Cochrane for Clinicians

Putting Evidence into Practice

Antihypertensive Drug Therapy for Mild to Moderate Hypertension During Pregnancy

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Clinical Question

Does treatment of mild to moderate hypertension in pregnancy with antihypertensive drugs improve pregnancy outcomes?

Evidence-Based Answer

Compared with placebo, antihypertensive drug therapy for mild to moderate hypertension (defined by the authors as a blood pressure of 140 to 169 mm Hg systolic or 90 to 109 mm Hg diastolic) caused by chronic hypertension, gestational hypertension, or preeclampsia during pregnancy does not affect any pregnancy outcomes. However, it does reduce the risk of developing severe hypertension (relative risk [RR] = 0.49; 95% CI, 0.40 to 0.60; number needed to treat [NNT] = 10). Beta blockers and calcium channel blockers are more effective than methyldopa in preventing severe hypertension (NNT = 26).[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

In the United States, approximately 1% of pregnant women have chronic hypertension. Women with chronic hypertension in pregnancy have a higher risk of developing adverse obstetric outcomes, including gestational diabetes mellitus, postpartum hemorrhage, fetal growth restriction, preterm birth, and neonatal death, as well as a higher risk of preeclampsia. Preeclampsia occurs in 2% to 8% of all pregnancies worldwide.[1,2] The authors of this review sought to determine the effect of treating pregnant women with mildly to moderately elevated blood pressure caused by hypertension, gestational hypertension, or preeclampsia.

This Cochrane review included 58 randomized controlled trials involving 5,909 women.[1] The overall quality of the studies included in the review was rated as moderate to poor by the authors, mostly because of a higher risk of performance and detections bias. Sixteen of the included studies were published after 2000, and the largest featured 314 women. High-income countries as well as middle- and low-income countries were well represented. Thirty-one trials (n = 3,485) compared antihypertensive drug therapies with placebo or no therapy, and 29 trials (n = 2,774) compared one antihypertensive drug with another.

This review included women with any form of hypertension in pregnancy (chronic, gestational, or preeclampsia) with mild to moderate elevations in blood pressure. The primary outcomes examined in the analysis of antihypertensive therapy vs. placebo were development of severe hypertension in pregnancy (in general, greater than 170/110 mm Hg, although the authors also included trials in which severe hypertension was defined as greater than 160 mm Hg systolic), development of proteinuria/preeclampsia, miscarriage and fetal/neonatal death, preterm birth (at less than 37 weeks of gestation), and infants small for gestational age. There was a significant decrease in the development of severe hypertension, again generally defined by the authors as systolic pressure greater than 170 mm Hg or diastolic pressure greater than 110 mm Hg in the antihypertensive therapy group (RR = 0.49; 95% CI, 0.40 to 0.60; NNT = 10). There was no difference in any of the other primary outcomes. Of the numerous secondary outcomes discussed, only one was significant: treatment of mild to moderate hypertension resulted in a decreased risk of neonatal respiratory distress (absolute risk reduction [ARR] = 0.53; 95% CI, 0.2 to 0.99).

In the analysis of trials comparing one antihypertensive drug with another, no statistically

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CME **This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 398.

SUMMARY TABLE

Antihypertensive Drug Therapy vs. Placebo or No Drugs for Mild to Moderate Hypertension in Pregnancy

Outcomes (during pregnancy or postpartum)	Probable outcome with antihypertensive drug therapy*	Probable outcome with placebo/no drugs	NNT (95% CI)	Participants (studies)	Quality of evidence
Severe hypertension	97 per 1,000 (95% CI, 79 to 119)	198 per 1,000	10 (8 to 13)	2,558 (20 RCTs)	Moderate
Proteinuria/preeclampsia	171 per 1,000	185 per 1,000	NA	2,851 (23 RCTs)	Low
Total reported fetal or neonatal deaths (including miscarriage)	28 per 1,000	41 per 1,000	NA	3,365 (29 RCTs)	Moderate
Small for gestational age	149 per 1,000	152 per 1,000	NA	2,686 (21 RCTs)	Moderate
Preterm birth (< 37 weeks of gestation)	266 per 1,000	277 per 1,000	NA	2,141 (15 RCTs)	Moderate

NA = not applicable (no statistical difference in outcomes); NNT = number needed to treat; RCTs = randomized controlled trials.

*—In women with mild to moderate hypertension during pregnancy who are receiving any antihypertensive drug (e.g., beta blockers, methyldopa, calcium channel blocker, alpha blocker, glyceryl trinitrate, sildenafil [Viagra]).

significant difference in outcomes could be demonstrated. The majority of studies used medication classes commonly prescribed in the United States during pregnancy (beta blockers, calcium channel blockers, or methyldopa), although other medications (i.e., vasodilators, ketanserin, glyceryl trinitrate, furosemide [Lasix], sildenafil [Viagra]) were represented. Patients treated with calcium channel blockers or beta blockers were less likely to develop severe hypertension than those treated with methyldopa (RR = 0.70; 95% CI, 0.59 to 0.93). With regard to secondary outcomes, women treated with beta blockers or calcium channel blockers were less likely than those treated with methyldopa to have a cesarean delivery (ARR = 0.84; 95% CI, 0.74 to 0.95). Treatment of mild to moderate hypertension did not result in any other outcome differences or adverse effects.

The American College of Obstetricians and Gynecologists,[2] Hypertension Canada/the Society of Obstetricians and Gynaecologists of Canada,[3] and the European Society of Cardiology/European Society of Hypertension[4] all recommend pharmacologic treatment of severe hypertension in pregnancy (which they define as systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 110 mm Hg or greater). Guidelines for the treatment of mild to moderate hypertension in pregnancy differ. The American College of Obstetricians and Gynecologists recommends that antihypertensive drug therapy be initiated only for systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 110 mm Hg or greater, with a goal treatment range of 120 to 159/80 to 109 mm Hg. Hypertension Canada/the Society of Obstetricians and Gynaecologists of Canada guidelines recommend antihypertensive drug therapy for an average systolic measurement of at least 140 mm Hg or diastolic measurement of at least 90 mm Hg with a diastolic target of 85 mm Hg. The European Society of Cardiology/European Society of Hypertension 2018 hypertension guidelines recommend treatment for blood pressure greater than 150/95 mm Hg. The National Institute for Health and Clinical Excellence guidelines, which were last released in 2010, recommended that blood pressure be maintained at less than 150/100 mm Hg, but they are currently being updated.[5]

The practice recommendations in this activity are available at http://www.cochrane.org/CD002252.

Editor's Note: The numbers needed to treat reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

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Effectiveness and Safety of Factor Xa Inhibitors in Patients with Atrial Fibrillation

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Clinical Question

Are factor Xa inhibitors as effective and safe as vitamin K antagonists in the prevention of embolic events in patients with atrial fibrillation (AFib)?

Evidence-Based Answer

Treatment of AFib with a factor Xa inhibitor results in a decrease in the combined end point of stroke and embolic events (odds ratio [OR] = 0.89; 95% CI, 0.82 to 0.97), as well as a decrease in intracranial hemorrhage (OR = 0.50; 95% CI, 0.42 to 0.59) and all-cause mortality (OR = 0.89; 95% CI, 0.83 to 0.95) compared with warfarin (Coumadin) therapy.[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

AFib affects 2.7 to 6.1 million Americans. Patients with AFib have a four- to fivefold increased risk of embolic stroke vs. those without.[2-4] In addition to rate control, a mainstay of AFib treatment focuses on anticoagulation to prevent thrombus formation and decrease stroke risk. Before the introduction of factor Xa inhibitors, the vitamin K antagonist warfarin was the anticoagulant used most often. Use of warfarin, however, requires laboratory monitoring and dietary restrictions that are challenging for patients and clinicians. The authors of this review examined the effectiveness and safety of factor Xa inhibitors compared with warfarin in preventing stroke and embolic events in patients with AFib.

This review included 13 randomized controlled trials with 67,688 participants with mean and median ages ranging from 65 to 74 years.[1] These trials directly compared factor Xa inhibitors with dose-adjusted warfarin. Seven factor Xa inhibitors were represented in the trials, but studies looking at apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto) contributed 90% of the data. Factor Xa inhibitors significantly decreased the incidence of the primary outcome, all strokes and systemic embolic events, compared with warfarin (OR = 0.89; 95% CI, 0.82 to 0.97; 13 studies; n = 67,477). Age-related subgroup analysis revealed that all strokes and systemic embolic events were significantly decreased in patients 75 years and older who were treated with factor Xa inhibitors compared with warfarin (OR = 0.76; 95% CI, 0.66 to 0.88; four studies; n = 21,885).

Secondary outcomes included adverse events such as intracranial hemorrhage, all-cause death, and major or nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis criteria. The use of factor Xa inhibitors significantly reduced the risk of intracranial hemorrhage (OR = 0.50; 95% CI, 0.42 to 0.59; 12 studies; n = 66,259) and the number of all-cause deaths (OR = 0.89; 95% CI, 0.83 to 0.95; 10 studies; n = 65,624). Bleeding, both major and nonmajor, was not statistically different between groups. There were no significant differences between factor Xa inhibitors and warfarin with respect to disabling or fatal strokes, ischemic strokes, myocardial infarction, or hepatotoxicity.

The 2014 American College of Cardiology/American Heart Association guidelines for the management of patients with AFib state that antithrombotic therapy should be based on shared decision-making, risk, and patient preference.[5] These guidelines, as well as the 2016 European Society of Cardiology guidelines, include factor Xa inhibitors as initial and/or suitable anticoagulant treatment options, although they are not endorsed over other options such as warfarin.[5,6] Although direct medical costs incurred through the use of factor Xa inhibitors are significantly greater than those with warfarin ($7.43 to $14.60

per pill vs. $0.36 for warfarin),[7] there are also indirect cost savings to consider, including decreases in laboratory equipment use, testing, patient visits, associated patient travel costs, and adverse events requiring hospitalization and treatment. Furthermore, the findings in the age-related subgroup analysis suggest that patients 75 years and older achieve the greatest benefit and stroke prevention from factor Xa inhibitor use compared with warfarin. If available and indicated, factor Xa inhibitors are a safe alternative to warfarin and may be preferred in some populations.

The practice recommendations in this activity are available at http://www.cochrane.org/CD008980.

The views expressed in this article are the authors' and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences, the Department of Defense, or the U.S. government.

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