

Management of Chronic Hypertension During Pregnancy

Summary

Under its Evidence-based Practice Program (<http://www.ahrq.gov/clinic/epc/>), the Agency for Healthcare Research and Quality (AHRQ) is developing scientific information for other agencies and organizations on which to base clinical guidelines, performance measures, and other quality improvement tools. Contractor institutions review all relevant scientific literature on assigned clinical care topics and produce evidence reports and technology assessments, conduct research on methodologies and the effectiveness of their implementation, and participate in technical assistance activities.

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Overview

Chronic hypertension, defined as hypertension diagnosed before pregnancy or before 20 weeks' gestation, complicates from 1 percent to 5 percent of all pregnancies. The incidence is expected to rise as the demographic trend towards childbearing at older ages continues. Chronic hypertension in pregnancy is associated with:

- Serious maternal and fetal complications, including superimposed preeclampsia.
- Fetal growth retardation.
- Premature delivery.
- Placental abruption.
- Stillbirth.

Superimposed preeclampsia accounts for much of the increased risk of complications. The complications have significant economic impact, including costs of treating sick mothers and neonates and costs of intensive antenatal monitoring aimed at early detection of complications.

This review was proposed to the Agency for Healthcare Research and Quality by the American College of Obstetricians and Gynecologists because of perceived widespread uncertainty about the best management of chronic hypertension during pregnancy. The review is a systematic review of existing literature and not a guideline. The particular focus of the review was prespecified as management of mild to moderate chronic hypertension (blood pressure less than 170/110 mmHg) for several reasons:

- First, the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure currently recommends nonpharmacological treatment for women with mild to moderate hypertension and no concomitant

cardiovascular risk factors. Actual treatment practice, however, varies in younger, low-risk women.

Second, antihypertensive agents are used widely in pregnancies complicated by mild to moderate chronic hypertension, despite unclear tradeoffs between potential benefits and harms. Multiple agents are available, and various guidelines recommend different

agents as either contraindicated or drugs of choice.

Third, recent trials have provided new data regarding effects of aspirin in preventing preeclampsia.

Fourth, there is wide variation in practice regarding antenatal monitoring strategies applied to women with chronic hypertension and uncertainty about benefits and harms for the mother and fetus.

Reporting the Evidence

The purpose of this report is to help clinicians make informed choices about therapeutic interventions for pregnant women with chronic hypertension and to aid organizations developing guidelines for the treatment of this condition. The report evaluates evidence regarding risks of chronic hypertension, benefits and adverse effects of pharmacotherapy (antihypertensives and aspirin), nonpharmacological treatment, and monitoring techniques.

An expert multidisciplinary panel formulated 10 specific questions that address key diagnostic and treatment decisions faced by clinicians who provide care for pregnant women with mild to moderate chronic hypertension:

1. What is appropriate management of women with chronic hypertension before pregnancy?
2. Do antihypertensive agents for the treatment of mild to moderate chronic hypertension (<170/110 mmHg) during pregnancy improve maternal and perinatal outcomes? Are there subsets of women, such as those with diabetes or renal disease, for whom?
3. Is pharmacological treatment of mild to moderate chronic hypertension during pregnancy harmful to mothers, fetuses, and infants? If harmful, what is the type and magnitude of specific harm for mothers, fetuses, or infants?
4. Are particular antihypertensive agents more effective or harmful than others in treating mild to moderate chronic hypertension during pregnancy?
5. Does nonpharmacological treatment of mild to moderate chronic hypertension during pregnancy improve maternal and perinatal outcomes?
6. Is nonpharmacological treatment as efficacious as pharmacological treatment to improve maternal and perinatal outcomes in women with chronic hypertension?
7. Does a combination of pharmacological and nonpharmacological treatment improve maternal and perinatal outcomes over either treatment alone?
8. What is an appropriate blood pressure level at which to treat chronic hypertension during pregnancy and when should therapy be initiated? What is an appropriate blood pressure level at which to maintain treatment?

9. Is aspirin beneficial in preventing maternal and fetal complications in pregnant women with mild to moderate chronic hypertension?
10. Is the use of special fetal monitoring techniques (biophysical profiles, Doppler velocimetry, nonstress tests, contraction stress tests, fundal measurements, amniotic fluid index, ultrasound fetal biometry, fetal movement counting) and strategies (priority ordering of testing, number of tests, or timing of tests) beneficial or harmful to mothers and fetuses? Are there particular subsets of women for whom special monitoring techniques are warranted?

The primary outcomes of interest were perinatal mortality, growth restriction, preterm birth, abruption, and superimposed preeclampsia. Secondary outcomes included Apgar scores, maternal complications, rate of cesarean delivery, and length of gestation. We anticipated that data would be absent or scant for some of the questions and that specific gaps in the currently available evidence base would be identified.

Methodology

English and non-English language literature was identified from multiple sources, including several electronic databases (e.g., MEDLINE, EMBASE, Biological Abstracts, CINAHL, Cochrane Controlled Trial Registry and Pregnancy and Childbirth Database, REPROTOX, and TERIS), pertinent textbooks, and references from retrieved articles and technical experts. Databases were searched back to 1947 or to their inception. Four overarching search strategies, based on the questions' population of interest, pertinent intervention or exposure, and relevant study designs, were used.

Two or more persons independently screened the 5,558 titles and abstracts identified in the searches. Two reviewers abstracted articles meeting inclusion criteria except for articles addressing adverse effects, which were reviewed by only one person. Data were synthesized descriptively, emphasizing methodological characteristics of the studies such as populations enrolled, definitions of selection and outcome criteria, interventions and comparisons, and study designs. Relationships between clinical outcomes, participant characteristics, and methodological characteristics were examined in evidence tables and graphical summaries such as forest plots and L'Abbe plots. Because of concerns about heterogeneity in study populations and interventions, quantitative methods were not used to combine trial results. We used random effects methods to estimate summary odds ratios or risk of perinatal mortality and abruption associated with chronic hypertension.

Findings

Benefits of Treating Hypertension Before Conception

Three trials, synthesized in a recent review, had evidence relevant to the preconception management of chronic hypertension. As the trials did not include women younger than 30 years of age and the recent review grouped women 30 to 54 years of age, it is difficult to generalize observed absolute benefits to the situation of preconception management. Regardless, the data involving 8,565 women with mild to moderate hypertension, ages 30

to 54, show approximately 250 (95 percent confidence interval [CI] 158 to 1,606) such women need to be treated for 5 years to prevent a fatal or nonfatal cardiovascular event such as stroke. Women who are either younger than those involved in the trials or who are treated for shorter intervals than 5 years can expect less clinical benefit from antihypertensive therapy. For example, assuming an annual risk of any adverse cardiovascular event of less than 0.5 percent (a safe assumption for most young women of childbearing age with mild to moderate chronic hypertension) and that relative risk reductions established in trials are relatively stable, approximately 8,000 women need to be treated annually to prevent one cardiovascular event (95 percent CI 2,500 to 50,000).

Benefits of Treating Hypertension During Pregnancy

Data were too scant to either prove or disprove clinical improvements of at least 20 percent when mild to moderate chronic hypertension during pregnancy was treated. Thirteen randomized trials addressed this question, but all were small and most were unblinded. Few women were given treatment in their first trimester. Eleven different drugs or drug combinations were studied; data on any one drug were very limited. Definitions of chronic hypertension and outcomes such as preeclampsia and growth retardation differed from trial to trial.

Adverse Effects of Antihypertensive Agents

The methodological quality of research evidence addressing adverse effects of antihypertensive drug therapy in pregnant women is weak. Establishing causation in pregnancy with dechallenge/rechallenge tests is not feasible, and large clinical trials enrolling pregnant women have not been done. Adverse teratogenic effects are studied primarily in animal studies, and adverse effects in pregnant women are most often described in case reports. Thus, limited information on the incidence and magnitude of adverse effect risks is available.

Regardless, several antihypertensive agents have been associated with specific adverse events:

Angiotensin-converting enzyme (ACE) inhibitors used in the second or third trimester have caused renal dysfunction in the fetus, leading to oligohydramnios and anuria. ACE inhibitors have been associated with pulmonary hypoplasia, growth retardation, and a unique hypoplasia of the fetal skull.

Among the beta-blockers, atenolol, especially when started early in pregnancy, has been associated with fetal growth retardation in several uncontrolled studies and one small trial. In most studies, the causal nature of the association was unclear either because multiple agents were administered simultaneously or because of inability to separate effects of the mother's underlying pathophysiology from effects of the drug.

Labetalol has been associated with intrauterine growth retardation in three randomized trials of hypertensive disorders other than chronic hypertension.

Other beta-blockers, such as metoprolol, pindolol, and oxprenolol, have not been associated with intrauterine growth retardation, but available data concerning these agents, particularly when started early in pregnancy, are more scarce than for atenolol and labetalol.

A meta-analysis of nine randomized trials that evaluated diuretics during pregnancy did not find an increased risk of attendant fetal adverse events, nor did a large cohort study. Neither methyldopa nor hydralazine has been associated with any pattern of fetal anomalies.

Effects of Nonpharmacological Interventions

No trials comparing nonpharmacological interventions with either pharmacological agents or no intervention were found. Although there were such trials in women with pregnancy-induced hypertension, the technical experts for this evidence report did not think such data are easily generalized to the woman with chronic hypertension for several reasons. The risk of outcomes varies depending on the underlying risk factor (e.g., chronic hypertension vs. pregnancy-induced hypertension). The pathophysiology of underlying adverse outcomes is not clearly elucidated and may vary somewhat depending on precipitating etiology. Moreover, treatment effects may be related to specific pathophysiological mechanisms that vary according to precipitating etiology. Even if there are common pathophysiological mechanisms for some outcomes, treatment effects could vary depending on timing of administration (e.g., before or after preeclampsia has occurred) and whether the common mechanism has been activated.

Optimum Levels for Initiating Therapy and Risks of Elevated Blood Pressure

Although 46 case-control and cohort studies were found that evaluated risks associated with chronic hypertension, the optimum blood pressure for initiating and maintaining treatment could not be gleaned from such studies. The studies were limited by many confounding factors but consistently showed that chronic hypertension was associated with approximately threefold increases in risk of perinatal mortality and approximately twofold increases in risks of abruption. Increased risks of preeclampsia and of smaller babies were consistent observations. Risks were higher in women with more severe hypertension, and increased fetal risks were apparent even without superimposed preeclampsia.

Effects of Low-Dose Aspirin

Only one trial was specifically designed to test effects of aspirin in pregnant women with chronic hypertension, although several trials had subset data on such women. The double-blind placebo controlled trial designed specifically to assess aspirin effects in chronic hypertension involved 774 women. Low-dose aspirin, 60 mg daily, begun before 26 weeks gestational age, did not significantly reduce preeclampsia, intrauterine growth retardation, and perinatal mortality or significantly increase abruption, postpartum hemorrhage, and neonatal intraventricular hemorrhage.

Although the trial was of moderate size, small reductions or increases in risk (greater than 10 percent to 20 percent) could have been missed. Six trials with subgroup data pertinent to expectant mothers with chronic hypertension were generally consistent with the single trial's findings, but subgroup data were unobtainable from 11 such trials.

Special Monitoring Techniques

No studies assessing benefits, harms, or costs of special fetal monitoring techniques in women with chronic hypertension were identified. Although numerous studies of various monitoring strategies were found, they typically evaluated the accuracy of a particular test compared with some other standard test or studied a mixed "high risk" sample of women. Subgroup data for women with chronic hypertension could not be extracted from reports of such studies. The few monitoring studies that limited enrollment to women with chronic hypertension were not considered because of unsuitable research designs, such as case reports or small case series without clinical outcomes.

Future Research

Clinicians must grapple with a number of important decisions in caring for pregnant women with mild to moderate chronic hypertension:

Is any special management necessary preconception?

Should antihypertensive therapy be prescribed?

If antihypertensive therapy is prescribed, should a specific drug be given? If so, at what blood pressure should it be started and to what target titrated?

Should specific agents be avoided?

If a woman with hypertension who is already well controlled with a particular antihypertensive agent becomes pregnant, should another agent be substituted?

Are any nonpharmacological interventions of benefit?

Is aspirin more beneficial than harmful? If used, what dose is appropriate and when should it be initiated and discontinued?

How intensively should women with mild to moderate chronic hypertension be monitored for complications and with what tests?

This evidence report shows that these clinically salient questions are not well addressed with rigorously designed research. A pervasive problem is that the evidence base on chronic hypertension in pregnancy is small. There are few studies, and available studies typically have small numbers of participants and low power to detect moderate or sometimes large effects for important outcomes. A potpourri of women with different "high risk" obstetrical conditions has been studied, which complicates interpretation of results and alters precision of outcome measurements. Potential adverse effects of many antihypertensive drugs in pregnancy are either poorly established or unclearly quantified because of selection biases and coincidental occurrences that are reported in case reports and surveillance studies. Virtually no relevant research data with important outcomes are available to guide selection of fetal monitoring strategies in pregnant women with chronic

hypertension.

Advancement of clinical knowledge regarding management of chronic hypertension during pregnancy requires a multipronged approach.

A better understanding of current practice, including its motivations and its variations, is needed. Racial disparities in management approaches warrant study, as well as whether disparities are due to varying patient factors such as access and preferences or to varying provider approaches.

Benefits and harms of commonly used, but unproven, therapies need to be tested in studies that are large, collaborative, multicenter, and population based and that enroll women with clearly established mild to moderate chronic hypertension. To detect moderate (20 percent) relative risk reductions in preeclampsia, intrauterine growth retardation, and perinatal death with adequate power (80 percent), randomized trials are needed with enrollments of approximately 1,000, 3,000, and 6,000 women with chronic hypertension, respectively. Trials testing important outcomes such as preterm birth, neonatal intensive care utilization, or combined outcomes could be smaller.

Because efficacy of pharmacological treatment is not proven, therapy begun early in the course of pregnancy should be compared with placebo as well as among alternative commonly used drugs.

Advancement of knowledge concerning incidences and risks of adverse effects requires more and better surveillance systems that routinely monitor adverse events and numbers of women exposed to particular agents. Population-based case control studies and more large multicenter cohort studies that give careful attention to both selection and reporting biases also will help elucidate adverse effects.

Finally, to establish appropriate and cost-effective methods of monitoring women with chronic hypertension during pregnancy, large trials are needed that compare alternative strategies and use clinically important outcomes. In the absence of such trials, creative studies with case control designs and careful control for confounding factors may be helpful.

Availability of Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality by the San Antonio Evidence-based Practice Center (<http://www.ahrq.gov/clinic/epc/sananepc.htm>) based at the University of Texas Health Science Center at San Antonio under contract No. 290-97-0012. Print copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 1-800-358-9295. Requesters should ask for Evidence Report/Technology Assessment Number 14, Management of Chronic Hypertension During Pregnancy (AHRQ Publication No. 00-E011).

The Evidence Report is available online at: <http://hstat.nlm.nih.gov/frs/dbaccess/preg> or can be downloaded as a zipped file at: <http://www.ahrq.gov/clinic/evrptfiles.htm>.

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