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Antihypertensive Medications in Management of Gestational Hypertension–Preeclampsia

PETER VON DADELSZEN, MBChB, DPhil, FRCSC*† and LAURA A. MAGEE, MD, MSc, FRCPC*‡

**Centre for Healthcare Innovation and Improvement, and the Departments of †Obstetrics and Gynaecology, and ‡Medicine, University of British Columbia, Vancouver, BC, Canada*

Introduction

Hypertension (diastolic blood pressure [dBP] of 90 mm Hg or higher) complicates 7% to 9% of pregnancies.[1,2] Approximately 1% are complicated by preexisting hypertension and 5% to 6% by gestational hypertension without proteinuria, of which 50% presents before term.[3] Preexisting hypertension is that which presents either before pregnancy or before 20 weeks' gestation and may be secondary to diabetes or other maternal disease, whereas nonproteinuric gestational hypertension is hypertension that presents at 20 or more weeks' gestation in the absence of proteinuria.[4]

Severe hypertension (dBP of 110 mm Hg or higher) in pregnancy accounts for most of the increased maternal risk (such as death or stroke) associated with pregnancy hypertension.[5] There is a consensus that maternal risk in this instance is decreased by antihypertensive therapy.[5–8] We discuss antihypertensive treatment options for severe hypertension in pregnancy first.

However, most women with preexisting or gestational hypertension have mild to moderate elevations of BP (dBP 90–109 mm Hg), and these levels of dBP are associated with much lower maternal risk compared with severe hypertension. Death and stroke are rare

Correspondence: Peter von Dadelszen, MBChB, DPhil, FRCSC, 2H30 4500 Oak Street, Vancouver, BC V6H 3N1, Canada. E-mail: pvd@cw.bc.ca
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(none reported among 27 trials enrolling 2890 women) and eclampsia is unusual (0.1%).[9–12] This group is discussed in the second section of this chapter.

International Guidelines

SEVERE HYPERTENSION IN PREGNANCY

In Canada, the United States, and the United Kingdom, reports into maternal mortality have consistently shown the excess maternal mortality associated with the hypertensive disorders of pregnancy, particularly the severe hypertension of preeclampsia.[5,13,14] In the most recent triennium in the U.K. series (1997–1999),[5] maternal mortality from hypertensive disease was most commonly attributed to intracerebral hemorrhage. There is general consensus that maternal risk is decreased by antihypertensive treatment that acutely lowers very high blood pressure.[6] Recognition of this specific risk has meant that the control of acutely raised blood pressure has become central for women with severe hypertension, particularly that of preeclampsia.[12,15]

Three short-acting antihypertensive agents (hydralazine, labetalol, and short-acting [sublingual or orally administered] nifedipine) are commonly used to control acute, very high blood pressure in women with severe hypertension in pregnancy who may require emergency cesarean section and often receive magnesium sulfate.[16] All 3 agents have their proponents and detractors.

For many years, hydralazine has been the recommended antihypertensive of first choice for severe pregnancy hypertension.[6–8] Its side effects (such as headache, nausea, and vomiting) are common and mimic symptoms of deteriorating preeclampsia. Although a precipitous hypotensive overshoot may occur with any antihypertensive agent used to treat the severe hypertension of preeclampsia,[17–19] a metaanalysis of clinical trials showed that maternal hypotension may be more common with parenteral hydralazine, which was also associated with an excess of cesarean sections, placental abruptions, and low Apgar scores (<7) at 5 minutes.[12]

Short-acting nifedipine has the clinical advantage of being able to be given as required by midwives or nurses in the absence of a doctor. However, uncertainty exists about how safe short-acting calcium channel blockers are for the mother.[20] When used for treating hypertension in patients with coronary artery disease or diabetes, these agents have been associated with excess cardiovascular morbidity and mortality.[21,22] Two case reports of transient neuromuscular weakness in patients taking nifedipine and magnesium sulfate have caused concern about concomitant use of these agents.[23,24] The withdrawal of short-acting nifedipine from some markets has been lamented by many experts in the field of pregnancy hypertension.[25]

Labetalol has been used extensively in pregnancy and has a favorable side effect profile. However, specific concern has been raised about the risk of neonatal bradycardia with parenteral labetalol.[26]

Therefore, we recently performed and published a metaanalysis of randomized, controlled trials (RCTs) for treatment of moderate to severe hypertension in pregnancy comparing the effects of short-acting antihypertensive agents (in comparison to parenteral hydralazine) on perinatal, maternal, and neonatal outcomes, particularly maternal hypotension.[15]

Which Antihypertensive Agent Should Be Used for Severe Pregnancy Hypertension?

For this review, we updated our previous literature review (1966–1997)[12] by searching Medline (1997–September 2002), the journal *Hypertension in Pregnancy* (handsearched), conference proceedings, bibliographies (including those of relevant publications in the Cochrane Database of Systematic Reviews), and textbooks. We looked for articles addressing the treatment of severe hypertension in pregnancy with short-acting

antihypertensive agents, comparing them with parenteral hydralazine.

For the Medline search, we used (and exploded) "antihypertensive agent," "bed rest," "plasma volume," "plasma substitute," or "hospitalization" AND "pregnancy," "pregnancy complications," "maternal mortality," "perinatology," "neonatology," "infant, newborn, diseases," "infant mortality," or "infant."

Criteria for inclusion were moderate to severe hypertension in pregnancy (regardless of type), randomized, controlled trial, hydralazine compared with another short-acting antihypertensive (generally through parenteral administration), and relevant clinical outcomes addressing maternal, perinatal, or pediatric benefit or risk. Articles in any language were included. Abstracts without accompanying articles were included if they met these criteria. We contacted authors for missing information or clarification, when necessary. Data were abstracted independently by 2 reviewers, and discrepancies were resolved by discussion.

The severity of hypertension was defined according to mean diastolic blood pressure at enrollment: mild (90–99 mm Hg), moderate (100–109 mm Hg), or severe (≥110 mm Hg). The type of hypertension was defined according to the National High Blood Pressure Education Program (NHBPEP) standards.[6]

Some trials enrolled mixed populations of women with either preexisting hypertension or gestational hypertension with or without proteinuria; we used the term "mixed" hypertension in such instances. Otherwise, we used preeclampsia when all trial participants had pregnancy-induced hypertension with proteinuria at enrollment and pregnancy-induced hypertension when women both with and without proteinuria were enrolled.

Data from trials of single drugs were accepted for maternal hemodynamic outcomes and stillbirth, and for neonatal outcomes if the antihypertensive could be expected to be in the maternal–fetal bloodstream at delivery and could affect the health of the neonate. In the case of duplicate publications, the most recent and complete data were included in the analysis.

Outcome definitions that were not standardized were documented at data abstraction and considered as potential sources of variation in outcome between studies. Maternal outcomes were persistent severe hypertension, need for additional antihypertensive therapy, maternal hypotension, cesarean section, placental abruption, maternal mortality or morbidity (eclampsia, intracerebral hemorrhage, HELLP [hemolysis, elevated liver enzymes, low platelets] syndrome, pulmonary edema, oliguria, and disseminated intravascular coagulation), and maternal side effects (overall and those thought to indicate deteriorating maternal preeclampsia: headache, visual symptoms, epigastric pain, and nausea or vomiting). Perinatal outcomes were adverse effects on fetal heart rate, stillbirth, Apgar scores at 1 and 5 minutes, neonatal death, neonatal bradycardia, tachycardia, hypotension, hypothermia, hypoglycemia, admission to neonatal intensive care unit, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis.

We used Cochrane review manager software (Revman version 4.0.1; Oxford, UK) for quantitative analyses. We determined heterogeneity between trials, and when heterogeneity between trials was found, we examined differences in study design (for example, method of randomization), characteristics of participants (for example, type of pregnancy hypertension), intervention (for example, drug and dosage), and outcome definitions (for example, the diastolic blood pressure at which additional antihypertensive therapy was prescribed). The summary statistic was relative risk (and 95% confidence interval), a relative effect measure appropriate for use when summarizing evidence. In addition, we calculated risk difference as recommended by the neonatal review group of the Cochrane Collaboration. Risk difference is a measure of absolute effect and is sensitive to between-trial differences in absolute event rates. In the

calculation of risk difference, all trials (even those without reported events in either arm of the trial) contribute to the summary statistic. Data were entered by subgroup according to the type of antihypertensive that was compared with hydralazine. The fixed-effects model was used on the assumption that any between-trial differences in outcome were the result of random variation, so trials were weighted on the basis of precision. For outcomes with significant differences between groups, the median event rate and its range were also presented.

Through this process, we identified 21 trials in 26 publications (1085 women) that met the inclusion criteria,[27–50] including the 10 trials in the previous metaanalysis.[12] Approximately half (12 of 21 trials) enrolled mixed populations of women with pregnancy hypertension; hypertension was usually severe (16 of 21 trials). In 2 trials, single doses were given,[35,41] and in 3 trials, patients were switched to oral antihypertensives when blood pressure had been stabilized.[33,37,38] Most commonly, hydralazine was compared with standard doses of other antihypertensives: nifedipine (8 trials), labetalol (5 trials), ketanserin (4 trials), urapidil (2 trials), epoprostenol (1 trial), or isradipine (1 trial with 3 publications).

Most trials were small, with a median of 37 women enrolled (range, 6–200). Half (11 of 21) described adequate methods of randomization, but 7 publications did not describe the method at all. Assessment of outcome was blinded in 4 trials and for some outcomes in 1 other trial. The quality of the methods had no discernible impact on outcome.

Table 1 presents the maternal and perinatal outcomes in trials that compared hydralazine with other antihypertensives. If the results of the trial that compared hydralazine and epoprostenol are excluded,[44] the results of outcomes to which this trial contributed (persistent severe hypertension, cesarean section, maternal side effects, perinatal mortality, and respiratory distress syndrome) are not changed.

Maternal Outcomes

Persistent severe hypertension was variably defined as dBP ≥90 mm Hg, 95 mm Hg, 100 mm Hg, or ≥110 mm Hg; mean arterial blood pressure ≥120 mm Hg; and failure to achieve a drop in systolic/diastolic blood pressure of 30/15 mm Hg. Hydralazine did not differ from other antihypertensives in impact on persistent severe hypertension or on use of additional antihypertensives (Table 1). However, the results differed by more than could be expected by chance alone, with the heterogeneity explained largely by the type of other antihypertensive. Hydralazine was associated with a trend toward lower rates of persistent severe hypertension (median event rate 0% [range 0%–20%] vs. labetalol 5% [0%–60%]; relative risk 0.29 [0.08–1.04]; 2 trials; chi square = 0.08, df = 1, P = 0.78; risk difference −0.11 [−0.21 to −0.02]; 4 trials; chi square = 6.91, df = 3, P = 0.08; Fig. 1) and was not associated with use of additional antihypertensives (5% [0%–10%] for hydralazine vs. 5% [0%–10%] for labetalol; relative risk 1.00 [0.07–13.9]; 1 trial; chi square = 0, df = 0; risk difference 0 [−0.12 to 0.12]; 2 trials; chi square = 0, df = 1, P = 1.00). Hydralazine was associated with a trend toward more persistent severe hypertension (29% [0%–32%]) compared with nifedipine or isradipine (5% [0%–40%]; relative risk 1.41 [0.95–2.1]; 4 trials; chi square = 11.7, df = 3, P = 0.009; risk difference 0.08 [−0.01 to 0.16]; 5 trials; chi square = 12.4, df = 4, P = 0.02; Fig. 1) and with use of additional antihypertensives (13% [0%–32%] for hydralazine vs. [5% {0%–24%}] nifedipine only; relative risk 2.13 [1.2–3.9]; 4 trials; chi square = 5.24, df = 3, P = 0.15; risk difference 0.08 [0.02– 0.14]; 5 trials; chi square = 12.3, df = 4, P = 0.02), but there was still significant heterogeneity between trials within this subgroup. In the 3 trials with nifedipine or isradipine in which hydralazine was associated with more severe hypertension, the methods of allocation concealment were either clearly inadequate[33,38] or unstated,[40–42] but

TABLE 1. Maternal and Perinatal Outcomes in Trials Comparing Hydralazine With Other Antihypertensives for Severe Hypertension of Pregnancy

	No. of Trials	No. of Women	RR (95% Confidential Interval)*	Chi-squared Heterogeneity (df)	*P* for Chi-square	RD (95% Confidential Interval)	Hetero-geneity (df)	*P* for Chi-square
Maternal outcomes								
Persistent severe hypertension	14	729	1.08 (0.79–1.49)	28.09 (9)	0.009	0.01 (−0.04–0.06)	44.36 (13)	<0.0001
Additional blood pressure	10	564	1.32 (0.83–2.13)	14.06 (6)	0.029	0.03 (−0.02–0.08)	22.92 (9)	0.006
Maternal hypotension	12	675	3.33 (1.49–7.14)	3.22 (6)	0.78	0.04 (0.01–0.08)	40.66 (12)	0.0001
Eclampsia	8	311	0.75 (0.20–2.86)	1.40 (3)	0.70	−0.01 (−0.05–0.04)	2.03 (7)	0.96
HELLP syndrome	2	142	2.33 (0.83–6.67)	3.70 (1)	0.05	0.08 (0.00–0.17)	18.87 (1)	<0.00001
Placental abruption	5	203	4.17 (1.19–14.28)	1.29 (4)	0.86	0.08 (0.01–0.15)	7.9 (4)	0.095
Cesarean section	14	650	1.30 (1.08–1.59)	12.19 (11)	0.35	0.08 (0.02–0.13)	25.67 (13)	0.02
ICH	1	44	3.03 (0.13–100.00)	0 (0)	N/A	0.05 (−0.08–0.17)	0 (0)	N/A
Pulmonary edema	3	161	4.00 (0.65–25.00)	1.09 (1)	0.30	0.05 (−0.01–0.12)	7.05 (2)	0.03
Oliguria	3	105	4.00 (1.22–12.5)	0.10 (2)	0.95	0.17 (0.05–0.29)	7.44 (2)	0.02
DIC	1	44	0.33 (0.01–7.69)	0 (0)	N/A	−0.05 (−0.17–0.08)	0 (0)	N/A
Maternal death	9	471	3.33 (0.52–20.00)	0 (2)	1.00	0.01 (−0.02–0.04)	2.11 (8)	0.98
Maternal side effects								
Any	12	494	1.49 (1.16–1.92)	27.51 (11)	0.004	0.12 (0.05–0.19)	51.38 (11)	<0.00001
Headache	11	528	1.61 (1.06)–2.38	14.34 (10)	0.16	0.07 (0.01–0.13)	29.15 (10)	0.001
Visual symptoms	1	44	9.09 (0.51–100.00)	0 (0)	N/A	0.18 (0.00–0.36)	0 (0)	N/A
Nausea/writing	6	210	2.22 (0.94–5.26)	4.17 (4)	0.38	0.08 (0.00–0.16)	12.61 (5)	0.03
Epigastric pain	1	44	0.67 (0.12–3.57)	0 (0)	N/A	−0.05 (−0.23–0.14)	0 (0)	N/A
Flushing	3	119	0.31 (0.12–0.79)	8.08 (2)	0.02	−0.20 (−0.32–0.08)	30.42 (2)	<0.00001
Palpitations	5	132	3.57 (1.72–7.69)	3.11 (4)	0.54	0.28 (0.15–0.41)	15.06 (4)	0.005
Tachycardia > 110 beats/min	5	305	5.56 (2.38–12.5)	4.42 (4)	0.35	0.18 (0.11–0.25)	11.96 (4)	0.02
Dizziness	5	153	1.82 (0.53–6.25)	3.35 (3)	0.34	0.04 (−0.04–0.12)	5.72 (4)	0.22
Bronchospasm	1	12	0.33 (0.17–6.67)	0 (0)	N/A	−0.17 (−0.59–0.25))	0 (0)	N/A
Changed drugs because of side effects	7	328	2.44 (0.38–14.28)	0.03 (1)	0.86	0.01 (−0.02–0.05)	1.65 (6)	0.95
Adverse fetal heart rate effects	12	552	1.61 (1.03–2.56)	8.87 (7)	0.26	0.07 (0.03–0.12)	45.97 (12)	<0.00001
Perinatal outcomes								
Perinatal death	17	744	1.43 (0.77–2.63)	4.21 (12)	0.98	0.02 (−0.02–0.05)	7.25 (16)	0.97
Stillbirth	17	744	2.00 (0.85–4.76)	0.66 (5)	0.99	0.02 (−0.01–0.05)	4.61 (16)	1.00
Neonatal death	17	729	1.00 (0.43–2.38)	3.74 (8)	0.88	0.00 (−0.03–0.03)	5.47 (16)	0.99
1-minute Apgar	3	52	2.70 (1.27–5.88)	4.03 (2)	0.13	0.36 (0.13–0.59)	4.48 (2)	0.11
5-minute Apgar	6	271	1.23 (0.69–2.22)	3.74 (5)	0.59	0.03 (−0.05–0.11)	5.85 (5)	0.32

TABLE 1. Continued

	No. of Trials	No. of Women	RR (95% Confidential Interval)*	Chi-squared Heterogeneity (df)	*P* for Chi-square	RD (95% Confidential Interval)	Hetero-geneity (df)	*P* for Chi-square
Admission to NICU	1	98	1.18 (0.59–2.38)	0 (0)	N/A	0.04 (−0.13–0.21)	0 (0)	N/A
Neonatal bradycardia	3	50	0.16 (0.02–1.11)	0.01 (1)	0.91	−0.24 (−0.42–0.06)	15.43 (2)	0.0004
Neonatal hypotension	1	19	5.88 (0.28–100.00)	0 (0)	N/A	0.17 (−0.20–0.53)	0 (0)	N/A
Neonatal hypothermia	1	25	Not estimable			0.00 (−0.16–0.16)	0 (0)	N/A
Neonatal hypoglycemia	3	64	0.88 (0.14–5.26)	0.84 (1)	0.36	−0.01 (−0.13–0.10)	0.94 (2)	0.63
Respiratory distress syndrome	6	250	1.56 (0.78–3.13)	2.68 (5)	0.75	0.05 (−0.03–0.12)	3.72 (5)	0.59
Intraventricular hemorrhage	2	72	4.17 (0.47–33.33)	0.11 (1)	0.74	0.07 (−0.05–0.18)	0.75 (1)	0.39
Necrotizing enterocolitis	1	53	2.86 (0.12–100.00)	0 (0)	N/A	0.04 (−0.06–0.14)	0 (0)	N/A

DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, low platelets; ICH, intracranial hemorrhage; N/A, not applicable; NICU, neonatal intensive care unit; RD, risk difference; RR, relative risk.

Reprinted from Magee et al. *BMJ.* 2003.[15]

FIGURE 1. Persistent severe maternal hypertension in trials that compared hydralazine with other antihypertensives. (Reprinted from Magee et al. *BMJ.* 2003.)[15]

other characteristics of the trials did not differ.

In comparison with ketanserin, hydralazine was not associated with a consistent effect on maternal blood pressure (Fig. 1); this effect was partially explained by the doses of hydralazine used. A low-dose hydralazine infusion (1 mg/hr intravenously, increased by 1 mg/hr every hour to a maximum of 10 mg/hr) was associated with a trend toward more persistent severe hypertension than ketanserin (5 mg intravenous bolus, then 4 mg/hr intravenously).[30,31] Higher-dose bolus hydralazine (5 mg intravenously every 20 min) was associated with

less persistent severe hypertension than ketanserin (10 mg intravenously every 20 min).[48]

Hydralazine was associated with more maternal hypotension than other antihypertensives (0% [0%–67%] vs. 0% [0%–17%]; Table 1, Fig. 2). Calculations of risk difference showed significant heterogeneity between trials, which was largely absent when subgroups of other antihypertensive agents were examined: hydralazine vs. labetalol (risk difference 0.10 [0–0.20); 4 trials; chi square = 6.46, df = 3, $P = 0.09$); hydralazine vs. nifedipine or isradipine (0.01 [−0.01 to 0.04]; 6 trials; chi square = 6.58, df = 5, $P = 0.25$); hydralazine vs. urapidil (0.16 [−0.11 to 0.42]; 1 trial); and hydralazine vs. ketanserin (0.18 [−0.04 to 0.39]; 2 trials; chi square = 0.51, df = 1, $P = 0.47$). In the hydralazine vs. labetalol subgroup in which there was still heterogeneity, the incidence of maternal hypotension with hydralazine ranged from 0% (in 10 patients) to 67% (in 4 of 6 patients); the rate of 67% occurred in the very small trial by Garden et al,[34] in which hydralazine was given in higher dosage (initially 10 mg/hr by intravenous infusion) than in other trials.

Several maternal outcomes occurred more often with hydralazine than with other antihypertensives: cesarean section (67% [8%–100%] vs. 59% [5%–100%] for other antihypertensives); placental abruption (18% [3%–20%] vs. 0% [0%–2%]); and maternal oliguria (17% [4%–41%] vs. 0% [0%–9%]) (Table 2); however, the risk difference analysis showed heterogeneity between trials. Groups did not differ in other measures of maternal morbidity—eclampsia, intracerebral hemorrhage, HELLP syndrome, pulmonary edema, disseminated intravascular coagulation, or mortality. However, the 2 trials that reported HELLP syndrome as an outcome differed by more than could be expected by chance alone.[30,31,38] Comparing hydralazine with nifedipine, Kwawukume and Ghosh reported no raised liver enzymes,[38] but in a comparison of hydralazine and ketanserin, Bolte et al reported a significantly higher incidence (45% vs. 9%) of HELLP syndrome (using Sibai's definition in the hydralazine group).[30,31]

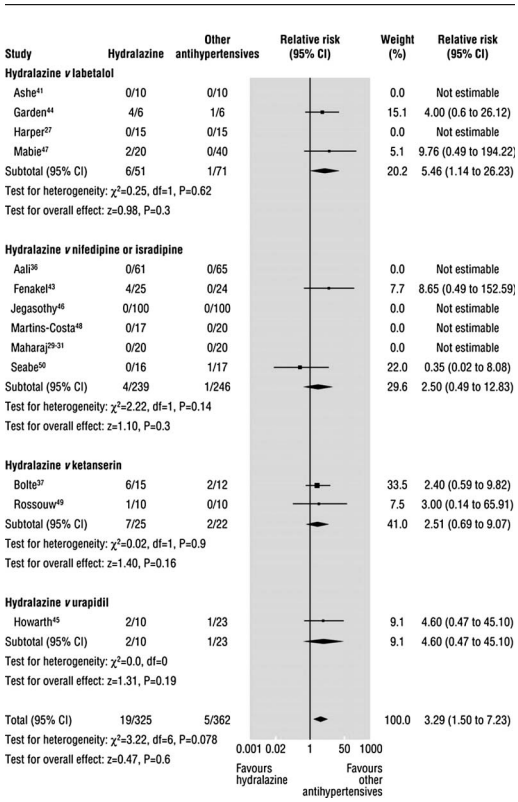

FIGURE 2. Maternal hypotension in trials that compared hydralazine with other antihypertensives (Reprinted from Figure 3 of Magee et al. *BMJ.* 2003.)[15]

In summary, hydralazine was associated with more persistent severe hypertension than nifedipine or isradipine, and more of the following outcomes when compared with all antihypertensives: maternal hypotension, placental abruption, cesarean section, and maternal oliguria. However, absolute event rates ranged widely within trials, and outcomes showed significant heterogeneity when risk difference was used as the summary statistic.

Maternal Side Effects

Hydralazine was associated with more maternal side effects (of any sort) and headache

TABLE 2. Summary: Neuromuscular Blockade Among the Calcium Channel Blocker Arms of Nifedipine/Nicardipine vs. Other Antihypertensive Trials in Which Magnesium Sulfate Was Given, This Study and the Magpie Trial

Studies	Neuromuscular Blockade in Nifedipine-Treated Arm	Subtotal	Percent [95% confidence interval] for Neuromuscular Blockade
Calcium channel blocker trials			
Martins-Costa et al*	0/9		
Fenakel et al*	0/24		
Aali and Nejad*	0/65		
Vermillion et al*	1/25		
Elatrous et al†	0/30		
		0/153	0 [0–2.38]
This study			
Magee et al 2005 (current study)	0/162		0 [0–2.25]
		0/315	0 [0–1.16]
Magpie Trial‡	0/55*		
		0/370	0 [0–0.99]

* Nifedipine was the calcium channel blocker administered.

† Nicardipine was the calcium channel blocker administered.

‡ Assuming that only 55 (3.74%) of the 1469 women who got nifedipine and $MgSO_4$ got them concomitantly.

Modified from Magee LA, et al. *Am J. Obstet Gynecol.* 2005 (in press).[55]

than other antihypertensives (40% [10%–82%] vs. 17% [0%–75%] and 29% [0%–67%] vs. 0% [0%–20%], respectively; Table 1). For any maternal side effects, the significant heterogeneity between trials was confined to the nifedipine subgroup (Fig. 3). In particular, the trial by Fenakel et al found that hydralazine was associated with fewer side effects than nifedipine.[33] The dose of hydralazine was higher than in the other 3 trials, and the dose of nifedipine was the same. However, the duration of treatment was longer than in other trials (days to weeks rather than hours to days) because women were changed to oral antihypertensive therapy.

Hydralazine was associated with more palpitations than other antihypertensives (18% [11%–81%] vs. 0% [0%–17%]; Table 1). Three of the 5 trials compared hydralazine with labetalol, and within this subgroup, the effect was significant (relative risk 5.26 [2.00–14.28]; 3 trials; chi square = 0.29, df = 2, P = 0.87; risk difference 0.48 [0.30–0.67]; 3 trials; chi square = 4.79, df = 2, P = 0.09).

Hydralazine was also associated with more maternal tachycardia than other antihypertensives (24% [10%–67%] vs. 0% [0%–6%]; Table 1). Three of the 5 trials were comparisons of hydralazine against nifedipine, and within this subgroup, the results were significant (relative risk 5.56 [2.17–14.29]; 3 trials; chi square = 4.10, df = 2, P = 0.13; risk difference 0.18 [0.11–0.25]; 3 trials; chi square = 11.96, df = 4, P = 0.02). Hydralazine was associated with less flushing than nifedipine (0%–12.5% vs. 0%–58%; only comparisons with nifedipine reported flushing); however, there was heterogeneity between trials. More flushing was reported in the trial by Fenakel et al, which treated women for longer than other trials.[33] Groups did not differ in visual symptoms, nausea or vomiting, epigastric pain, dizziness, or bronchospasm (Table 1).

Despite the high prevalence of side effects (in 85 of 227 patients given hydralazine and 61 of 257 patients given other antihypertensives), few women changed drugs because they experienced side effects (3 of

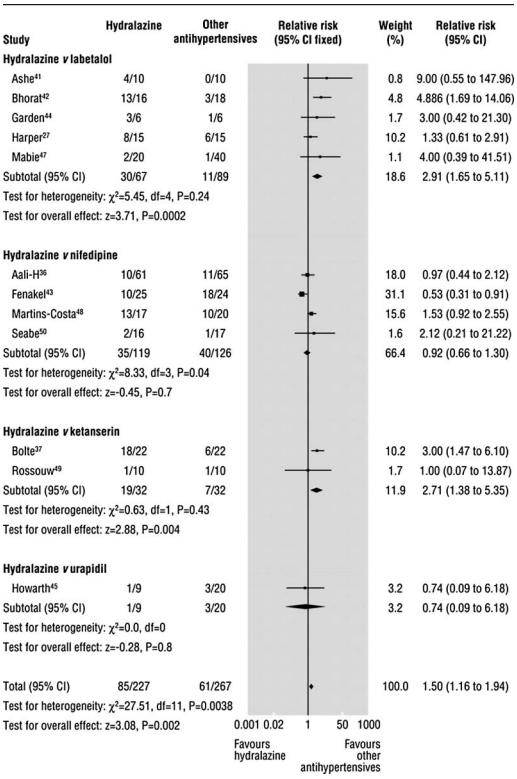

FIGURE 3. Any maternal side effect reported in trials that compared hydralazine with other antihypertensives. (Reprinted from Magee et al. *BMJ.* 2003.)[15]

161 changing from hydralazine, 1 of 167 changing from other antihypertensives); the proportion did not differ between groups.

In summary, hydralazine was associated with more maternal side effects than labetalol or ketanserin, and more headache, palpitations, and maternal tachycardia than other antihypertensives. Whether hydralazine was associated with more side effects than nifedipine was unclear. For all outcomes, absolute event rates ranged widely within trials and significant heterogeneity was seen when risk difference was used as the summary statistic.

Adverse Effects on Fetal Heart Rate

Adverse effects on fetal heart rate were defined as "acute fetal distress"[32,33,36,46]; need for cesarean section as a result of fetal distress[38] or a decelerative fetal heart rate pattern[48]; "deterioration in the cardiotocographic tracings"[43]; abnormal fetal heart rate patterns in the 6 hours after treatment[49,50]; "abnormal" fetal heart rate in labor[39]; fetal heart rate decelerations[40–42]; late decelerations during continuous fetal heart rate monitoring[28]; or "CTG abnormalities."[27] Hydralazine was associated with more adverse effects on fetal heart rate than other antihypertensives (11% [0%–56%] vs. 0% [0%–50%]), with the significant heterogeneity isolated to the hydralazine vs. labetalol subgroup (Fig. 4). The doses of hydralazine and labetalol were lower in the trial of Ashe et al (3.7 mg/hr hydralazine given intravenously vs. 20 mg/hr labetalol given intravenously with increases every 30 min)[28] and higher in the trial of Mabie et al (5 mg hydralazine given intravenously every 10 min vs. 20 mg labetalol given intravenously, then 30 mg given intravenously every 10 min)[39]; otherwise, the differences remained unexplained, although both trials were small and the 95% confidence intervals overlapped substantially.

Perinatal Outcomes

Hydralazine was associated with more low Apgar scores at 1 minute than other antihypertensives (67% [38%–83%] vs. 15% [14%–67%]; Table 1), but the incidence of low Apgar scores at 5 minutes did not differ between groups. Hydralazine was associated with less neonatal bradycardia than labetalol (0% [0%–0%] vs. 21% [0%–100%]), but the results differed more than could be expected by chance alone. Few trials reported other perinatal outcomes, and these outcomes (perinatal mortality; admission to neonatal intensive care unit; neonatal hypotension, hypothermia or hypoglycemia; or complications of prematurity: respiratory distress syndrome, intraventricular hemorrhage, or necrotizing enterocolitis) did not differ between groups. However, Figure 5 shows a statistical trend toward more stillbirths with

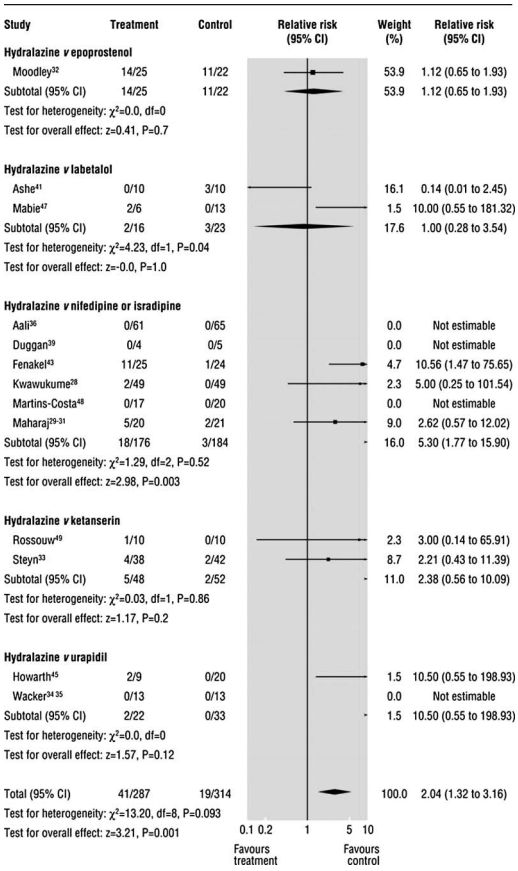

FIGURE 4. Adverse effects on fetal heart rate (FHR) in trials that compared hydralazine with other antihypertensives. (Reprinted from Magee et al. *BMJ.* 2003.)[15]

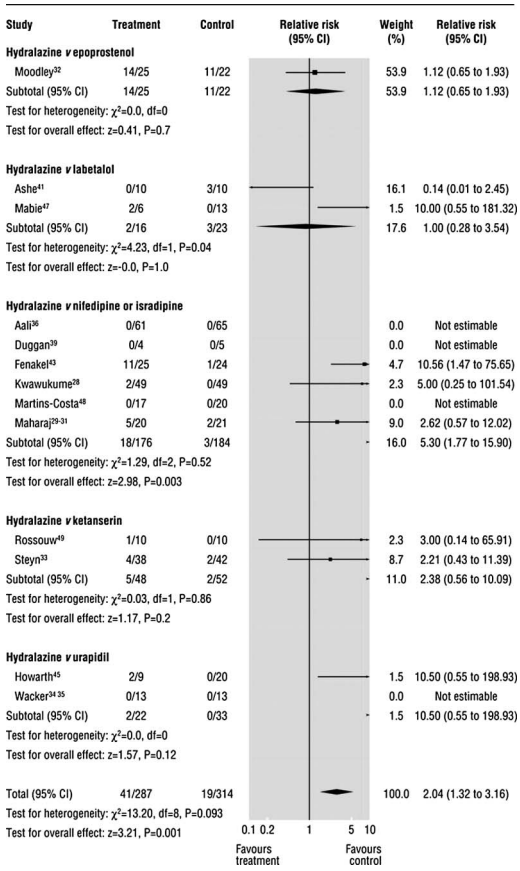

FIGURE 5. Stillbirth in trials that compared hydralazine with other antihypertensives. (Reprinted from Magee et al. *BMJ.* 2003.)[15]

hydralazine than with other antihypertensives (0% [0%–31%] vs. 0% [0%–22%]).

In summary, hydralazine was associated with more low Apgar scores at 1 minute and a trend toward an increase in stillbirth compared with other antihypertensives. Hydralazine was associated with less neonatal bradycardia than labetalol.

Discussion

This metaanalysis of RCTs for the treatment of severe hypertension in pregnancy shows that hydralazine was associated with some poorer maternal and perinatal outcomes than other antihypertensives, particularly labetalol and nifedipine. Hydralazine was found to be a less effective antihypertensive than nifedipine or isradipine and did not clearly differ from labetalol. In comparison with all other antihypertensives, hydralazine was associated with more of several adverse outcomes: maternal hypotension, placental abruption, adverse effects on fetal heart rate, cesarean section, maternal oliguria, stillbirth (statistical trend only), and low Apgar score at 1 minute. Hydralazine was associated with less neonatal bradycardia than labetalol, but no trials since our previous metaanalysis reported this outcome.

Hydralazine was more poorly tolerated than other antihypertensives. More maternal side effects were seen than with labetalol or ketanserin. More headaches (raising the issue of imminent eclampsia), palpitations, and maternal tachycardia were seen than with other antihypertensives, with the exception of nifedipine; in trials that showed these side effects, outcomes differed more than could be expected by chance alone, possibly because of differences in design of the trials.

These results are biologically plausible. Rapid or excessive falls in maternal blood pressure may decrease placental perfusion (reflected by abnormal fetal heart rate patterns) and lead to placental abruption, cesarean section, and low Apgar scores at 1 minute (with recovery by 5 min with resuscitation). The unpredictability of the timing and magnitude of the blood pressure-lowering effect of hydralazine may make its use in pregnancy problematic. The results of this metaanalysis do not support recent recommendations favoring initial use of hydralazine over other antihypertensives (including ketanserin).[6]

Nifedipine seems to be a reasonable alternative to hydralazine. In 2 case reports, profound muscle weakness and respiratory arrest were associated with concomitant use of nifedipine and magnesium sulfate.[23,24] However, no neuromuscular blockade was described in any of the trials comparing hydralazine with nifedipine or isradipine, even though magnesium sulfate was given to all[33] or some[38] women, and no such blockade was reported in the Magpie trial, in which 29% of women allocated to receive magnesium sulfate also received nifedipine.[51] Therefore, any risk of neuromuscular blockade is likely to be low, and the effect is reversible with calcium gluconate. We discuss this in greater detail subsequently.

Parenteral labetalol also seems to be a reasonable alternative to hydralazine. Although it may be less effective in preventing recurrent severe hypertension, labetalol controlled severe hypertension in 87% of women and was similar to other antihypertensive agents in the need to prescribe further antihypertensives. No new trials were available to update the previously observed association between parenteral labetalol and (usually transient) neonatal bradycardia[12]; neonatologists should continue to be made aware when intravenous labetalol has been used during labor and delivery.

Ketanserin, an agent investigated most widely in The Netherlands and South Africa, compared favorably with hydralazine.

Of course, there are other limitations to this review that have not been discussed. Metaanalysis is based on a retrospective and observational study design, which relies on published data. However, trials provide the least biased form of information about therapeutic interventions and outcome, and the results of this metaanalysis are biologically plausible.

The most recent Cochrane review found no good evidence that 1 short-acting antihypertensive is better than another, with the exception of ketanserin, which is associated with more persistent hypertension.[52] The Cochrane inclusion and exclusion criteria differed somewhat from those in this study, but the most important difference seems to be in the reviews' methods. In the absence of significant between-trial heterogeneity in outcome, we pooled the results from all trials comparing hydralazine and other antihypertensives, whereas the Cochrane review had 5 subgroups of trials comparing hydralazine and other antihypertensives, with different outcomes reported in each group. In our review, pooling had the advantage of not being based on the assumption that different antihypertensives would cause differences in maternal or perinatal outcome, and where differences between trials existed, pooling informed the reader about how differences in design of the studies and in the intervention may have influenced the results. Pooling resulted in greater statistical power where significant heterogeneity between trials did not exist and allowed overall conclusions to be drawn from the data.

CONCLUSIONS

The results of this review should generate uncertainty about the agent of first choice for treating severe hypertension in pregnancy. Definitive data from adequately powered clinical trials are needed, with the most promising comparison being that of nifedipine with labetalol (or perhaps ketanserin if it is available locally). Such trials should include cesarean section for fetal distress as an outcome. One trial has compared nifedipine with labetalol, but only 50 women were enrolled and cesarean section was not reported.[53] The results of this review support the use of antihypertensive agents other than hydralazine for the acute management of severe hypertension in pregnancy.

INTERACTION BETWEEN NIFEDIPINE AND $MgSO_4$

As stated, there has been considerable hesitancy in some quarters for practitioners to use nifedipine at the same time as magnesium sulfate in response to influential case reports.[17,23,24] To address this issue, we have undertaken a study to determine whether the use of nifedipine and magnesium sulfate together increase serious Mg-related effects.[54,55] In this retrospective chart review, we investigated women admitted to BC Women's Hospital (1997–2001) who were given intravenous magnesium sulfate for suspected preeclampsia. Serious Mg-related effects were compared between 162 "cases" (receiving magnesium sulfate and contemporaneous nifedipine) and 215 controls (receiving magnesium sulfate and either another antihypertensive [N = 32] or no antihypertensive [N = 183]). Chi squared test, Fisher exact test, or Student *t* test were used for data comparison between "cases" and all controls (except for maternal hypotension). $P < 0.05$ was considered statistically significant.

We found that "cases" (vs. all controls) had no excess of neuromuscular weakness (53.1% vs. 46.0%, $P = 0.21$) or other serious Mg-related effects despite having more severe preeclampsia and a longer magnesium sulfate infusion. Two controls had neuromuscular blockade. "Cases" (vs. "no antihypertensive" controls) had less maternal hypotension (41.4% vs. 53.0%, $P = 0.04$).

In addition, after data synthesis, we were able to identify 12 RCTs of nifedipine/calcium channel blocker (CCB) vs. hydralazine (N = 9), labetalol (N = 2) or chlorpromazine. Six RCTs clearly administered magnesium sulfate to all or a specified number of women.[27,33,38,43,53,56] Short-acting nifedipine (N = 5) or nicardipine[56] was administered; no trial report was described. In 3 RCTs, it was not clear that magnesium sulfate was administered.[37,47,57] In 3 RCTs, magnesium sulfate was not administered.[32,42,45]

Table 2 presents the assumed incidence of neuromuscular blockade in each of the trials in which magnesium sulfate was administered to women in the CCB arm; no blockade was described in these 153 women. Taken together with this study, the estimate (97.5% confidence interval) of neuromuscular blockade with use of nifedipine/nicardipine and magnesium sulfate together is 0% (1–1.16). Furthermore, in Magpie,[51] 1469 women in the magnesium sulfate arm received nifedipine. Table 2 shows the hypothetical situation in which only 3.74% of these women are assumed to have received the 2 drugs together. In this scenario, the risk of neuromuscular blockade with use of nifedipine and magnesium sulfate together is $<1\%$.

Therefore, we have concluded that using nifedipine and magnesium sulfate together does not appear to be associated with an excess of serious Mg-related effects.[54]

MILD-TO-MODERATE HYPERTENSION IN PREGNANCY

The Effect of Blood Pressure Control on Maternal and Perinatal Outcomes

The Nature of Risks to the Mother For nonpregnant women with mild to moderate hypertension, there is good evidence that *years* of antihypertensive therapy decrease long-term cardiovascular risk.[58–60] However, in the absence of associated maternal

disease (eg, diabetes or hypertension-related target organ damage), there is no evidence that *months* of antihypertensive therapy decrease long-term cardiovascular risk. Typically, elevated BP among nonpregnant women is monitored over *months* before initiating antihypertensive medication. In hypertensive pregnant women, BP is typically elevated only over *months*, given the midtrimester nadir in BP.[6]

The Nature of Risks to the Baby It is difficult to ascertain the risk of perinatal complications by type of hypertension because of methodological problems with published studies. Most of the data come from tertiary care centers; definitions of maternal and perinatal outcomes vary; factors (including antihypertensive therapy) that may confound the BP/fetal growth relationship are not accounted for; and studies were undertaken during periods when perinatal care was less advanced.[61]

Despite problems with the published literature, both preexisting hypertension and nonproteinuric gestational hypertension have been associated with a high risk of adverse perinatal outcome. For preexisting hypertension, the perinatal mortality rate may be as high as 40 per 1000.[62–65] Among women with preexisting hypertension or nonproteinuric gestational hypertension, the risk of a small-for-gestational-age (SGA) infant (<10th percentile) is approximately 15%.[62–65]

Approximately 20% of women with preexisting hypertension and 40% with nonproteinuric gestational hypertension who present before 34 weeks will develop superimposed preeclampsia.[62–68] For these women, the risks of adverse perinatal outcome are even higher, with the risk of SGA increasing to approximately 40%.[6,62–65,69,70] Previously, it was thought that SGA infants had been "stressed" in utero by a decrease in substrate for growth and had fewer perinatal complications.[71] However, the converse is actually true. Being SGA *increases* the risk of short-term neonatal complications, adverse neurologic outcomes and cognitive function in childhood, and cardiovascular and endocrine complications in adulthood, possibly because of irreversible in utero metabolic adaptations (the Barker hypothesis).[72–75]

RELEVANT SYSTEMATIC REVIEWS

We have conducted 4 relevant systematic reviews of RCTs.[12,76–78] These reviews are summarized subsequently.

Twenty-seven RCTs examined the impact of differential BP control for mild to moderate pregnancy hypertension on maternal and perinatal outcomes.[10–12,79–81] Twenty-six trials compared "tight" control, aiming for a dBP of less than 90 mm Hg with "less tight" control, aiming for a dBP of 100 to 110 mm Hg.[9–12,79–81] One trial compared "tight" to "very tight" control.[9] Although the RCTs did not report outcome by type of hypertension and were too small to examine the risk of BP control in terms of perinatal complications or SGA infants, these trials provide the least biased information on treatment effectiveness. Thirty-five trials compared 1 antihypertensive with another, applying the same dBP treatment goals to women in both treatment groups.[16,33,82–97]

There was a tendency for "less tight" control to be associated with a lower risk of SGA infants (<10th percentile) compared with "tight" control (odds ratio [OR] 0.84 [0.65–1.09]).[77,78] The between-trial heterogeneity in outcome, which was not fully explained by antihypertensive type, was explored by metaregression analysis.[77,78] There was a significant and linear correlation between the decrease in mean arterial pressure and both an increase in the incidence of SGA infants (Fig. 6) and a reduction in birthweight (Fig. 7).

On the other hand, "less tight" control was associated with an increased risk of respiratory distress syndrome (RDS) (OR 3.92 [1.96–7.82]). However, little confidence can be placed in this finding because only 6 of 22 trials reported on RDS and the incidence of RDS was unusually high in the "less tight" group (6.4%) considering that most infants were delivered at term. Finally, there is no biologic explanation for why

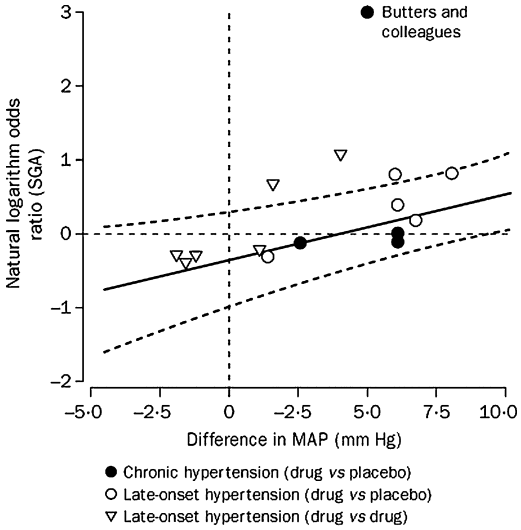

FIGURE 6. Relation between fall in mean arterial pressure and proportion of small-for-gestational-age infants. Spearman's $r = 0.69$ ($P = 0.007$) without Butters and colleagues' trial, $r = 0.64$ ($P = 0.01$) with that trial. (Reprinted from von Dadelszen et al. *Lancet*. 2000.)[77]

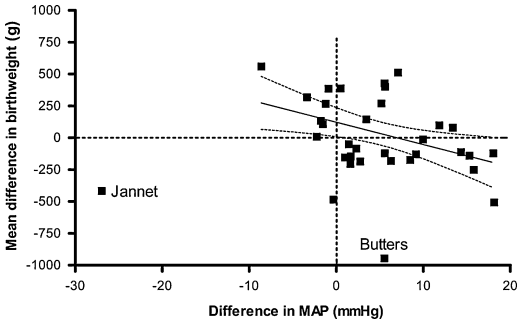

FIGURE 7. Relationship between fall in mean arterial pressure and low birthweight. MAP, mean arterial pressure (diastolic blood pressure + pulse pressure/3). Excluding Butters et al and Jannet et al, treatment-induced mean difference in MAP was associated with lower mean birth weight (slope: −17.55 [standard deviation 6.67], $r^2 = 0.19$, Spearman's nonparametric $P = 0.031$, Pearson's parametric $P = 0.013$). (Reprinted from von Dadelszen, Magee. *J Obstet Gynaecol Can*. 2002.)[78]

"less tight" control should increase the rate of RDS, because there was no concomitant change in the rate of preterm birth overall or among trials that reported RDS (OR 1.23, 95% confidence interval 0.83–1.82; N = 5 trials).

"Less tight" control also increased the risk of severe hypertension (OR 2.66 [2.12–3.33]), hospitalization (OR 2.18 [1.54–3.07]), and proteinuria at delivery (OR 1.32 [1.06–1.63]).[12] However, the increase in the risk of severe hypertension and proteinuria was not associated with an increase in the incidence of preterm birth and thus may not have been clinically important.

CONCLUSION

In summary, it is not clear how best to manage mild to moderate nonproteinuric preexisting hypertension or gestational hypertension, remote from term. "Less tight" control may be beneficial by decreasing the risk of SGA infants. However, "less tight" control may be harmful by increasing the risk of RDS, the risk of severe hypertension, antenatal hospitalization, and proteinuria at delivery. The reviews do not provide sufficient evidence on which to base clinical decisions because of reporting bias and uncertainty about the clinical importance of the outcomes. A large RCT needs to be conducted now.

WHICH ANTIHYPERTENSIVE AGENT(S) SHOULD BE USED FOR PREGNANCY HYPERTENSION?

Hypertensive disorders of pregnancy are themselves associated with an increase in the risk of adverse pregnancy outcomes, such as SGA infants. One must always bear in mind that there is a baseline risk of adverse pregnancy outcomes. These include the 1% to 5% risk of a major malformation (regardless of drug therapy in pregnancy), in addition to baseline rates of SGA infants and adverse neurodevelopmental outcomes. All antihypertensive agents have been shown or should be assumed to cross the

placenta and reach the fetal circulation. None of the commonly used classes of antihypertensive drugs has been shown to be teratogenic when taken in early pregnancy. Angiotensin-converting enzyme inhibitors (and presumably, angiotensin-receptor antagonists), when taken later in pregnancy, are associated with a characteristic fetopathy and are the only antihypertensive agents contraindicated in pregnancy. It would appear that any antihypertensive agent may increase the risk of SGA infants by lowering BP and, presumably, placental perfusion. However, as a result of a lack of sufficient information, no reliable conclusions can be made about the impact of antihypertensive agents (even methyldopa) on long-term child development.

For all antihypertensive agents, only large increases in reproductive risk (including major malformations) can be ruled out by existing data. As such, "no evidence of harm" cannot be regarded as equivalent to "evidence of no harm," and the clinician must have clear therapeutic goals in mind when initiating treatment in pregnancy. Given that BP falls in early pregnancy and most young women have no other major cardiovascular risk factors, hypertension-related target organ damage or other relevant disease, clinicians should consider discontinuing antihypertensive therapy early in pregnancy. Use of oral agents later in pregnancy is of uncertain benefit and may have a negative impact intrauterine fetal growth.

Orally administered antihypertensive agents should be used in standard doses in pregnancy. Agents used for the acute severe hypertension of preeclampsia should be initiated at lower doses, given that women with preeclampsia are intravascularly volume-depleted and at increased risk of hypotension.

All commonly used antihypertensive agents, including labetalol, methyldopa, nifedipine, and captopril, are considered to be compatible with breast feeding, based on their pharmacology and low detectable drug levels in breast milk.

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