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FROM THE FAMILY PRACTICE INQUIRIES NETWORK

What treatments are safe and effective for mild to moderate hypertension in pregnancy?

Nancy Blum, DOCathy Kamens, MD

Department of Family Practice and Community Medicine, University of TexasSouthwestern Medical Center at Dallas;

Helen Mayo, MLS

University of Texas Southwestern Medical Center Library, Dallas

EVIDENCE-BASED ANSWER

There is considerable debate concerning the treatment of mild to moderate essential hypertension during pregnancy. Evidence suggests that because of the potential risk of fetal intrauterine growth restriction, treatment of hypertension should be delayed until maternal blood pressure reaches 150–160 mm Hg systolic or 100–110 mm Hg diastolic, as long as the mother has no preexisting end organ damage.

Methyldopa has been the drug of choice for oral treatment, as it is the only medication to have any extended follow-up study. However, a recent meta-analysis raised the possibility of increased fetal mortality (strength of recommendation [SOR]: **A**, based on systematic review of randomized controlled trials).

Labetalol is an effective alternative, but concerns remain that treatment with any beta-blocker increases the risk that infants will be small for gestational age (SGA) (SOR: **B**, based on small randomized controlled trials with inconsistent results).

There is limited evidence that calcium channel blockers and diuretics are safe alternatives, although evidence is insufficient to prove a clear benefit (SOR: **B**, based on limited randomized controlled trials). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), due to similar mechanisms of action, are contraindicated in pregnancy (SOR: **B**, based on multiple case studies). No other class of anti-hypertensive medications is proven to be harmful in pregnancy.

EVIDENCE SUMMARY

Treatment of maternal hypertension during pregnancy is based on maternal and fetal outcomes. Multiple meta-

analyses of randomized controlled trials show that the major maternal outcomes improved by treating mild to moderate hypertension are decreased progression to severe hypertension (number needed to treat [NNT]=12; 95% confidence interval [CI], 9–17) and decreased need for additional antihypertensive therapy.[1,2] The relative risk (RR) for preventing preeclampsia was 0.99 (95% CI, 0.84–1.18). The risk of preterm delivery was 1.00 (95% CI, 0.87–1.15).

The data for fetal outcomes are important, as the maternal benefits of treatment remain small.[3] Much of the debate centers on decreasing uteroplacental perfusion, which may lead to decreased fetal growth. One meta-analysis reviewed 45 trials to evaluate the potential increase in SGA infants caused by any antihypertensive treatment, through quantifying the fall in mean arterial pressure. The analysis found an average decrease in birthweight of 145 g for a 10 mm Hg fall in mean arterial pressurewith no increased perinatal morbidity.[4] The clinical significance of this is unclear.

In comparing one agent with another, methyldopa was the most commonly tested agent, with 14 randomized controlled trials of more than 1010 subjects demonstrating its efficacy at reducing blood pressure. Other antihypertensive agents appear better than methyldopa in terms of reducing the risk of infant mortality (RR=0.49; 95% CI, 0.24–0.99),[1] but the studies were small and used weak methods, and this finding may be due to bias.[5] Meta-analyses of beta-blocker trials show a borderline increase in SGA infants, with no related increase in perinatal mortality, as well as a decrease in the incidence of respiratory distress syndrome.[6]

Diuretics are effective antihypertensives, especially when combined with other agents, but they are known to decrease the circulating plasma volume, potentially decreasing uteroplacental perfusion. They are generally viewed as safe, as long as the mother is not already at increased risk for perfusion abnormalities (eg, preeclamptic states).[7] Calcium channel blockers, though generally regarded as safe and effective, have mostly been evaluated for use late in pregnancy, so their benefit-to-risk ratio remains uncertain.[8]ACE inhibitors and, by extension, ARBs, due to their similar mechanisms of action, are contraindicated in pregnancy, having been linked to miscarriage, fetal death, fetal renal failure, and malformation.[5,9-11]

RECOMMENDATIONS FROM OTHERS

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin states there is no evidence that antihypertensive treatment for mild to moderate hypertension improves maternal or fetal outcomes, even for women who are already receiving hypertension treatment at the time of pregnancy. ACOG suggests treatment may be stopped during pregnancy, or not initiated until blood pressures reach 150–160 mm Hg systolic or 100–110 mm Hg diastolic, unless the mother has underlying renal or cardiovascular disease.[9]

The National High Blood Pressure Education Program recommends the same guidelines as ACOG,[10] whereas the Canadian Hypertension Society consensus panel has chosen 140/90 mm Hg as the level at which treatment should be initiated.[11]

The *British Medical Journal* Clinical Evidence Guidelines reiterate that the evidence does not support the benefit of treating mild to moderate hypertension, except in reducing the progression to severe hypertension.[5] Methyldopa is consistently the drug of choice in all those making a specific recommendation,[9-11] although it

should be noted these recommendations were published before the 2003 Cochrane Review.[1]

CLINICAL COMMENTARY:

Benefits from treatment do not outweigh risks unless maternal BP moderately high

James Holt, MD

East Tennessee State University, Johnson City

I have always felt uneasy with treatment of mild to moderate hypertension in pregnancy, as chronic hypertension must be differentiated from preeclampsia; and the treatments seem counterintuitive. I often see new obstetric patients well into the third trimester, and how I should initially treat an elevated blood pressure has been unclear. Adding the welfare of the unborn baby raises the stakes further.

This Clinical Inquiry helps my decision about initiating treatment, as the benefits from treatment do not outweigh the risks to mother and fetus unless the maternal blood pressure is moderately high, and the recommended thresholds for treatment are rather high for women with no end organ damage. If I must treat her, it appears the best (but not perfect) option is methyldopa.

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