Review: Drugs for mild-to-moderate hypertension in pregnancy reduce risk for severe hypertension but not preeclampsia

Abalos E, Duley L, Steyn D, Henderson-Smart DJ. **Antihypertensive drug therapy for mild to moderate hypertension during pregnancy.** Cochrane Database Syst Rev. 2007;(1):CD002252.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Hospitalists ★★★★★★☆ Nephrology ★★★★★★☆

QUESTIONS

In pregnant women with mild-to-moderate hypertension, what are the benefits and risks of antihypertensive drugs? Is one type of antihypertensive drug better than another?

METHODS

Data sources: Cochrane Pregnancy and Childbirth Group's Trials Register (March 2006); Cochrane Central Register of Controlled Trials (2005, issue 3); and MEDLINE, LILACS, and EMBASE/Excerpta Medica (to November 2005).

Study selection and assessment: Randomized controlled trials (RCTs) that evaluated any antihypertensive drug (compared with placebo or no antihypertensive drug [control] or another type of antihypertensive drug) for mild-to-moderate hypertension (systolic blood pressure [BP] 140 to 169 mm Hg and diastolic BP 90 to 109 mm Hg) during pregnancy. Quasi-randomized studies and those involving treatment for < 7 days were excluded. 46 RCTs (n = 4282) met the selection criteria: 28 RCTs compared antihypertensive drugs with control (n = 3200) and 19 RCTs compared 2 types of antihypertensive drugs (n = 1282). Quality of individual trials was assessed based on allocation concealment, blinding, and withdrawals.

Outcomes: Severe hypertension, preeclampsia, fetal or neonatal death, preterm birth, and small-for-gestational age (SGA) infants.

MAIN RESULTS

Most trials were of moderate-to-poor quality. Meta-analysis showed that antihypertensive drugs reduced severe hypertension more than control, but groups did not differ for preeclampsia, fetal or neonatal death, preterm birth, or SGA infants (Table). In 9 RCTs (n = 904), β-blockers showed a borderline increase in SGA infants (relative risk 1.4, 95% CI 0.99 to 1.9) compared with control; however, in direct comparisons (5 RCTs, n = 478), β-blockers did not differ from methyldopa for this outcome. β-blockers reduced severe hypertension more than methyldopa (Table); calcium-channel blockers did not differ from β-blockers (1 RCT, n = 100) or methyldopa (2 RCTs, n = 46) for this outcome. Different types of antihypertensive drugs did not differ for preeclampsia, fetal or neonatal death, preterm birth, or SGA infants.

CONCLUSION

In pregnant women with mild-to-moderate hypertension, antihypertensive drugs reduce risk for severe hypertension more than placebo or no antihypertensive drug, but no other effects on maternal or perinatal outcomes were shown.

Sources of funding: Medical Research Council UK and World Health Organization.

For correspondence: Dr. E. Abalos, Centro Rosarino de Estudios Perinatales, Rosario, Santa Fe, Argentina. E-mail crep@crep.com.ar.

Antihypertensive (anti-HT) drugs vs placebo or no anti-HT drug (control) or another anti-HT drug for mild-to-moderate hypertension in pregnancy*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Anti-HT drugs	Control		
Severe hypertension	19 (2409)	9.7%	19%	50% (39 to 59)	10 (8 to 13)
Preeclampsia	22 (2702)	18%	18%	3% (–13 to 17)	Not significant
Fetal or neonatal death	26 (3081)	2.7%	3.7%	27% (–8 to 50)	Not significant
				RRI (CI)	NNH
Preterm birth	14 (1992)	28%	27%	2% (–11 to 16)	Not significant
Small-for-gestational age	19 (2437)	13%	12%	4% (–16 to 27)	Not significant
		β-blockers	Methyldopa	RRR (CI)	NNT (CI)
Severe hypertension	8 (493)	25%	32%	21% (1 to 37)	12 (6 to 275)

*Abbreviations defined in Glossary. Weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from relative risks and control event rates in article using a fixed-effects model.

COMMENTARY

The relative benefits and risks of antihypertensive therapy for mild-to-moderate hypertension in pregnancy remain unclear because maternal cardiovascular health and fetal well-being compete. Most hypertensive pregnant women are otherwise well and do not require blood pressure treatment over a period of months; the uteroplacental vasculature does not autoregulate blood flow, and so perfusion reflects maternal blood pressure.

Why treat mild-to-moderate hypertension in pregnancy? Although the stated objective is "to prevent or delay progression to preeclampsia," the excellent review by Abalos and colleagues provides no evidence that antihypertensive agents are likely to decrease the incidence of preeclampsia. This finding makes sense. Preeclampsia is not primarily a hypertensive disease, despite being defined by its most common clinical manifestations: hypertension and proteinuria. Rather, preeclampsia is a placental disorder that becomes apparent when fetal demands exceed uteroplacental supply. Trials and quantitative overviews should focus on the complications of preeclampsia, not on the diagnosis itself.

Abalos and colleagues reviewed a host of small, moderate-to-poor–quality trials. Antihypertensive drugs clearly decrease the risk for severe hypertension; whether this decrease alone is worthwhile is unclear because, although severe hypertension was common (30% with methyldopa use), no strokes were reported. Thus, the key issue becomes perinatal outcomes, which did not differ between groups, although confidence intervals were wide.

A definitive trial is needed. In the meantime, if a decision is made to give antihypertensive therapy, the clinician will need to make a choice among treatment options. Most guidance from the review relates to β-blockers; these subgroup analyses had the greatest power. β-blockers may be associated with lower birth weights. The conclusion that β-blockers may be more effective antihypertensive agents than methyldopa is tenuous (the data were heterogeneous, and the result was of borderline statistical significance). The scant neurodevelopmental data (even for methyldopa) are insufficient to guide choice of one antihypertensive agent over another. Antihypertensive choice is not informed by the many other subgroup analyses of few included trials. This large number of comparisons is acceptable for hypothesis generation in a retrospective and observational exercise, such as meta-analysis, but they do not provide clear evidence for clinical decisions.

Laura A. Magee, MD
University of British Columbia
Vancouver, British Columbia, Canada