

β -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 β -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. The authors identified all pregnant women redeeming a prescription for β -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: 911'685 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 10th 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, fetal 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: The authors identified 2459 pregnancies exposed to β -blockers. β -Blocker exposure during pregnancy was found to be associated with increased risk of SGA (adjusted OR 1.97, 95% CI 1.75 to 2.23), preterm birth (adjusted OR 2.26, 95% CI 2.03 to 2.52) and perinatal mortality (adjusted OR 1.89, 95% CI 1.25 to 2.84). Analyses were adjusted for socioeconomic and maternal variables. The authors found similar risk profiles for pregnancies exposed to labetalol and for pregnancies exposed to other β -blockers.

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

ARTICLE SUMMARY

Article focus

- There is contradictory evidence concerning the consequences of β -blocker treatment during pregnancy.
- This survey explores the effects of β -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 β -blockers.

Key messages

- Redeeming prescriptions of β -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 β -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

β -Blockers are widely used in the treatment of chronic hypertension,^{1–4} migraine,⁵ essential tremor⁶ and various other conditions. There is contradictory evidence concerning the consequences of β -blocker treatment during pregnancy. Some studies report an association between β -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

associated with increased risk of perinatal mortality.^{12 13} We set out to investigate whether the use of β -blockers during pregnancy was associated with being born SGA, preterm birth and perinatal mortality in a nationwide survey between 1995 and 2008.

METHODS

Study population

We used data obtained from three nationwide registries: the Danish Fertility Database,¹⁴ the Danish National Hospital Register¹⁵ and the National Prescription Register.¹⁶ Data concerning income and educational level were obtained, respectively, from the Income Statistics Register¹⁷ and the Danish Education Register,¹⁸ both of which are provided by Statistics Denmark. In Denmark, all citizens are given a unique 10-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 20th 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 1977¹⁵ in accordance with the Danish revision of the 10th International Classification of Diseases 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 β -blockers as the redemption of at least two prescriptions between 6 months before conception and the 20th week of gestation. At least one

of these prescriptions had to be redeemed between conception and the 20th week of gestation.

We assessed exposure to β -blockers by identifying redeemed prescriptions with ATC code C07. Furthermore, we identified the most frequently redeemed β -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 β -blockers.

We divided β -blocker exposure into exposure to labetalol and exposure to other β -blockers. The latter group was formed because there were few redeemed prescriptions of individual β -blockers other than labetalol. We compared risks associated with exposure to β -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 comedication 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 10th 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, fetal 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 V.9.2 (SAS Institute Inc.). 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 and >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 and ≥ 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 socioeconomic variables in model 1 and additional confounding variables: smoking

status, comedication (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 and >20).

When estimating the risk of perinatal mortality, analyses were further adjusted for previous stillbirths. ORs are presented with 95% CIs. For description of basic characteristics, we used frequencies with percentages. We used χ^2 tests to analyse differences in the propor-

tions 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 β -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 β -blocker prescriptions.

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

Characteristics	β -Blocker exposed (n=2459), n (%)	β -Blocker unexposed (n=909 228), n (%)	p Value*	Propensity matched, (n=9662), n (%)	p Value*
Educational level					
Low	739 (30.05)	311 600 (35.45)	<0.001	2965 (30.69)	0.991
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)					
0–36 770	509 (23.99)	226 228 (24.84)	<0.001	1924 (19.91)	0.989
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)	
\geq 74 700	693 (28.18)	227 448 (24.98)		2770 (28.67)	
Parity					
1	900 (36.60)	394 661 (43.29)	<0.001	3487 (28.87)	0.998
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)					
<20	18 (0.73)	26 321 (2.89)	<0.001	68 (0.56)	1.000
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†					
0	1548 (80.29)	572 642 (81.15)	0.427	6140 (81.81)	0.385
1–10	251 (13.02)	90 033 (12.76)		913 (12.16)	
11–20	114 (5.19)	36 201 (5.13)		394 (5.25)	
>20	15 (0.78)	4849 (0.69)		59 (0.79)	
Statins					
Used	5 (0.20)	111 (0.01)	<0.001	14 (0.14)	0.492
Not used	2454 (99.8)	909 115 (99.99)		9648 (99.86)	
Antiobesity preparations (A10)					
Used	9 (0.40)	1539 (0.17)	0.018	23 (0.24)	0.251
Not used	2450 (99.6)	907 687 (99.83)		9639 (99.76)	
Insulins and analogues					
Used	101 (4.11)	4208 (0.46)	<0.001	412 (4.14)	0.782
Not used	2358 (95.89)	905 018 (99.53)		9250 (95.74)	
Pre-eclampsia diagnosis (O13–O15)					
Yes	99 (4.03)	7806 (0.86)	<0.001	–	
No	2360 (95.97)	901 420 (99.14)		–	

* χ^2 tests were used to assess the overall p value for the group comparison.

†Information on smoking was only available for 1996–2007.

RESULTS

Table 1 presents maternal characteristics in β -blocker-exposed and unexposed women (number and percentage of pregnancies). We identified 2381 pregnancies exposed to only one β -blocker, 1452 exposed to labetalol only and 929 exposed to other β -blockers. Ninety-eight pregnancies were exposed to more than one β -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 β -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 β -blocker-exposed group. The proportion of pregnancies complicated by pre-eclampsia was higher among β -blocker-exposed pregnancies. There was no difference in smoking prevalence between β -blocker-exposed and unexposed women (table 1).

Women redeeming labetalol prescriptions were older, had a higher education level and a higher prevalence of pre-eclampsia and smoking than women exposed to other β -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 comedication with statins and antiobesity preparations between the two groups. Diagnoses of migraine and arrhythmias were more common among women exposed to any other β -blocker. Women exposed to other β -blockers had higher parity than those exposed to labetalol.

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

Small for gestational age

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 β -blocker. We found a higher proportion of SGA among women exposed to β -blockers compared with unexposed women. Women exposed to labetalol or to other β -blockers had similarly higher ORs 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 β -blockers. We found an association between preterm birth and β -blocker exposure compared with unexposed women. Those exposed to labetalol or to other β -blockers had similarly higher ORs 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 β -blockers. We found a higher

Table 2 Basic characteristics for pregnancies exposed to labetalol compared with pregnancies exposed to other β -blockers

Characteristics	Labetalol (n = 1452), n (%)	Other β -blockers (n = 929), n (%)	p Value*
Educational level			
Low	391 (26.93)	321 (34.55)	<0.001
Medium	571 (39.33)	369 (39.72)	
High	462 (31.82)	226 (24.33)	
Annual household income (GBP)			
0–36 770	202 (13.91)	289 (31.11)	0.138
36 771–52 703	223 (15.36)	357 (38.43)	
52 704–74 699	228 (15.70)	413 (44.46)	
\geq 74 700	275 (19.94)	393 (42.30)	
Parity			
0	512 (35.26)	363 (39.07)	0.004
1	586 (40.36)	308 (33.15)	
2	256 (17.63)	179 (19.27)	
\geq 3	98 (6.75)	79 (8.50)	
Age (years)			
<20	7 (0.58)	10 (1.08)	<0.001
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†			
0	933 (64.26)	565 (60.82)	<0.001
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			
Yes	5 (0.34)	9 (0.97)	0.052
No	1447 (99.66)	920 (99.03)	
Statins			
Yes	5 (0.34)	1 (0.10)	0.261
No	1447 (99.66)	928 (99.90)	
Insulins and analogues			
Yes	83 (5.72)	16 (1.72)	<0.001
No	1369 (94.28)	913 (92.28)	
Migraine			
Yes	26 (1.79)	46 (4.95)	<0.001
No	1426 (98.21)	883 (95.05)	
Pre-eclampsia diagnosis			
Yes	74 (5.10)	21 (2.26)	0.001
No	1378 (94.90)	908 (97.84)	
Arrhythmia			
Yes	23 (1.58)	82 (8.83)	<0.001
No	1429 (98.42)	847 (91.17)	
Essential tremor			
Yes	—	3 (0.33)	0.030
No	1452 (100)	926 (99.67)	

* χ^2 tests were used to assess the overall p value for the group comparison.

†Information on smoking was only available for 1996–2007.

rate of perinatal mortality among women exposed to β -blockers (table 3).

When stratifying for different β -blockers, we found 30 perinatal deaths among labetalol-exposed pregnancies.

Table 3 ORs with 95% CIs for SGA, preterm birth and perinatal death for exposure to β -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 β -blockers (n=2459)	446 (18.14)	1.93 (1.74 to 2.14)	1.99 (1.79 to 2.21)	1.97 (1.75 to 2.23)
Labetalol only (n=1452)	258 (17.77)	1.88 (1.64 to 2.15)	1.95 (1.70 to 2.24)	2.02 (1.72 to 2.37)
Other β -blockers (n=929)	179 (19.27)	2.08 (1.76 to 2.44)	2.11 (1.79 to 2.49)	2.01 (1.66 to 2.43)
Methyldopa (n=515)	61 (11.84)	1.17 (0.89 to 1.53)	1.32 (1.01 to 1.73)	1.43 (1.04 to 1.96)
CCBs (n=86)	21 (24.42)	2.30 (1.42 to 3.73)	2.24 (1.36 to 3.67)	1.88 (1.02 to 3.49)
Preterm birth				
Unexposed (n=909 226)	109 163 (12.01)	Reference	Reference	Reference
All β -blockers (n=2459)	697 (28.34)	2.9 (2.66 to 3.14)	2.71 (2.48 to 2.97)	2.26 (2.03 to 2.52)
Labetalol only (n=1452)	473 (32.58)	3.54 (3.17 to 3.95)	3.33 (2.98 to 3.72)	2.74 (2.39 to 3.13)
Other β -blockers (n=929)	206 (22.17)	2.08 (1.78 to 2.43)	1.93 (1.65 to 2.26)	1.69 (1.41 to 2.03)
Methyldopa (n= 515)	216 (41.94)	5.29 (4.44 to 6.31)	5.03 (4.21 to 6.01)	4.21 (3.38 to 5.23)
CCBs (n=86)	26 (30.23)	2.55 (1.63 to 3.99)	2.50 (1.60 to 3.89)	2.15 (1.26 to 3.67)
Perinatal mortality				
Unexposed (n=909 226)	6048 (0.67)	Reference	Reference	Reference
All β -blockers (n=2459)	44 (1.79)	2.72 (2.02 to 3.67)	2.69 (1.98 to 3.65)	1.89 (1.25 to 2.84)
Labetalol only (n=1452)	30 (2.07)	3.15 (2.19 to 4.52)	3.24 (2.25 to 4.67)	2.08 (1.26 to 3.44)
Other β -blockers (n=929)	13 (1.39)	2.12 (1.22 to 3.66)	1.92 (1.08 to 3.40)	1.72 (0.85 to 3.48)
Methyldopa (n=515)	4 (0.78)	1.15 (0.43 to 3.07)	1.16 (0.43 to 3.12)	0.35 (0.05 to 2.50)
CCBs (n=86)	1 (1.16)	1.78 (0.25 to 12.57)	2.00 (0.28 to 14.83)	3.26 (0.45 to 23.77)

Analyses are adjusted for maternal age, household income, educational level, parity, birth year and prior stillbirths.

*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).

Labetalol exposure was associated with increased risk of perinatal mortality (table 3).

We identified 13 perinatal deaths among pregnancies exposed to other β -blockers. Exposure to other β -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 four 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).

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

Additionally, we found an association between exposure to CCBs and increased risk of preterm birth in all models. As with methyldopa, exposure to CCBs 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 β -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 to 2.19); preterm birth, OR 2.40 (95% CI 2.16 to 2.67); perinatal mortality, OR 3.22 (95% CI 2.15 to 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 β -blockers during pregnancy and being born SGA, preterm birth and perinatal mortality. In addition, we found an association between redeeming prescriptions of methyldopa and CCBs, being born SGA and preterm birth. Methyldopa and CCBs were not found to be associated with perinatal mortality.

We found exposure to any β -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 β -blockers (OR 6.00, 95% CI 1.06 to 33.87) and labetalol (OR 2.26, 95% CI 1.04 to 4.88).⁹ Labetalol is generally considered safe for use during pregnancy.^{1 8 21}

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

We found an association between exposure to β -blockers and perinatal mortality. When stratifying for different β -blockers, we found this association to be statistically significant for exposure to labetalol and other β -blockers. When adjusting our analysis for maternal comorbidity, comedication 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 trimesters⁹: OR 1.70 (95% CI 1.00 to 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 β -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

CCBs are considered to be safe during pregnancy.^{3 22} We found that exposure to CCBs 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 CCB exposure during pregnancy and perinatal mortality.

We chose to analyse two outcomes previously reported to be associated with β -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 β -blocker-exposed pregnancies. We compared risks associated with exposure to β -blockers with exposure to methyldopa and CCBs 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 β -blockers during pregnancy and perinatal mortality.

This association was not found for exposure to methyldopa and CCBs, which might be due to the small number of cases.

We believe that the similar risks found for exposure to the various β -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 β -blockers (table 2). After adjustments were made for these variables, we found comparable risk profiles for labetalol-exposed pregnancies and pregnancies exposed to other β -blockers. Most β -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 β -blockers without intrinsic sympathomimetic activity.²⁴ This effect on placental haemodynamics could explain growth retardation of fetuses exposed to β -blockers during pregnancy and might result in children being born SGA and preterm.

We defined exposure as redemption of at least two prescriptions between 6 months before conception and the 20th week of gestation. At least one of these prescriptions had to be redeemed between conception and 20th 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 β -blockers, methyldopa and CCBs 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 socioeconomic factors. The national Danish registers cover the entire nation and are considered valid. As part of the national healthcare 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 β -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 β -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 contain 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*²⁶ conducted in a cohort of pregnant Danish women in the county of North Jutland, compliance with prescribed β -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 β -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 β -blockers and being born SGA, preterm birth and perinatal mortality. Risk profiles for pregnancies exposed to labetalol and to other β -blockers were similar. The increasing use and uncertainty of effects and possible side effects of treatment with β -blockers during pregnancy call for further studies to validate our findings.

Contributors KMP, EJ-S, JTA and HEP conceptualised the study. MP, KB, LK and CT-P assisted with the study design. KMP performed the analyses assisted by EJ-S, and JTA, MP, KB, LK, CT-P and HEP assisted in the interpretation. KMP, EJ-S, JTA, MP, KB, LK, CT-P and HEP wrote and revised the final manuscript. Figure design was done by KMP, EJ-S, JTA, MP, KB, LK, CT-P and HEP. All authors approved the final version to be published.

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REFERENCES

- Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med* 1996;335:257–65.
- Magee LA, Ornstein MP, von Dadelszen P. Fortnightly review: management of hypertension in pregnancy. *BMJ* 1999;318:1332–6.
- Afifi Y, Churchill D. Pharmacological treatment of hypertension in pregnancy. *Curr Pharm Des* 2003;9:1745–53.
- Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2003; (3):CD002863.
- Lyons KE, Pahwa R. Pharmacotherapy of essential tremor: an overview of existing and upcoming agents. *CNS Drugs* 2008;22:1037–45.
- Modi S, Lowder DM. Medications for migraine prophylaxis. *Am Fam Physician* 2006;73:72–8.
- Sibai BM, Gonzalez AR, Mabie WC, *et al*. Comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. *Obstet Gynecol* 1987;70:323–7.
- Magee LA, Elran E, Bull SB, *et al*. Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials. *Eur J Obstet Gynecol Reprod Biol* 2000;88:15–26.
- Nakhai-Pour HR, Rey E, Berard A. Antihypertensive medication use during pregnancy and the risk of major congenital malformations or small-for-gestational-age newborns. *Birth Defects Res B Dev Reprod Toxicol* 2010;89:147–54.
- Lydaki C, Lip GY, Beevers M, *et al*. Atenolol and foetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999;12:541–7.
- Abalos E, Duley L, Steyn DW, *et al*. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2007;(1):CD002252.
- Zeitlin J, El AM, Jarreau PH, *et al*. Impact of foetal growth restriction on mortality and morbidity in a very preterm birth cohort. *J Pediatr* 2010;157:733–9.
- Challis JR, Lye SJ, Gibb W, *et al*. Understanding preterm labor. *Ann N Y Acad Sci* 2001;943:225–34.
- Knudsen LB. The Danish fertility database. *Dan Med Bull* 1998;45:221–5.
- Andersen TF, Madsen M, Jorgensen J, *et al*. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–8.
- Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;44:445–8.
- Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health* 2011;39(7 Suppl):103–5.
- Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011;39(7 Suppl):91–4.
- Pedersen CB, Gotzsche H, Moller JO, *et al*. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441–9.
- Knudsen LB, Børllum Kristensen F. Monitoring perinatal mortality and perinatal care with a national register: content and usage of the Danish Medical Birth Register. *Community Med* 1986;8:29–36.
- Karthikeyan VJ, Lip GY. Hypertension in pregnancy: pathophysiology and management strategies. *Curr Pharm Des* 2007;13:2567–79.
- Magee LA, Schick B, Donnenfeld AE, *et al*. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. *Am J Obstet Gynecol* 1996;174:823–8.
- Podymow T, August P. Update on the use of antihypertensive drugs in pregnancy. *Hypertension* 2008;51:960–9.
- Lennestad R, Otterblad OP, Kallen JO. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. *Eur J Clin Pharmacol* 2009;65:615–25.
- World Health Organization. *Levels & Trends in Child Mortality. Report 2011. Estimates Developed by the UN Inter-agency for Child Mortality Estimation*. World Health Organization, 2011. http://www.who.int/child_adolescent_health/documents/child/childmortality_booklet_2011.pdf. Ref type: online source.
- Olesen C, Sondergaard C, Thrane N, *et al*. Do pregnant women report use of dispensed medications? *Epidemiology* 2001;12:497–501.