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Research article

Use of antihypertensive medications in pregnancy and the risk of adverse perinatal outcomes: McMaster Outcome Study of Hypertension In Pregnancy 2 (*MOS HIP 2*)

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Abstract

Background: Uncertainty remains about the potential harmful effects of antihypertensive therapy on the developing fetus, especially for beta-blockers (βb).

Methods: We prospectively enrolled all singleton women with a blood pressure ≥ 140/90 mm Hg during pregnancy. The main analysis included 1948 women with all forms of hypertension and compared the use of βb drugs, non-βb drugs or a combination of both, to no treatment. The primary study outcome was a composite of the diseases of prematurity, need for assisted ventilation for greater than 1 day, or perinatal death. A sub-group analysis evaluated the four treatment options among 583 singleton women with chronic hypertension before 20 weeks gestation.

Results: In the main analysis, no association was observed between βb use and the primary composite outcome [adjusted odds ratio (OR) 1.4, 95% CI 0.9–2.2], while an association was seen with non-βb therapy (OR 5.0, 95% CI 2.6–9.6) and combination therapy (OR 2.9, 95% CI 1.8–4.7). In the sub-group of 583 women with hypertension before 20 weeks, use of a non-βb drug (OR 4.9, 95% CI 1.7–14.2) or combination therapy (OR 2.9. 95% CI 1.1–7.7) was significantly associated with the primary composite outcome, while βb monotherapy was not (OR 1.4, 95% CI 0.6–3.4).

Conclusions: Maternal use of antihypertensive medications other than βbs was associated with both major perinatal morbidity and mortality, while βb monotherapy was not. The combined use of βb and non-βb medications demonstrated the strongest association. Before definitive conclusions can be drawn, a large multicentre randomized controlled trial is needed to address the issues of both maternal efficacy and fetal safety with the use of one or more antihypertensive agents in pregnancy.

Background

The effects of maternal antihypertensive drug use during pregnancy on fetal growth and well being remain uncertain [1]. Meta-analyses of randomized clinical trials have

highlighted the possible association between antihypertensive therapy and both intrauterine growth restriction (IUGR) and small for gestational age birthweight (SGA) [2], especially with the use of beta-blockers (βb) [3]. Pooling data from these clinical trials is questionable, however, because of large differences in design, patient characteristics and the various therapies studied [4]. When the results of clinical trials were systematically analyzed on an individual basis, without pooling, there was no evidence for fetal harm or growth restriction with βb use [5], with the exception of one small trial [6].

Despite the availability of level I evidence, knowledge about the effects of βb and other antihypertensive drugs on perinatal health remains limited. For example, few studies have evaluated the use of multiple drug therapy in pregnancy, especially within a routine clinical practice setting. Second, previous studies that compared βb with other antihypertensive agents typically enrolled fewer than 100 women, thereby lacking adequate statistical power to address rare but important adverse perinatal events, including perinatal mortality [5]. Accordingly, we undertook a study of the association between antihypertensive drug use in pregnancy and the risk of major perinatal events, while controlling for other important determinants of perinatal well-being. Our primary goal was to examine whether βbs were associated with higher perinatal morbidity and mortality compared to either no therapy or use of non-βb antihypertensive agents.

Methods

Data collection

We conducted a cohort study from January 1986 to December 1995. We prospectively enrolled all pregnant women whose sitting systolic blood pressure was ≥ 140 mm Hg or whose diastolic pressure was ≥ 90 mm Hg. All participants were originally seen through the Obstetrics Service at the McMaster University Medical Center, either on an outpatient or inpatient basis. The patients were consecutively recruited before delivery, and accounted for approximately 98 percent of all hypertensive pregnant women who delivered at our hospital. McMaster University Medical Centre is a major referral center for high-risk obstetrics patients and has a level III nursery.

Each participant's hospital identification number was recorded at the time of presentation, and mother and infant data were subsequently abstracted from their hospital charts by two authors (R.B. and E.B.) three months after the patient's date of confinement. The three-month delay allowed for the recording of complete information on early infant outcomes. Data were recorded using a standard data collection form and entered into a computer database (SPSS, SPSS Inc, Chicago, IL).

The four types of hypertension in pregnancy were classified according to the taxonomy and definitions of the 1990 National High Blood Pressure Education Program Working Group [7]. Hence, women with *de novo* pregnancy-acquired hypertension were sub-divided into those with gestational hypertension or preeclampsia, while those with chronic hypertension (i.e., hypertension before 20 weeks gestation) were separated into those with or without superimposed preeclampsia. The development of preeclampsia was defined by hypertension in association with the presence of at least 2+ proteinuria or 300 mg of urinary protein per 24-hour specimen collection [7].

Antihypertensive drug use

Antihypertensive drug use was defined as the receipt of at least one dose of that agent, regardless of the route of administration, dose or duration of use, gestational age at initiation, or type or degree of hypertension. Information on the drug dose or its duration of use was not recorded. Antihypertensive agents were classified as βbs (i.e., atenolol, propranolol, metoprolol, acebutatolol or labetolol), non-βb drugs (i.e., nifedipine, methyldopa, hydralazine, captopril, enalapril, furosemide or hydrochlorothiazide), or combined/multiple concomitant therapy (i.e., βb plus non-βb drug). Magnesium sulphate was not considered to be an antihypertensive drug.

Although no formal standard for the use of antihypertensive therapy in pregnancy was in effect at McMaster University, there was a general consensus among the attending Obstetricians and Perinatologists. Therapy was typically administered to women whose BP was greater than 140/90 mm Hg in the presence of proteinuria, headache, or symptoms suggestive of preeclampsia, and at a BP greater than 150/95 mm Hg in the absence of any symptoms.

Perinatal outcomes

The primary study outcome was the composite of either a disease of prematurity (i.e., necrotizing enterocolitis, periventricular hemorrhage and/or hyaline membrane disease), need for assisted ventilation for greater than 1 day, and/or perinatal death after 20 weeks gestation and up to 30 days after birth [8,9]. Secondary outcomes included SGA, defined as a birthweight below the 10th centile for gestational age [10,11]; preterm birth before 32 or 37 weeks gestation [12,13]; development of one or more diseases of prematurity; need for mechanical ventilation for greater than 1 day [11]; perinatal death; or admission to the neonatal intensive care unit (NICU) [14,15].

Statistical analysis

In the main analysis, the association between antihypertensive drug use (i.e., βb drugs, non-βb drugs, or a com-

bination of both) was compared to non-use as the referent for each study outcome. Using multiple logistic regression analysis, estimates of the odds ratio were adjusted for maternal age, parity, pre-pregnancy weight (by quartiles), history of delivery before 34 weeks, history of hypertension in a previous pregnancy, cigarette smoking, pre-pregnancy diabetes mellitus, pre-pregnancy renal dysfunction, use of prednisone, receipt of betamethasone for fetal lung maturity (not included in the analyses of SGA and preterm delivery), and gestational age at which blood pressure (BP) first increased above 140 mm Hg systolic or 90 mm Hg diastolic.

To evaluate the effect of a potentially longer duration of drug use, we conducted a subgroup analysis of women with hypertension before 20 weeks gestation, using the same exposure variables as in the main analysis. Individual study outcomes included the primary composite outcome of perinatal morbidity and mortality, SGA, and preterm birth before 32 and 37 weeks gestation. We adjusted for the variables included in the main analysis, in addition to the presence of preeclampsia, but no longer controlled for the gestational age at which the BP first rose above 140/90 mm Hg. Preeclampsia was included to account for the possible confounding effect of superimposed preeclampsia on preterm birth, SGA or the diseases of prematurity [16].

In the main analysis, baseline maternal characteristics were compared across groups using either one-way ANOVA for continuous variables or the chi-square test for categorical data. All p-values were two-sided, and significance was set at a value of 0.05. Statistical analyses were performed using SAS Version 8 (SAS Institute Inc., Cary, North Carolina). The McMaster University Medical Ethics Committee was consulted at the commencement of the study in 1986. The committee determined that formal consent was not required because all maternal and newborn personal identifiers were omitted during data entry, which preserved patient anonymity and prevented future patient contact.

Results

During the study period, there were 21 723 births at McMaster University Medical Centre. A total of 1948 singleton hypertensive pregnancies (9 percent) were studied, of which of 864 women (44.4 percent) had gestational hypertension, 459 (23.6 percent) isolated chronic hypertension, 501 (25.7 percent) isolated preeclampsia, and 124 (6.4 percent) had chronic hypertension with superimposed preeclampsia. Selected baseline characteristics are shown in Table 1.

The various therapies used among all hypertensive women, as well as those with chronic hypertension, are shown in Table 2. Approximately half of all women did not receive an antihypertensive drug, while the remainder received either monotherapy (29.2%) or multiple drugs (20.5%). Of the 968 women with any form of hypertension who also received active drug therapy, 783 (80.9%) were on at least a βb and 631 (65.2%) on a non-βb. Atenolol comprised over 90% of all βb drug use, and labetolol less than 5% (Table 2). Of the non-βb drugs, short- or long-acting nifedipine was used most frequently among all hypertensive women (39%) as well as those with chronic hypertension (48%), followed by methyldopa (28% and 38%, respectively) and hydralazine (13% and 20%, respectively).

Main analysis of women with all forms of hypertension

Compared to women who received no antihypertensive treatment, use of βbs was not associated with an increased risk for the primary composite outcome (rate 30.9%; OR 1.4, 95% CI 0.9–2.2), while both non-βb therapy (rate 56.7%; OR 5.0, 95% CI 2.6–9.6) and multiple therapy (rate 59.2%; OR 2.9, 95% CI 1.8–4.7) were (Table 3). Similar associations were observed for the diseases of prematurity and the need for neonatal ventilation for more than 24 hours (Table 3). Admission to the NICU was significantly more likely among the offspring of mothers who received βb (OR 2.4, 95% CI 1.6–3.5), and was even more pronounced in the non-βb (OR 9.9, 95% CI 4.7–21.0) and multiple therapy (OR 19.2, 95% CI 10.9–30.4) groups. Compared with the rate of 1.9% in the reference (non-treatment) group, βb use was not associated with an significantly elevated rate of perinatal death (rate 3.7%; OR 1.5, 95% CI 0.6–3.4), while non-βb therapy (rate 5.8%; OR 2.6, 95% CI 1.1–6.3) and combination therapy (rate 7.1%; OR 3.1, 95% CI 1.4–6.8) were (Table 3).

A higher risk for SGA was observed among the offspring of women who received a βb agent (OR 2.3, 95% CI 1.3–3.4), a non-βb agent (OR 2.1, 95% CI 1.3–3.4), or both (OR 2.7, 95% CI 1.8–3.9) (Table 4). The rate of preterm delivery before 32 weeks was also higher with βb use than with no active treatment (14.7% versus 1.9%, respectively; OR 7.6, 95% CI 4.1–14.1), rising to 20.7% with non-βb therapies (OR 13.4, 95% CI 6.8–26.2) and to 34.7% with combined therapy (OR 21.1, 95% CI 11.6–38.3). Similar associations were seen for preterm delivery before 37 weeks (βb group: OR 5.1, 95% CI 3.8–6.9; non-βb group: OR 10.3, 95% CI 7.0–15.3); combination therapy: OR 41.2, 95% CI 27.7–61.2) (Table 4).

Subgroup analysis of women with chronic hypertension

There were 583 women with hypertension before 20 weeks gestation (Table 5). Both non-βb (OR 4.9, 95% CI 1.7–14.2) and combined antihypertensive therapy (OR 2.9. 95% CI 1.1–7.7) were significantly associated with

Table 1: Baseline characteristics of women with various forms of hypertension during singleton pregnancies

Characteristic	**No anti-hypertensive drug (n = 980)**	**β-blocker drug (n = 428)**	**Non-β-blocker drug (n = 188)**	**β-blocker and non-β-blocker drug (n = 352)**	***Statistical comparison across groups***
Maternal age (yr)					
Mean (SD)	29.5 (4.9)	29.8 (4.9)	29.2 (5.8)	28.8 (5.6)	p = 0.04
No. (%)					
< 20	22 (2.3)	10 (2.3)	8 (4.3)	20 (5.7)	
20–35	845 (86.2)	366 (85.5)	146 (77.6)	288 (81.8)	
> 35	113 (11.5)	52 (12.2)	34 (18.1)	44 (12.5)	
No. (%) primigravidae	448 (45.7)	175 (40.9)	83 (44.2)	125 (35.5)	p = 0.008
*No. (%) with prior preterm delivery before 34 weeks**	50 (12.8)	33 (20.9)	16 (21.1)	29 (27.4)	p = 0.002
No. (%) with pre-pregnancy diabetes mellitus	42 (4.3)	14 (3.3)	16 (8.5)	6 (1.7)	p = 0.001
No. (%) with renal dysfunction	34 (3.5)	25 (6.0)	22 (11.8)	22 (6.4)	p < 0.0001
No (%) smokers	96 (9.8)	38 (9.1)	17 (9.1)	37 (10.8)	p = 0.9
Mean (SD) pre-pregnancy weight, kg	71.7 (16.4)	71.3 (16.6)	71.2 (18.5)	69.4 (15.9)	p = 0.2
No. (%) according to hypertension type					
Gestational hypertension	627 (64.0)	165 (38.6)	33 (17.6)	39 (11.1)	p < 0.001
Chronic hypertension	229 (23.4)	122 (28.5)	58 (30.9)	50 (14.2)	p < 0.001
Chronic hypertension plus superimposed preeclampsia	18 (1.8)	22 (5.1)	25 (13.3)	59 (16.8)	p < 0.001
Isolated preeclampsia	106 (10.8)	119 (27.8)	72 (38.3)	204 (58.0)	p < 0.001

*Excludes all primigravidae

Table 2: Antihypertensive therapy among singleton pregnant women with either all forms of hypertension or hypertension before 20 weeks gestation

	No. (%)	
Drug use	***Women with all forms of hypertension (n = 1948)***	***Women with hypertension before 20 weeks gestation (n = 583)***
By number of drugs		
None	980 (50.3)	247 (42.4)
Single agent	569 (29.2)	207 (35.5)
Multiple agents	399 (20.5)	129 (22.1)
Total	**1948 (100.0)**	**583 (100.0)**
By drug class		
*i) Beta-blockers**		
Atenolol	743 (94.9)	236 (92.9)
Labetolol	29 (3.7)	10 (3.9)
Propranolol	8 (1.0)	6 (2.4)
Acebutalol	3 (0.4)	2 (0.8)
Total	**783 (100.0)**	**254 (100.0)**
*ii) Non-beta-blockers**		
Nifedipine	301 (47.7)	93 (38.9)
Methyldopa	175 (27.7)	91 (38.1)
Hydralazine	129 (20.4)	30 (12.6)
Enalapril or captopril	19 (3.0)	19 (7.9)
Hydrochlorothiazide	5 (0.8)	5 (2.1)
Furosemide	2 (0.3)	1 (0.4)
Total	**631 (100.0)**	**239 (100.0)**

*Represents use of that agent either alone or in combination with one or more drugs.

Table 3: Rate and adjusted odds ratios (OR) for adverse perinatal outcomes among the offspring of women with any form of hypertension, according to type of antihypertensive therapy received during pregnancy

	Individual outcomes									
	Primary composite outcome*		Diseases of prematurity$		Ventilation > 1 day		Neonatal intensive care unit admission		Perinatal death	
Type of antihypertensive therapy	Rate (%)**	Adjusted OR (95% CI)#	Rate (%)	Adjusted OR (95% CI)	Rate (%)	Adjusted OR (95% CI)	Rate (%)	Adjusted OR (95% CI)	Rate (%)	Adjusted OR (95% CI)
None	19.5	1.0	15.1	1.0	3.4	1.0	27.4	1.0	1.9	1.0
β-blocker	30.9	1.4 (0.9–2.2)	26.2	1.4 (0.9–9.2)	10.9	2.3 (0.9–5.9)	48.7	2.4 (1.6–3.5)	3.7	1.5 (0.6–3.4)
Non-β-blocker	56.7	5.0 (2.6–9.6)	49.1	4.4 (2.1–9.2)	24.6	6.9 (2.3–20.6)	77.2	9.9 (4.7–21.0)	5.8	2.6 (1.1–6.3)
Both β-blocker and non-β-blocker	59.2	2.9 (1.8–4.7)	55.6	2.8 (1.7–4.8)	31.0	3.7 (1.4–9.4)	87.4	18.2 (10.9–30.4)	7.1	3.1 (1.4–6.8)

*Defined as a composite of either hyaline membrane disease (HMD), necrotizing enterocolitis (NEC), periventricular hemorrhage (PVH), assisted ventilation > 1 day, or perinatal death after 20 weeks gestation and up to 30 days after birth. **Represents the rate for each perinatal outcome according to type of antihypertensive therapy $Includes HMD, NEC and/or PVH. #All odds ratios were adjusted for maternal age, parity, pre-pregnancy weight, history of delivery before 34 weeks, history of hypertension in a previous pregnancy, cigarette smoking, pre-pregnancy diabetes mellitus, pre-pregnancy renal dysfunction, use of prednisone, receipt of betamethasone for fetal lung maturity, and gestational age at which blood pressure first increased above 140/90 mm Hg.

the primary composite outcome, while use of a βb alone was not (OR 1.4, 95% CI 0.6–3.4). Compared to no treatment, isolated βb use was associated with both SGA (OR 2.3, 95% CI 1.1–4.5) and preterm delivery before 32 (OR 4.0, 95% 1.3–12.4) or 37 weeks (OR 4.0, 95% CI 2.3–6.9) (Table 5). A significant relationship was also seen for combined therapy, with an even higher risk for preterm birth before 37 weeks (OR 18.9, 95% CI 9.6–37.3). Finally, although treatment with a non-βb drug was not associated with SGA (OR 1.3, 95% CI 0.5–3.4) or preterm birth before 32 weeks (OR 2.0, 95% CI 0.5–7.4), it was associated with preterm delivery before 37 weeks (OR 4.2, 95% CI 2.2–8.1) (Table 5).

Discussion

In a large prospective cohort of women with hypertension during pregnancy, maternal use of antihypertensive medications other than βbs was associated with both major perinatal morbidity and mortality, while βb use was not. The greatest risks for adverse perinatal outcomes were related to the combined use of βb and non-βb medications. All forms of antihypertensive therapy were associated with a higher risk for SGA, preterm birth and admission to the NICU, and multiple therapy had the strongest association with these events. Similar relationships were evident in the sub-group of women with chronic hypertension during pregnancy, except that use of a non-βb drug was not associated with SGA or preterm birth before 32 weeks.

Several study limitations should caution the reader from drawing definitive conclusions about the impact of antihypertensive therapy on perinatal outcome. First, we did not obtain information on drug dose, duration of use or route of administration. Thus, this study provides no information about the existence of a dose-response relationship between drug use and adverse perinatal events. Because this was not a randomized clinical trial, bias due to confounding by indication was likely present, in that women with milder forms of hypertension may have received lower doses of oral therapy (e.g., atenolol), while those with more severe hypertension were probably prescribed a higher dose of an intravenous medication (e.g., hydralazine). However, we do know that because the most commonly used agents in this study – atenolol, nifedipine and methyldopa – were not available intravenously, their use probably extended beyond the acute management of severe maternal hypertension with impending delivery. Similarly, although we did not discriminate between the types of βb prescribed in our study sample, or between the various types of non-βb drugs, we may assume that most of these relationships are reflective of the use of atenolol, nifedipine and methyldopa.

Table 4: Rate and adjusted odds ratios (OR) for small for gestational age birthweight (SGA) and preterm birth among the offspring of women with any form of hypertension, according to type of antihypertensive therapy received during pregnancy

			Preterm birth			
	SGA		Before 32 weeks		Before 37 weeks	
Type of anti-hypertensive therapy	**Rate (%)***	**Adjusted OR (95% CI)****	**Rate (%)**	**Adjusted OR (95% CI)**	**Rate (%)**	**Adjusted OR (95% CI)**
None	9.0	1.0	1.9	1.0	12.2	1.0
β-blocker	19.9	2.3 (1.6–3.3)	14.7	7.6 (4.1–14.1)	45.3	5.1 (3.8–6.9)
Non-β-blocker	20.7	2.1 (1.3–3.4)	20.7	13.4 (6.8–26.2)	62.2	10.3 (7.0–15.3)
Both β-blocker and non-β-blocker	28.5	2.7 (1.8–3.9)	34.7	21.1 (11.6–38.3)	87.5	41.2 (27.7–61.2)

*Represents the rate for each perinatal outcome according to type of antihypertensive therapy **All odds ratios were adjusted for maternal age, parity, pre-pregnancy weight, history of delivery before 34 weeks, history of hypertension in a previous pregnancy, cigarette smoking, pre-pregnancy diabetes mellitus, pre-pregnancy renal dysfunction, use of prednisone, and gestational age at which blood pressure first increased above 140/90 mm Hg.

βb medications are contraindicated in individuals with specific diseases like asthma, a common condition whose presence in pregnancy has been associated with an increased risk for preeclampsia, preterm delivery and SGA [17]. Accordingly, absence of βb use may have been confounded by the presence of other diseases like asthma, which could explain the relatively lower degree of perinatal morbidity with βb therapy compared to non-βb treatments. Similarly, there may have been a lower threshold for induction of labor or Cesarean delivery among women who were referred to our center for the management of more complex or severe maternal hypertension or fetal disease. Thus, because these data may be biased, and their internal and external validity questioned, they may not be applicable to some women with stable, mild and asymptomatic hypertension.

Two Cochrane Collaboration systematic reviews have examined the use of βbs [3] as well as all types of medication [18] for the treatment of pregnant women with mild to moderate hypertension. In the first review, comprising 14 randomized trials of oral βbs versus placebo or no therapy [3], βbs decreased the risk of progression to severe hypertension (relative risk [RR] 0.37, 95% CI 0.26–0.53) and the need for additional antihypertensive drugs (RR 0.44, 95% CI 0.31–0.62) [3]. However, there was insufficient data to draw conclusions about the effect on perinatal mortality or preterm delivery, but βbs were minimally associated with SGA (RR 1.34, 95% CI 1.01–1.79). Among 11 trials, βbs appeared to be both equally effective and as safe as methyldopa [3]. In the second review, comparing antihypertensive drugs with placebo or no treatment, active therapy reduced the risk of severe hypertension (24 trials; RR 0.52, 95% CI 0.41–0.64), but not preeclampsia (19 trials; RR 0.99, 95% CI 0.84–1.18), perinatal death (23 trials; RR 0.71, 0.46–1.09), preterm birth (12 trials; RR 0.98, 95% CI 0.85–1.13), or SGA (17 trials; RR 1.13, 0.91–1.42) [18]. Thus, within a heterogeneous group of randomized trials [5], treatment of mild to moderate hypertension, whether in the form of βbs or other drugs, remains controversial.

The advantage of a large, prospective study like MOS HIP 2 is its ability to examine several important "hard" perinatal outcomes, and to generate estimates of effect size with statistical certainty. MOS HIP 2 provided information on perinatal outcomes within the realm of clinical practice, and included a broad array of women with different mechanisms and degrees of hypertension. By adjusting for multiple potential confounders, such as the gestational age at which the BP rose, we may have reduced the likelihood that antihypertensive drug use was merely a marker of both the acuity and degree of hypertension and, accordingly, the associated risk of preterm delivery and neonatal prematurity. Similarly, by limiting our sub-group analysis to women with chronic hypertension, we increased the likelihood that maternal exposure to antihypertensive therapy would be of longer duration. In doing so, there remained no relationship between βb use and the primary endpoint of major perinatal disease or death, an association that was observed for both non-βb and combination drug therapy.

The debate about whether βb drugs [3,5] or antihypertensive treatment in general [2,18] may cause IUGR neither begins nor ends with the current study. Even

Table 5: Rate and adjusted odds ratios (OR) for the primary composite outcome, small for gestational age birthweight (SGA) and preterm birth among the offspring of women with chronic hypertension, according to type of antihypertensive therapy received during pregnancy

					Preterm birth			
	Primary composite outcome*		SGA		Before 32 weeks		Before 37 weeks	
Type of antihypertensive therapy	Rate (%)	Adjusted OR (95% CI)#	Rate (%)	Adjusted OR (95% CI)	Rate (%)	Adjusted OR (95% CI)	Rate (%)	Adjusted OR (95% CI)
None	12.9	1.0	7.3	1.0	2.0	1.0	12.2	1.0
β-blocker	26.1	1.4 (0.6–3.4)	18.8	2.3 (1.1–4.5)	10.4	4.0 (1.3–12.4)	39.6	4.0 (2.3–6.9)
Non-β-blocker	48.8	4.9 (1.7–14.2)	14.5	1.3 (0.5–3.4)	12.0	2.0 (0.5–7.4)	48.2	4.2 (2.2–8.1)
Both β-blocker and non-β-blocker	53.7	2.9 (1.1–7.7)	26.6	2.9 (1.3–6.3)	26.6	5.3 (1.7–16.3)	80.7	18.9 (9.6–37.3)

*Defined as a composite of either hyaline membrane disease, necrotizing enterocolitis, periventricular hemorrhage, assisted ventilation > 1 day, or perinatal death after 20 weeks gestation and up to 30 days after birth. #All odds ratios were adjusted for maternal age, parity, pre-pregnancy weight, history of delivery before 34 weeks, history of hypertension in a previous pregnancy, cigarette smoking, pre-pregnancy diabetes mellitus, pre-pregnancy renal dysfunction, development of proteinuria, use of prednisone, receipt of betamethasone for fetal lung maturity (which is excluded for the analysis of SGA and preterm delivery), and the presence of ≥ 2+ proteinuria or 300 mg of urinary protein per 24-hour specimen.

randomized clinical trials [2,3,5] of active therapy are biased by the presence of co-intervention, cross-over, contamination and drop-outs. For example, in a well-publicized clinical trial by Butters et al., 33 women with mild primary hypertension were randomized to atenolol or placebo at approximately 16 weeks gestation [6]. Infants of mothers assigned atenolol weighed an average of 910 g less than those in the placebo group, but four women in the placebo group withdrew from the study. A second trial compared atenolol with placebo for the treatment of mild gestational hypertension during the third trimester, with no difference in birthweight between groups; however, data were reported on only 85 of 120 women (70.8%) randomized [19]. A recent clinical trial randomized 56 asymptomatic women with an increased cardiac output before 24 weeks gestation to either atenolol or placebo [20]. For the primary outcome of preeclampsia, the relative risk was 0.3 (95% CI 0.07–1.4) in favor of atenolol, and only in the small sub-group of nulliparous women was treatment with atenolol significantly associated with a 440 g mean lower mean birthweight (p = 0.02). Thus, although it is possible that atenolol may cause some degree of growth restriction, this has not been demonstrated when the drug is compared to another form of active treatment [3], or in the presence of more severe hypertension, when maternal benefit may be greater. Finally, no class effect has been demonstrated for βbs in general [4].

It may not be surprising that the risk of preterm delivery in our study was significantly associated with the use of antihypertensive therapy, since the initiation of therapy might simply reflect the onset of either new or worsening hypertension and the need for delivery. However, it is possible that βbs possess tocophilic properties that could predispose a woman to preterm labor. At least two placebo-controlled clinical trials have used intravenous βbs in the management of dysfunctional labor, reporting lower rates of Caesarian delivery with active treatment [21,22]. The relative degree of association observed in this study was substantially lower with βb than non-βb antihypertensive drugs, for delivery before 32 (OR 7.6 versus OR 13.4 among all women, respectively) or 37 weeks (OR 5.1 versus OR 10.3, respectively).

Combined antihypertensive therapy was a strong marker for preterm birth and a moderate indicator of SGA. Interestingly, however, the associated risk for other serious perinatal outcomes, such as the primary composite outcome, was either less than or similar to that for monotherapy with a non-βb drug (Tables 3 and 5). Further research might investigate whether there are differences in placental blood flow and fetal growth according to treatment regimen (monotherapy vs. combined antihypertensive therapy).

Although no significant association was seen between βb use and major perinatal morbidity or mortality, it cannot

be inferred that they are "safer" for the fetus. Rather, assuming that the current study was both valid and adequately powered to evaluate major perinatal outcomes, we may conclude that either 1) βbs are prescribed for maternal hypertension when there is less threat to the fetus or mother, while non-βb drugs are used in isolation or in combination with βbs when that threat is greater; or 2) βbs are, in fact, less harmful to the fetus compared to other antihypertensive drugs. Thus, these findings, which are hypothesis generating, should be tested by a study capable of demonstrating causation.

A large international randomized active-control clinical trial is urgently needed to help resolve the controversy surrounding the safety and efficacy for mother and child of treating hypertension during pregnancy. The reasons for such a large double-masked clinical trial are many [23], including the fact that the condition is common; the choices for therapy are few, unlikely to change for several years and inexpensive; and the time to outcome is less than 40 weeks. Women with a BP greater than 160/100 mm Hg without evidence of preeclampsia or impending delivery could be enrolled.

Randomization could be stratified according to the presence of hypertension before versus after 20 weeks gestation, and treatment might compare a βb to a dihydropyridine calcium channel blocker or methyldopa, for example. Maternal outcomes should include mode of delivery [21,22], progression to preeclampsia or eclampsia [20], and drug side effects [5], while perinatal outcomes should encompass those included in the current study.

Competing interests

None declared.

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