Management of mild chronic hypertension during pregnancy: a review
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Authors' objectives
To conduct a systematic review of evidence relating to the management of mild chronic hypertension during pregnancy. This included the associated risks, benefits and harms of treatment with antihypertensive agents, non-pharmacologic measures and aspirin, and the benefits of various monitoring strategies.

Searching
The following electronic databases were searched for citations in any language: Biological Abstracts, CINAHL, the Cochrane Library, EMBASE, FEDRIP, HealthSTAR, HTA, MEDLINE, the Motherisk Program, REPROTOX and TERIS; and the databases of CCOHTA, Conseil d'Evaluation des Technologies de la Sante, the Health Services Utilization and Research Commission, the Institute for Clinical Evaluative Sciences, and the National Institute of Maternal and Child Health and Development (publications and clearing house). In addition, the references of articles and reviews were examined and a technical panel was consulted. All sources were searched from 1947, or their inception, until February 1999.

Searches on harmful effects were supplemented with information from a primary text that routinely reviews and categorises teratogenic risks and two routinely updated textbooks that report serious adverse effects seen in nongravid populations (see Other Publications of Related Interest nos.1-3).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for assessing maternal and perinatal outcomes from antihypertensive treatment, and for assessing the benefits of aspirin.

Case reports, case-control, cohorts, surveillance studies, RCTs and systematic reviews were eligible for assessing the harmful effect of antihypertensive treatment.

Case series, cohort studies and RCTs were eligible for assessing foetal monitoring techniques and strategies.

Specific interventions included in the review
Pharmacologic antihypertensive agents, non-pharmacologic interventions, aspirin and foetal monitoring techniques.

The pharmacologic agents used in the identified trials included diuretics, beta-blockers and calcium-channel blockers (bendrofluazide, hydralazine, hydrochlorothiazide, metoprolol, atenolol, labetalol, isradipine sustained-release, pindolol, ketanserin, methyldopa and nifedipine).

No trials of non-pharmacologic interventions or foetal monitoring techniques met the review criteria.

Participants included in the review
Pregnant females with mild-to-moderate chronic hypertension or with chronic hypertension were eligible. Mild-to-moderate chronic hypertension was defined as a blood-pressure (BP) of less than 170/110 mmHg, diagnosed either before pregnancy or before 20 weeks' gestation. Chronic hypertension was defined as known hypertension before pregnancy and/or a BP of greater than 140/90 mmHg before 20 weeks.

The participants in the trials of pharmacologic antihypertensives were a mixed group of high- and low-risk chronic hypertensive women with an initial BP reported from 6 to 37 weeks' gestation.

For trials assessing the harmful effects of antihypertensive treatment, the criteria for selection were pregnant or non-gravid participants with exposure to an antihypertensive agent.
For studies of aspirin, the participants in the trials had to be pregnant and have mild-to-moderate chronic hypertension.

For the assessment of foetal monitoring techniques and strategies, the participants in the trials had to be pregnant and have chronic hypertension.

Outcomes assessed in the review
The outcomes assessed were maternal and/or foetal morbidity (pre-eclampsia) or mortality. The harmful effects of treatment (teratogenic, foetal or maternal) were also assessed.

How were decisions on the relevance of primary studies made?
Two reviewers screened the titles and abstracts in accordance with the preliminary inclusion criteria; searches on harmful effects were screened by only one person. At least two independent reviewers screened the full text of the initially included articles to determine the final selection.

Assessment of study quality
The authors recorded data on the methodologic characteristics of the studies. For example, the populations enrolled, definitions of selection and comparisons, cointerventions, biases in outcome assessment or intervention administration, and study design. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two persons with clinical and methodological expertise abstracted the data from therapy trials, a physician with methodological expertise reviewed the data on risks, and a pharmacotherapist abstracted the data on adverse events. The authors of the papers were contacted when information on critical design features or outcome data were missing from the published reports. All abstractions were based on the full reports of articles, not abstracts. The reliability of the abstractions was not tested formally; any disagreements were resolved by consensus. Data were extracted on the methodologic characteristics, interventions, BP at baseline, drop-outs and outcomes.

Methods of synthesis
How were the studies combined?
Relations among clinical outcomes, participant characteristics, and methodological characteristics were examined using evidence tables and graphic summaries, such as forest plots.

The authors stated that the randomised trials were not combined quantitatively because of marked variance among the trials.

How were differences between studies investigated?
Differences between the studies were discussed narratively.

Results of the review
There were 13 RCTs (1,055 participants) of pharmacologic antihypertensive agents and 7 RCTs (1,473 participants) of aspirin. No trials of non-pharmacologic interventions or foetal monitoring met the review criteria.

Thirteen small RCTs were reported as having inadequate power to rule in or rule out moderate-to-large (20 to 50%) benefits of antihypertensive treatment. There was limited information on the incidence of adverse effects attributable to antihypertensive agents. Possible adverse effects were foetal renal failure when angiotensin-converting enzyme inhibitors are used in the second or third trimester, and growth restriction when atenolol is used early in pregnancy. The trials showed that aspirin neither reduces nor increases perinatal and maternal morbidity, but they did not rule out possible small to moderate beneficial or adverse effects. No studies provided guidance on the benefits or consequences of various non-pharmacologic therapies or monitoring strategies.
Authors' conclusions
The treatment and monitoring regimens that are beneficial are unclear but some treatments, such as angiotensin-converting enzyme inhibitors, are best avoided. Current evidence is too scant to prove or disprove the clinical benefit of treating mild hypertension in pregnancy with antihypertensive medication.

CRD commentary
The review questions were clearly stated and all major data sources were searched. Attempts were made to locate unpublished material and no language restrictions were applied. The text suggested that the studies were assessed for methodological quality, but it was unclear how the assessment was performed and not all the results were presented. The decision not to pool the results was appropriate given the diversity of the study designs and the variability in the interventions and participants among the RCTs.

This was a very complex review, which attempted to address several questions. It may have been more reasonable to address the questions separately rather than in a single paper, or to have separated them more clearly within this paper. Nevertheless, the conclusions are supported by the data presented. More details of the aspirin studies would have been useful.

Implications of the review for practice and research
Practice: The authors state that, since the evidence for efficacy of antihypertensive treatment for mild hypertension during pregnancy is lacking, safety considerations are paramount for clinicians who elect to prescribe antihypertensive medication in this indication.

Research: The authors state that further research is needed. They suggest the following: a better understanding of current practice is required; the benefits and harms of commonly used but unproven therapies must be tested in large collaborative multicentre and population-based studies that enrol women with clearly established mild chronic hypertension; pharmacologic therapy begun early in the course of pregnancy should be compared against placebo and commonly used alternative therapies; more and better surveillance systems that routinely monitor adverse events and the numbers of women exposed to particular agents are required; and large trials that compare alternative strategies and use clinically important outcomes are required to establish appropriate and cost-effective methods of monitoring women with chronic hypertension during pregnancy.

Funding
Agency for Healthcare Research and Quality.

Bibliographic details

PubMedID
11094241

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Abruptio Placentae /etiology; Antihypertensive Agents /therapeutic use; Chronic Disease; Female; Humans; Hypertension /drug therapy /therapy; Infant; Infant Mortality; Patient Selection; Pregnancy; Pregnancy Complications, Cardiovascular /drug therapy /therapy; Risk Assessment

**AccessionNumber**
12000002190

**Date bibliographic record published**
30/04/2003

**Date abstract record published**
30/04/2003

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.