure compared with unexposed women. Those exposed to labetalol or to other beta-blockers had similarly higher odds ratios than unexposed women (table 3).

Perinatal mortality

We identified 6048 perinatal deaths in the unexposed population (table 3). There were 44 perinatal deaths among infants exposed to beta-blockers. We found a higher rate of perinatal mortality amongst women exposed to beta-blockers (table 3).

When stratifying for different beta-blockers we found 30 perinatal deaths among labetalol-exposed pregnancies. Labetalol exposure was associated with increased risk of perinatal mortality (table 3).

We identified 13 perinatal deaths among pregnancies exposed to other beta-blockers. Exposure to other beta-blockers was found to be significantly associated with perinatal mortality in the unadjusted model and model 1. However, adjusting our analysis for additional confounding variables (Model 2) rendered the association statistically insignificant (table 3).

Other analyses

We identified 515 pregnancies exposed to methyldopa (table 3). We found 61 children born SGA, 216 preterm births and 4 perinatal deaths among these pregnancies. We found a positive association between children born SGA and exposure to methyldopa, and between methyldopa exposure and increased risk of preterm birth. Exposure to methyldopa during pregnancy was not significantly associated with perinatal mortality (table 3).

Table 3. ORs with 95% CIs for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

Table 3 Odds Ratios (ORs) with 95% CI for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

Analyses are adjusted for maternal age, household income, educational level, parity, birth year and prior stillbirths.
[a]Model 2 is furthermore adjusted for smoking and comedication with statins, antiobesity preparations, insulins and diagnoses of pre-eclampsia/eclampsia. The cohort in model 2 comprises all births between 1996 and 2007 (n=778 304)

Exposure	N (%)	Crude OR (95% CI)	Adjusted (model 1) OR (95% CI)	Adjusted (model 2) OR (95% CI)
		SGA		
Unexposed (n=909 226)	93 662 (10.30)	Reference	Reference	Reference
All beta-blockers (n=2459)	446 (18.14)	1.93 (1.74-2.14)	1.99 (1.79-2.21)	1.97 (1.75-2.23)
Labetalol only (n=1452)	258 (17.77)	1.88 (1.64-2.15)	1.95 (1.70-2.24)	2.02 (1.72-2.37)
Other beta-blockers (n=929)	179 (19.27)	2.08 (1.76-2.44)	2.11 (1.79-2.49)	2.01 (1.66-2.43)
Methyldopa (n= 515)	61 (11.84)	1.17 (0.89-1.53)	1.32 (1.01-1.73)	1.43 (1.04-1.96)
CCBs (n=86)	21 (24.42)	2.30 (1.42-3.73)	2.24 (1.36-3.67)	1.88 (1.02-3.49)
		Preterm birth		
Unexposed (n=909 226)	109 163 (12.01)	Reference	Reference	Reference
All beta-blockers (n=2459)	697 (28.34)	2.9 (2.66-3.14)	2.71 (2.48-2.97)	2.26 (2.03-2.52)
Labetalol only (n=1452)	473 (32.58)	3.54 (3.17-3.95)	3.33 (2.98-3.72)	2.74 (2.39-3.13)
Other beta-blockers (n=929)	206 (22.17)	2.08 (1.78-2.43)	1.93 (1.65-2.26)	1.69 (1.41-2.03)
Methyldopa (n= 515)	216 (41.94)	5.29 (4.44-6.31)	5.03 (4.21-6.01)	4.21 (3.38-5.23)
CCBs (n=86)	26 (30.23)	2.55 (1.63-3.99)	2.50 (1.60-3.89)	2.15 (1.26-3.67)
		Perinatal mortality		
Unexposed (n=909 226)	6048 (0.67)	Reference	Reference	Reference
All beta-blockers (n=2459)	44 (1.79)	2.72 (2.02-3.67)	2.69 (1.98-3.65)	1.89 (1.25-2.84)
Labetalol only (n=1452)	30 (2.07)	3.15 (2.19-4.52)	3.24 (2.25-4.67)	2.08 (1.26-3.44)
Other beta-blockers (n=929)	13 (1.39)	2.12 (1.22-3.66)	1.92 (1.08-3.40)	1.72 (0.85-3.48)
Methyldopa (n= 515)	4 (0.78)	1.15 (0.43-3.07)	1.16 (0.43-3.12)	0.35 (0.05-2.50)
CCBs (n=86)	1 (1.16)	1.78 (0.25-12.57)	2.00 (0.28-14.83)	3.26 (0.45-23.77)

We found 86 pregnancies exposed to calcium channel blockers (table 3). These included 17 children born SGA, 18 preterm births and 1 perinatal death. We found an association between exposure to calcium channel blockers and children born SGA in all models.

Additionally, we found an association between exposure to calcium channel blockers and increased risk of preterm birth in all models. As with methyldopa, exposure to calcium channel blockers during pregnancy was not found to be associated with perinatal mortality (table 3).

Analyses for exposure to ACE inhibitors were not performed since we identified only 48 pregnancies exposed to them.

Post hoc we analysed the effect of exposure to all beta-blockers using a propensity score-matched control group (Table 1) and found similar results to those of the primary analyses: SGA, OR=1.93 (95% CI, 1.71–2.19); preterm birth, OR=2.40 (95% CI, 2.16–2.67); perinatal mortality, OR=3.22 (95% CI, 2.15–4.82).

DISCUSSION

In the present study, which we believe to be the largest of its kind to date, we found an association between redeeming prescriptions of beta-blockers during pregnancy and being born SGA, preterm birth, and perinatal mortality. In addition, we found an association between redeeming prescriptions of methyldopa and calcium channel blockers, being born SGA, and preterm birth. Methyldopa and calcium channel blockers were not found to be associated with perinatal mortality.

We found exposure to any beta-blocker to be associated with being born SGA. Our results are in accordance with a recent study reporting increased risk of being born SGA among pregnancies exposed to selective beta-blockers (OR=6.00; 95% CI, 1.06–33.87) and labetalol (OR=2.26; 95% CI, 1.04–4.88).[9] Labetalol is generally considered safe for use during pregnancy.[1,8,21]

Exposure to beta-blockers was found to be associated with preterm birth. When stratifying for different beta-blockers we found an increased risk of preterm birth after exposure to labetalol, and all other beta-blockers, respectively.

We found an association between exposure to beta-blockers and perinatal mortality. When stratifying for different beta-blockers we found this association to be statistically significant for exposure to labetalol and other beta-blockers**.** When adjusting our analysis for maternal co-morbidity, co-medication, and smoking, only labetalol was found to be associated with perinatal mortality.

Methyldopa is mainly used to treat chronic hypertension during pregnancy as first-line therapy.[1] Previous studies did not find any associations between methyldopa exposure and being born SGA or preterm birth.[1,3] Methyldopa has not been found to have effects on placental haemodynamics.[1] However, a recent case-control study reported an increased risk of being born SGA among pregnancies exposed to centrally acting adrenergic agents during the second and third trimesters[9]: OR=1.70 (95% CI, 1.00–2.89). We found that methyldopa exposure was associated with being born SGA and preterm birth. This could be due to indicative antihypertensive treatment with methyldopa in pregnant women with diabetes or pregnancy related diabetes. The prevalence of diabetes among methyldopa-exposed pregnancies was found to be higher: 11.1% compared with 3.9% among beta-blocker-exposed pregnancies. Increased risk of preterm birth was still seen after adjusting our analyses for additional confounding variables in model 2. We found no association between exposure to methyldopa and perinatal mortality. These findings are consistent with those of a previous study.[3]

Calcium channel blockers are considered to be safe during pregnancy.[3,22] We found that exposure to calcium channel blockers was associated with being born SGA and with preterm birth. The risk of being born SGA and preterm of birth remained after adjusting our analyses for additional confounding variables in model 2. We found no statistically significant association between calcium channel blocker exposure during pregnancy and perinatal mortality.

We chose to analyse two outcomes previously reported to be associated with beta-blocker exposure during pregnancy —SGA and preterm birth[1,10,23] — that have been associated with increased perinatal mortality in previous studies.[12,13] Therefore we investigated the risk of perinatal mortality among beta-blocker-exposed pregnancies. We compared risks associated with exposure to beta-blockers with exposure to methyldopa and calcium channel blockers to assess possible confounding by indication. Our analyses show a similar risk of being born SGA and an

increased risk of preterm birth for all recommended agents during pregnancy. There are various possible explanations for this finding. It is possible that the underlying indication for treatment, maternal disease, is the true risk factor. Possible maternal diseases include hypertension, either predating or complicating pregnancy. Accordingly, we were not able to rule out a potential effect of maternal disease on perinatal outcomes.

We found an association between exposure to beta-blockers during pregnancy and perinatal mortality. This association was not found for exposure to methyldopa and calcium channel blockers, which might be due to the small number of cases.

We believe that the similar risks found for exposure to the various beta-blockers and SGA, preterm birth, and perinatal mortality are a class effect. This seems to be true in spite of statistically significant differences in the basic characteristics of women exposed to labetalol and those exposed to other beta-blockers (table 2). After adjustments were made for these variables, we found comparable risk profiles for labetalol-exposed pregnancies and pregnancies exposed to other beta-blockers. Most beta-blockers are known to cross the placenta,[21,24] and effects on placental haemodynamics have been observed in both human and animal studies. A mechanism has been proposed of diminished placental blood flow due to the selective vasoconstriction of placental vessels by beta-blockers without intrinsic sympathomimetic activity.[24] This effect on placental haemodynamics could explain growth retardation of foetuses exposed to beta-blockers during pregnancy and might result in children being born SGA and preterm.

We defined exposure as redemption of at least two prescriptions between six months before conception and the twentieth week of gestation. At least one of these prescriptions had to be redeemed between conception and twentieth week of gestation. We believe that this model increases the probability of identifying continuous use that extends into pregnancy.

The rate of perinatal mortality in Denmark is low (table 3).[25] A large number of women exposed to beta-blockers, methyldopa, and calcium channel blockers are therefore needed to identify a possible risk increase associated with these outcomes. Our cohort comprises all births in Denmark between 1995 and 2008. This minimises confounding due to race, educational level, and other socio-economic factors. The national Danish registers cover the entire nation and are considered valid. As part of the national health care reimbursement scheme, Danish pharmacies are required by law to register all redeemed prescriptions. Approximately 97.5% of all redeemed prescriptions are registered in the Danish Prescription register.[16] Our study includes data on exposure to beta-blockers based on information on prescriptions paid for at the pharmacy, and not only prescribed by the physician, thereby increasing the probability of exposure. Furthermore, our study was not confounded by recall bias since information was recorded prospectively. The Danish Fertility Database contains more than 99% of all births during the study period.[14]

Limitations of our study include missing information on maternal weight and alcohol consumption. We were unable to adjust for treatment indication and severity of maternal disease. Given the study design, we were not able to address this issue further, nor were we able to rule out confounding by indication, the underlying maternal disease, as a possible explanation for our findings. Consequently we were unable to differentiate between a possible class effect of beta-blockers and the effect of the underlying maternal disease.

Unfortunately information on diagnoses of essential hypertension was not available, since these are known risk factors for our primary outcomes.

The prevalence of pre-eclampsia and eclampsia in the cohort is based on primary discharge diagnoses from hospital admissions. We did not use secondary diagnoses, since these in general are not validated. We estimated exposure from National Prescription Registry data, which contains information on all redeemed prescriptions.[16] Overestimation of exposure is therefore a

possibility, since we cannot adjust for a potential lack of compliance. However, in a study by Olesen et al. conducted in a cohort of pregnant Danish women in the county of North Jutland,[26] compliance with prescribed beta-blockers was estimated to be complete, strengthening the validity of our analyses. Furthermore, overestimation of exposure would bias the estimates towards unity.

There is a general consensus that labetalol is safer than other beta-blockers during pregnancy and this drug is rapidly becoming the first-line choice in conditions such as chronic hypertension during pregnancy.[21,23] We found an association between redeeming prescriptions for beta-blockers and being born SGA, preterm birth, and perinatal mortality. Risk profiles for pregnancies exposed to labetalol and to other beta-blockers were similar. The increasing use and uncertainty of effects and possible side effects of treatment with beta-blockers during pregnancy call for further studies to validate our findings.

Conflicts of interests

The authors have no relevant conflict of interests.

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Contributorship Statement

KMP, EJS, JTA, MP, KB, LK, CTP, HEP

KMP, EJS, JTA and HEP conceptualized the study. MP, KB, LK and CTP assisted with the study design. KMP preformed the analyses assisted by EJS and JTA, MP, KB, LK, CTP and HEP assisted in the interpretation. KMP, EJS, JTA, MP, KB, LK, CTP and HEP wrote and revised the final manuscript. Figure design was done by KMP, EJS, JTA, MP, KB, LK, CTP and HEP. All authors approved the final version to be published.

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Beta-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study

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ABSTRACT

Objective: To investigate the association between exposure to beta-blockers during pregnancy and the risk of being born small for gestational age (SGA), preterm birth, and perinatal mortality in a nationwide cohort.

Design: A population-based retrospective cohort study, using the Danish Fertility Database. We identified all pregnant women redeeming a prescription for beta-blockers using the National Prescription Registry. Multivariate logistic regression models were used to assess the association between exposure and our outcomes.

Setting: Register based survey.

Participants: 911685 births between 1995 and 2008 obtained from the Danish Fertility Database.

Outcome measures: Being born SGA was defined as having a birth weight below the tenth percentile for the corresponding gestational week. Preterm birth was defined as birth before the 37th gestational week. Perinatal mortality was defined as either death occurring within the first 28 days of life, or stillbirth. Before 2004, foetal deaths were recorded as stillbirths if they occurred after 28 weeks of gestation, but since then stillbirth is recorded for deaths after 22 gestational weeks.

Results: We identified 2459 pregnancies exposed to beta-blockers. Beta-blocker exposure during pregnancy was found to be associated with increased risk of SGA; adjusted OR=1.97 (95% CI, 1.75–2.23), preterm birth; adjusted OR=2.26 (95% CI, 2.03–2.52) and perinatal mortality; adjusted OR=1.89 (95 % CI, 1.25–2.84). Analyses were adjusted for socio-economic and maternal variables. We found similar risk profiles for pregnancies exposed to labetalol and for pregnancies exposed to other beta-blockers.

Conclusion: We found that exposure to beta-blockers during pregnancy was associated with being born SGA, preterm birth and perinatal mortality. Our findings show that labetalol is not safer than other beta-blockers during pregnancy~~, and future treatment of pregnant women with beta-blockers should therefore be based primarily on the individual needs of the mother and not the unborn child~~.

ARTICLE SUMMARY

Article focus

- There is contradictory evidence concerning the consequences of beta-blocker treatment during pregnancy.
- This survey explores the effects of beta-blocker exposure during pregnancy in a Danish birth cohort comprising all births in Denmark between 1995 and 2008. In addition we compared risks associated with exposure to labetalol with exposure to other beta-blockers.

Key messages

- Redeeming prescriptions of beta-blockers was found to be significantly associated with increased risk of being born SGA, preterm birth, and perinatal mortality.
- We found comparable risk profiles in labetalol-exposed pregnancies and in pregnancies exposed to any other beta-blocker.

Strengths and limitations of this study

- This study is the largest of its kind to date, and covers an entire nation which minimises risk of selection bias.
- Given the study design, we were not able to adjust for treatment indication and severity of maternal disease, nor were we able to rule out confounding by indication, the underlying maternal disease, as a possible explanation for our findings.

INTRODUCTION

Beta-blockers are widely used in the treatment of chronic hypertension,[1-4] migraine,[5] essential tremor[6], and various other conditions. There is contradictory evidence concerning the consequences of beta-blocker treatment during pregnancy. Some studies report an association between beta-blocker treatment and small for gestational age (SGA) newborns, and preterm birth,[4,7-10] while others do not.[2,11] Preterm birth and being born SGA are both associated with increased risk of perinatal mortality.[12,13] We set out to investigate whether the use of beta-blockers during pregnancy was associated with being born SGA, preterm birth and perinatal mortality in a nationwide survey between 1995 and 2008.

METHOD

Study population

We used data obtained from three nationwide registries: the Danish Fertility Database,[14] the Danish National Hospital Register[15], and the National Prescription Register.[16] Data concerning income and educational level were obtained respectively from the Income Statistics Register[17] and the Danish Education register,[18] both of which are provided by Statistics Denmark. In Denmark all citizens are given a unique ten-digit identification number at birth.[19] This number can be used to link information between nationwide registers.

Using the Danish Fertility Database we identified 974 805 births between 1995 and 2008. We removed 52 603 records lacking information on pregnancy duration and 7681 records with coding errors. In addition, we excluded 2836 records with pregnancy-induced hypertension, defined as having redeemed an antihypertensive drug prescription after the twentieth week of gestation, but never before. The final study population thus comprised 911 685 births.

The Danish Fertility Database contains information on maternal age, date of birth, and previous births, as well as on each child's sex, gestational age, weight, and mortality.[14] Time of conception is based on ultrasound estimates in early pregnancy, or information on last menstrual period.

Information on redeemed prescriptions was retrieved from the National Prescription Register, which holds information on date of redemption, quantity, strength, and form.[16] Drugs are coded in accordance with the Anatomical Therapeutic Chemical (ATC) classification.

The Danish National Hospital Register contains information on diagnoses of somatic admissions and outpatients at all Danish hospitals since 1977[15] in accordance with the Danish revision of the 10th International Classification of Diseases (ICD)-system. We used primary discharge diagnoses and disregarded secondary diagnoses, because secondary diagnoses in general are not validated. We identified diagnoses of pre-eclampsia and eclampsia, migraine, essential tremor, arrhythmias and maternal smoking. Pre-eclampsia and eclampsia were defined as women diagnosed with O13, O14, or O15. Migraine was defined as G43 or G44, essential tremor as G250 and arrhythmias as I47, I48, and I49. Maternal smoking was defined as women diagnosed with UT00, UT20, UT21, UT22, and UT23.

Identification of Exposure

We defined exposure to beta-blockers as the redemption of at least two prescriptions between six months before conception and the twentieth week of gestation. At least one of these prescriptions had to be redeemed between conception and the twentieth week of gestation.

We assessed exposure to beta-blockers by identifying redeemed prescriptions with ATC code C07. Furthermore, we identified the most frequently redeemed beta-blockers in Denmark: labetalol (C07AG01), metoprolol (C07AB02), atenolol (C07AB03), propranolol (C07AA05), pindolol

(C07AA03), and sotalol (C07AA07). Fewer than 50 pregnancies were exposed to any of the remaining beta-blockers.

We divided beta-blocker exposure into exposure to labetalol and exposure to other beta-blockers. The latter group was formed because there were few redeemed prescriptions of individual beta-blockers other than labetalol. We compared risks associated with exposure to beta-blockers with exposure to methyldopa (C02AB01, C02AB02), calcium channel blockers (C08C), and ACE inhibitors (C09A) to assess possible confounding by indication.

Maternal diabetes mellitus was defined as redeeming a prescription for insulin or an insulin analogue (ATC code A10A). Furthermore, we assessed co-medication with statins (ATC code C10) and antiobesity drugs (ATC code A08A). We identified pregnant women redeeming prescriptions with these drugs in order to adjust for diabetes mellitus, obesity, and statin use since these women have different risk profiles for the defined outcomes.

Definition of Outcomes

Being born SGA was defined as having a birth weight below the tenth percentile for the corresponding gestational week. Preterm birth was defined as birth before the 37th gestational week. Perinatal mortality was defined as either death occurring within the first 28 days of life, or stillbirth. Before 2004, foetal deaths were recorded as stillbirths if they occurred after 28 weeks of gestation, but since then stillbirth is recorded for deaths after 22 gestational weeks.[20]

Statistical analyses

Data were managed and analysed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Logistic regression models were developed for dichotomous variables adjusted for maternal age, year of conception, annual household income, parity, and educational level (model 1). Maternal age was

divided into five groups: <20, 21-25, 26-30, 31-35, >35 years (no missing values). Annual household income at year of birth was divided into quartiles (1266 missing values). Subjects were divided into quartiles according to the number of previous births, including stillbirths (37 missing values): 0, 1, 2, ≥3 births. Year of conception was ordered into three categories (1994-1998, 1999-2003, and 2004-2008). Educational level was divided into tertiles by highest level of education achieved at the year of birth. For missing information we used information from the following calendar year (32 745 missing values).

We constructed a separate logistic regression model (model 2) including the socio-economic variables in model 1 and additional confounding variables: smoking status, co-medication (yes/no) with statins, antiobesity drugs, insulin and insulin analogues, and diagnoses of pre-eclampsia/eclampsia. These confounders were included in model 2 due to the high frequency of missing data, because information on smoking and diagnoses of pre-eclampsia/eclampsia were not available for the years 1995 and 2008. Maternal smoking was divided into four categories according to the number of cigarettes smoked daily (0, 1-10, 11-20, >20).

When estimating the risk of perinatal mortality, analyses were further adjusted for previous stillbirths. Odds ratios are presented with 95% confidence intervals (95% CIs). For description of basic characteristics we used frequencies with percentages. We used Chi-square tests to analyse differences in the proportions of the different classes of categorical baseline characteristics. Statistical significance was defined as $p<0.05$. All tests were two-sided.

In addition, we carried out a propensity score-matched regression analysis to consolidate our findings. We calculated a propensity score for the likelihood of redeeming a beta-blocker during pregnancy by multivariate logistic regression conditional on baseline covariates. Using the Greedy matching macro (http://mayoresearch.mayo.edu/mayo/research/biostat/upload/gmatch.sas), we matched each case to four controls on the basis of the propensity score (table 1). We did not match

on diagnoses of pre-eclampsia/eclampsia since a large fraction of these cases redeemed beta-blocker prescriptions.

RESULTS

Table 1 presents maternal characteristics in beta-blocker-exposed and unexposed women (number and percentage of pregnancies). We identified 2381 pregnancies exposed to only one beta-blocker, 1452 exposed to labetalol only, and 929 exposed to other beta-blockers. 98 pregnancies were exposed to more than one beta-blocker. We found 515 pregnancies exposed to methyldopa, 86 pregnancies to calcium channel blockers (CCBs), and 48 pregnancies exposed to ACE inhibitors. Women exposed to beta-blockers during pregnancy were older, had higher income, and higher parity than unexposed women. The proportions of women redeeming prescriptions for statins, antiobesity preparations, and insulins were higher among the beta-blocker-exposed group. The proportion of pregnancies complicated by pre-eclampsia was higher among beta-blocker-exposed pregnancies. There was no difference in smoking prevalence between beta-blocker-exposed and unexposed women (table 1).

	Beta-blocker-exposed	Beta-blocker-unexposed		Propensity matched	
	(n=2459)	(n=909228)		(n=9662)	
Characteristics	**n (%)**	**n (%)**	**p-value[a]**	**n (%)**	**p-value[a]**
Educational level			<0.001		0.991
Low	739 (30.05)	311 600 (35.45)		2965 (30.69)	
Medium	972 (39.53)	285 450 (32.47)		3883 (40.19)	
High	707 (28.75)	279 431 (31.79)		2814 (29.12)	
Annual household income (GBP)			<0.001		0.989
0- 36 770	509 (23.99)	226 228 (24.84)		1924 (19.91)	
36 771 – 52 703	594 (24.16)	227 195 (24.96)		2337 (24.19)	
52 704 – 74 699	662 (26.92)	227 089 (24.94)		2631 (27.23)	
≥ 74 700	693 (28.18)	227 448 (24.98)		2770 (28.67)	
Parity			<0.001		0.998
1	900 (36.60)	394 661 (43.29)		3487 (28.87)	
2	918 (37.33)	338 989 (37.18)		3658 (30.28)	
3	455 (18.50)	129 482 (14.20)		1788 (14.80)	
>3	186 (7.56)	46 057 (5.05)		729 (6.04)	
Age (years)			<0.001		1.000
<20	18 (0.73)	26 321 (2.89)		68 (0.56)	
21-25	174 (7.07)	147 298 (16.16)		699 (5.79)	
26-30	700 (28.47)	350 105 (38.40)		2757 (22.82)	
31-35	930 (37.82)	281 154 (30.84)		3665 (30.34)	
>35	637 (24.90)	104 339 (11.44)		2473 (20.47)	
Daily cigarettes[b]			0.427		0.385
0	1548 (80.29)	572 642 (81.15)		6140 (81.81)	
1-10	251 (13.02)	90 033 (12.76)		913 (12.16)	
11-20	114 (5.19)	36201 (5.13)		394 (5.25)	
>20	15 (0.78)	4849 (0.69)		59 (0.79)	
Statins			<0.001		0.492
Used	5 (0.20)	111 (0.01)		14 (0.14)	
Not used	2454 (99.8)	909 115 (99.99)		9648 (99.86)	
Antiobesity preparations (A10)			0.018		0.251
Used	9 (0.40)	1539 (0.17)		23 (0.24)	
Not used	2450 (99.6)	907 687 (99.83)		9639 (99.76)	

Table 1. Basic characteristics for pregnancies exposed to beta-blockers, compared with unexposed pregnancies and propensity score-matched pregnancies.

Insulins and analogues			<0.001	0.782
Used	101 (4.11)	4208 (0.46)		412 (4.14)
Not used	2358 (95.89)	905 018 (99.53)		9250 (95.74)
Pre-eclampsia diagnosis(O13-O15)			<0.001	
Yes	99 (4.03)	7806 (0.86)		-
No	2360 (95.97)	901 420 (99.14)		-

[a]Chi-square tests were used to assess the overall p value for the group comparison.

[b]Information on smoking was only available for 1996-2007.

Women redeeming labetalol prescriptions were older, had a higher education level, and a higher prevalence of preeclampsia and smoking than women exposed to other beta-blockers (table 2). The proportion of women redeeming prescriptions for insulin was larger among the labetalol-exposed group. There was no difference in income or co-medication with statins and antiobesity preparations between the two groups. Diagnoses of migraine and arrhythmias were more common among women exposed to any other beta-blocker. Women exposed to other beta-blockers had higher parity than those exposed to labetalol.

Table 2. Basic characteristics for pregnancies exposed to labetalol, compared with pregnancies exposed to other beta-blockers.

Characteristics	Labetalol (n=1452) n (%)	Other beta-blockers (n=929) n (%)	p-value[a]
Educational level			<0.001
Low	391 (26.93)	321 (34.55)	
Medium	571 (39.33)	369 (39.72)	
High	462 (31.82)	226 (24.33)	
Annual household income (GBP)			0.138
0 – 36 770	202 (13.91)	289 (31.11)	
36 771 – 52 703	223 (15.36)	357 (38.43)	
52 704 – 74 699	228 (15.70)	413 (44.46)	
≥74 700	275 (19.94)	393 (42.30)	
Parity			0.004
0	512 (35.26)	363 (39.07)	
1	586 (40.36)	308 (33.15)	

2	256 (17.63)	179 (19.27)	
≥3	98 (6.75)	79 (8.50)	
Age (years)			<0.001
<20	7 (0.58)	10 (1.08)	
21-25	69 (4.75)	97 (10.44)	
26-30	406 (27.96)	275 (29.60)	
31-35	586 (40.36)	314 (33.79)	
>35	384 (26.45)	233 (25.08)	
Daily cigarettes[b]			<0.001
0	933 (64.26)	565 (60.82)	
1-10	130 (8.95)	112 (12.06)	
11-20	44 (3.03)	62 (6.67)	
>20	9 (6.19)	6 (0.65)	
Antiobesity drugs			0.052
Yes	5 (0.34)	9 (0.97)	
No	1447 (99.66)	920 (99.03)	
Statins			0.261
Yes	5 (0.34)	1 (0.10)	
No	1447 (99.66)	928 (99.90)	
Insulins and analogues			<0.001
Yes	~~1369~~83 (5.72)	16 (1.72)	
No	~~83~~1369 (94.28)	913 (92.28)	
Migraine			<0.001
Yes	26 (1.79)	46 (4.95)	
No	1426 (98.21)	883 (95.05)	
Pre-eclampsia diagnosis			0.001
Yes	~~1378 (94.90)~~74 (5.10)	~~908 (97.84)~~21 (2.26)	
No	~~74 (5.10)~~ 1378 (94.90)	~~21 (2.26)~~908 (97.84)	
Arrhythmia			<0.001
Yes	23 (1.58)	82 (8.83)	
No	1429 (98.42)	847 (91.17)	
Essential tremor			0.030
Yes	-	3 (0.33)	
No	1452 (100)	926 (99.67)	

[a]Chi square tests were used to assess the overall p value for the group comparison.

[b]Information on smoking was only available for 1996-2007.

Table 3 presents ORs with 95% CIs for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

SGA

We found 93 662 children born SGA in the unexposed population (table 3). There were 446 children born SGA among pregnancies exposed to some kind of beta-blocker. We found a higher proportion of SGA among women exposed to beta-blockers compared with unexposed women. Women exposed to labetalol or to other beta-blockers had similarly higher odds ratios than unexposed women (table 3).

Preterm birth

We identified 109 163 preterm births in the unexposed population (table 3). There were 697 preterm births among pregnancies exposed to beta-blockers. We found an association between preterm birth and beta-blocker exposure compared with unexposed women. Those exposed to labetalol or to other beta-blockers had similarly higher odds ratios than unexposed women (table 3).

Perinatal mortality

We identified 6048 perinatal deaths in the unexposed population (table 3). There were 44 perinatal deaths among infants exposed to beta-blockers. We found a higher rate of perinatal mortality amongst women exposed to beta-blockers (table 3).

When stratifying for different beta-blockers we found 30 perinatal deaths among labetalol-exposed pregnancies. Labetalol exposure was associated with increased risk of perinatal mortality (table 3).

We identified 13 perinatal deaths among pregnancies exposed to other beta-blockers. Exposure to other beta-blockers was found to be significantly associated with perinatal mortality in the unadjusted model and model 1. However, adjusting our analysis for additional confounding variables (Model 2) rendered the association statistically insignificant (table 3).

Other analyses

We identified 515 pregnancies exposed to methyldopa (table 3). We found 61 children born SGA, 216 preterm births and 4 perinatal deaths among these pregnancies. We found a positive association between children born SGA and exposure to methyldopa, and between methyldopa exposure and increased risk of preterm birth. Exposure to methyldopa during pregnancy was not significantly associated with perinatal mortality (table 3).

Table 3. ORs with 95% CIs for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

Table 3 Odds Ratios (ORs) with 95% CI for SGA, preterm birth and perinatal death for exposure to beta-blockers during pregnancy.

Exposure	N (%)	Crude OR (95% CI)	Adjusted (model 1) OR (95% CI)	Adjusted (model 2) OR (95% CI)
		SGA		
Unexposed (n=909 226)	93 662 (10.30)	Reference	Reference	Reference
All beta-blockers (n=2459)	446 (18.14)	1.93 (1.74-2.14)	1.99 (1.79-2.21)	1.97 (1.75-2.23)
Labetalol only (n=1452)	258 (17.77)	1.88 (1.64-2.15)	1.95 (1.70-2.24)	2.02 (1.72-2.37)
Other beta-blockers (n=929)	179 (19.27)	2.08 (1.76-2.44)	2.11 (1.79-2.49)	2.01 (1.66-2.43)
Methyldopa (n= 515)	61 (11.84)	1.17 (0.89-1.53)	1.32 (1.01-1.73)	1.43 (1.04-1.96)
CCBs (n=86)	21 (24.42)	2.30 (1.42-3.73)	2.24 (1.36-3.67)	1.88 (1.02-3.49)
		Preterm birth		
Unexposed (n=909 226)	109 163 (12.01)	Reference	Reference	Reference
All beta-blockers (n=2459)	697 (28.34)	2.9 (2.66-3.14)	2.71 (2.48-2.97)	2.26 (2.03-2.52)
Labetalol only (n=1452)	473 (32.58)	3.54 (3.17-3.95)	3.33 (2.98-3.72)	2.74 (2.39-3.13)
Other beta-blockers (n=929)	206 (22.17)	2.08 (1.78-2.43)	1.93 (1.65-2.26)	1.69 (1.41-2.03)
Methyldopa (n= 515)	216 (41.94)	5.29 (4.44-6.31)	5.03 (4.21-6.01)	4.21 (3.38-5.23)
CCBs (n=86)	26 (30.23)	2.55 (1.63-3.99)	2.50 (1.60-3.89)	2.15 (1.26-3.67)
		Perinatal mortality		
Unexposed (n=909 226)	6048 (0.67)	Reference	Reference	Reference
All beta-blockers (n=2459)	44 (1.79)	2.72 (2.02-3.67)	2.69 (1.98-3.65)	1.89 (1.25-2.84)
Labetalol only (n=1452)	30 (2.07)	3.15 (2.19-4.52)	3.24 (2.25-4.67)	2.08 (1.26-3.44)
Other beta-blockers (n=929)	13 (1.39)	2.12 (1.22-3.66)	1.92 (1.08-3.40)	1.72 (0.85-3.48)
Methyldopa (n= 515)	4 (0.78)	1.15 (0.43-3.07)	1.16 (0.43-3.12)	0.35 (0.05-2.50)
CCBs (n=86)	1 (1.16)	1.78 (0.25-12.57)	2.00 (0.28-14.83)	3.26 (0.45-23.77)

We found 86 pregnancies exposed to calcium channel blockers (table 3). These included 17 children born SGA, 18 preterm births and 1 perinatal death. We found an association between exposure to calcium channel blockers and children born SGA in all models.

Additionally, we found an association between exposure to calcium channel blockers and increased risk of preterm birth in all models. As with methyldopa, exposure to calcium channel blockers during pregnancy was not found to be associated with perinatal mortality (table 3). Analyses for exposure to ACE inhibitors were not performed since we identified only 48 pregnancies exposed to them.

Post hoc we analysed the effect of exposure to all beta-blockers using a propensity score-matched control group (Table 1) and found similar results to those of the primary analyses: SGA, OR=1.93 (95% CI, 1.71–2.19); preterm birth, OR=2.40 (95% CI, 2.16–2.67); perinatal mortality, OR=3.22 (95% CI, 2.15–4.82).

DISCUSSION

In the present study, which we believe to be the largest of its kind to date, we found an association between redeeming prescriptions of beta-blockers during pregnancy and being born SGA, preterm birth, and perinatal mortality. In addition, we found an association between redeeming prescriptions of methyldopa and calcium channel blockers, being born SGA, and preterm birth. Methyldopa and calcium channel blockers were not found to be associated with perinatal mortality.

We found exposure to any beta-blocker to be associated with being born SGA. Our results are in accordance with a recent study reporting increased risk of being born SGA among pregnancies exposed to selective beta-blockers (OR=6.00; 95% CI, 1.06–33.87) and labetalol (OR=2.26; 95% CI, 1.04–4.88).[9] Labetalol is generally considered safe for use during pregnancy.[1,8,21]

Exposure to beta-blockers was found to be associated with preterm birth. When stratifying for different beta-blockers we found an increased risk of preterm birth after exposure to labetalol, and all other beta-blockers, respectively.

We found an association between exposure to beta-blockers and perinatal mortality. When stratifying for different beta-blockers we found this association to be statistically significant for exposure to labetalol and other beta-blockers**.** When adjusting our analysis for maternal co-morbidity, co-medication, and smoking, only labetalol was found to be associated with perinatal mortality.

Methyldopa is mainly used to treat chronic hypertension during pregnancy as first-line therapy.[1] Previous studies did not find any associations between methyldopa exposure and being born SGA or preterm birth.[1,3] Methyldopa has not been found to have effects on placental haemodynamics.[1] However, a recent case-control study reported an increased risk of being born SGA among pregnancies exposed to centrally acting adrenergic agents during the second and third trimesters[9]: OR=1.70 (95% CI, 1.00–2.89). We found that methyldopa exposure was associated with being born SGA and preterm birth. This could be due to indicative antihypertensive treatment with methyldopa in pregnant women with diabetes or pregnancy related diabetes. The prevalence of diabetes among methyldopa-exposed pregnancies was found to be higher: 11.1% compared with 3.9% among beta-blocker-exposed pregnancies. Increased risk of preterm birth was still seen after adjusting our analyses for additional confounding variables in model 2. We found no association between exposure to methyldopa and perinatal mortality. These findings are consistent with those of a previous study.[3]

Calcium channel blockers are considered to be safe during pregnancy.[3,22] We found that exposure to calcium channel blockers was associated with being born SGA and with preterm birth. The risk of being born SGA and preterm of birth remained after adjusting our analyses for additional confounding variables in model 2. We found no statistically significant association between calcium channel blocker exposure during pregnancy and perinatal mortality.

We chose to analyse two outcomes previously reported to be associated with beta-blocker exposure during pregnancy —SGA and preterm birth[1,10,23] — that have been associated with increased perinatal mortality in previous studies.[12,13] Therefore we investigated the risk of perinatal mortality among beta-blocker-exposed pregnancies. We compared risks associated with exposure to beta-blockers with exposure to methyldopa and calcium channel blockers to assess possible confounding by indication. Our analyses show a similar risk of being born SGA and an

increased risk of preterm birth for all recommended agents during pregnancy. There are various possible explanations for this finding. It is possible that the underlying indication for treatment, maternal disease, is the true risk factor. Possible maternal diseases include hypertension, either predating or complicating pregnancy. Accordingly, we were not able to rule out a potential effect of maternal disease on perinatal outcomes.

We found an association between exposure to beta-blockers during pregnancy and perinatal mortality. This association was not found for exposure to methyldopa and calcium channel blockers, which might be due to the small number of cases.

We believe that the similar risks found for exposure to the various beta-blockers and SGA, preterm birth, and perinatal mortality are a class effect. This seems to be true in spite of statistically significant differences in the basic characteristics of women exposed to labetalol and those exposed to other beta-blockers (table 2). After adjustments were made for these variables, we found comparable risk profiles for labetalol-exposed pregnancies and pregnancies exposed to other beta-blockers. Most beta-blockers are known to cross the placenta,[21,24] and effects on placental haemodynamics have been observed in both human and animal studies. A mechanism has been proposed of diminished placental blood flow due to the selective vasoconstriction of placental vessels by beta-blockers without intrinsic sympathomimetic activity.[24] This effect on placental haemodynamics could explain growth retardation of foetuses exposed to beta-blockers during pregnancy and might result in children being born SGA and preterm.

We defined exposure as redemption of at least two prescriptions between six months before conception and the twentieth week of gestation. At least one of these prescriptions had to be redeemed between conception and twentieth week of gestation. We believe that this model increases the probability of identifying continuous use that extends into pregnancy.

The rate of perinatal mortality in Denmark is low (table 3).[25] A large number of women exposed to beta-blockers, methyldopa, and calcium channel blockers are therefore needed to identify a possible risk increase associated with these outcomes. Our cohort comprises all births in Denmark between 1995 and 2008. This minimises confounding due to race, educational level, and other socio-economic factors. The national Danish registers cover the entire nation and are considered valid. As part of the national health care reimbursement scheme, Danish pharmacies are required by law to register all redeemed prescriptions. Approximately 97.5% of all redeemed prescriptions are registered in the Danish Prescription register.[16] Our study includes data on exposure to beta-blockers based on information on prescriptions paid for at the pharmacy, and not only prescribed by the physician, thereby increasing the probability of exposure. Furthermore, our study was not confounded by recall bias since information was recorded prospectively. The Danish Fertility Database contains more than 99% of all births during the study period.[14]

Limitations of our study include missing information on maternal weight and alcohol consumption. We were unable to adjust for treatment indication and severity of maternal disease. Given the study design, we were not able to address this issue further, nor were we able to rule out confounding by indication, the underlying maternal disease, as a possible explanation for our findings. Consequently we were unable to differentiate between a possible class effect of beta-blockers and the effect of the underlying maternal disease.

Unfortunately information on diagnoses of essential hypertension was not available, since these are known risk factors for our primary outcomes.

The prevalence of pre-eclampsia and eclampsia in the cohort is based on primary discharge diagnoses from hospital admissions. We did not use secondary diagnoses, since these in general are not validated. We estimated exposure from National Prescription Registry data, which contains information on all redeemed prescriptions.[16] Overestimation of exposure is therefore a

possibility, since we cannot adjust for a potential lack of compliance. However, in a study by Olesen et al. conducted in a cohort of pregnant Danish women in the county of North Jutland,[26] compliance with prescribed beta-blockers was estimated to be complete, strengthening the validity of our analyses. Furthermore, overestimation of exposure would bias the estimates towards unity.

There is a general consensus that labetalol is safer than other beta-blockers during pregnancy and this drug is rapidly becoming the first-line choice in conditions such as chronic hypertension during pregnancy.[21,23] We found an association between redeeming prescriptions for beta-blockers and being born SGA, preterm birth, and perinatal mortality. Risk profiles for pregnancies exposed to labetalol and to other beta-blockers were similar. ~~Our findings therefore suggest that future treatment of pregnant women with beta-blockers should be based primarily on the individual needs of the mother and not of the unborn child.~~ The increasing use and uncertainty of effects and possible side effects of treatment with beta-blockers during pregnancy call for further studies to validate our findings.

Conflicts of interests

The authors have no relevant conflict of interests.

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