Authors' objectives
To assess the effectiveness and adverse events of pharmacological and non-pharmacological antihypertensive interventions in pregnancy.

Searching
Sixteen electronic databases (including MEDLINE, EMBASE, CINAHL and HealthSTAR) were searched using an extensive search strategy that was listed in tables and appendices in the report. Searches regarding harms were supplemented with information from a primary test that routinely systematically reviews and categorises teratogenicity risks. There were no language restrictions. Bibliographical searches covered the years 1947 to 1999. The authors examined the references of pertinent articles and contacted technical experts for additional relevant data.

Study selection
Study designs of evaluations included in the review
The inclusion criteria for study design were randomised controlled trials (RCTs) or systematic reviews of RCTs. The authors included case series and cohort studies for the assessment of benefits and harms of special foetal monitoring techniques and optimum treatment levels and harms.

Specific interventions included in the review
The inclusion criteria for the interventions specified antihypertensive pharmacological or non-pharmacological therapies compared with a placebo, usual care or another agent.

Participants included in the review
The inclusion criteria for the participants specified women of childbearing age or pregnant with 'mild to moderate' chronic hypertension. For the assessment of harm, non-gravid participants were included.

Outcomes assessed in the review
The inclusion criteria for primary outcomes were perinatal mortality, growth restriction, pre-term birth, abruption and superimposed pre-eclampsia. The secondary outcomes were stated as Apgar scores, maternal complications, rate of Caesarean delivery and length of gestation.

How were decisions on the relevance of primary studies made?
Two authors independently screened and selected the retrieved articles for the review, except for studies addressing adverse effects which were screened by one reviewer.

Assessment of study quality
The authors assessed the internal validity of the studies for adequacy of randomisation (method and concealment of assignment), whether the trial was single or double blind, cointerventions and the number of drop-outs. 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 authors with clinical and methodological expertise independently performed the data extraction for the review. The abstractors were not blinded either to the study title or to the author's names. Any disagreements in the abstractions were resolved by consensus.

Methods of synthesis
How were the studies combined?
The studies were synthesised in a narrative with regard to the methodological characteristics of the studies, such as populations enrolled, definitions of selection and outcome criteria, sample sizes, adequacy of randomisation process, interventions and comparisons, cointerventions, biases in outcome assessment or intervention administration, and study designs. The studies were studied and discussed around a framework of ten clinical questions.

In addition to the narrative synthesis, statistical pooling was also performed, where appropriate, using random-effects models. The absolute risk reduction or mean difference was used for RCTs; however, these were not statistically pooled due to heterogeneity. For the retrospective case-control or cohort studies, the odds ratio was used to estimate the risk for adverse outcomes.

How were differences between studies investigated?
The authors examined relationships between clinical outcomes, participant characteristics, and methodological characteristics in evidence tables and graphical summaries such as forest plots and L’Abbe plots. Subgroup analyses and meta-regression were used to evaluate whether the risk estimates systematically varied with respect to the aforementioned characteristics.

Results of the review
A total of 215 studies were included in the review.

Benefits of treating hypertension before conception (3 trials): the review found that it was difficult from the evidence to generalise observed absolute benefits in the situation of preconception management. In women aged 30 to 54 years, approximately 259 women need to be treated annually to prevent one fatal or nonfatal cardiovascular event such as stroke (95% confidence interval, CI: 158, 1,606). In younger women, approximately 8,000 women would need to be treated annually to prevent one cardiovascular event (95% CI: 2,500, 50,000).

Benefits of treating hypertension during pregnancy (13 trials): the data were too scant to either prove or disprove clinical improvements of at least 20% when mild to moderate chronic hypertension during pregnancy was treated.

Effects of low-dose aspirin (1 trial): low-dose aspirin, 60 mg daily, begun before 26 weeks' gestational age, did not significantly reduce pre-eclampsia, intra-uterine growth retardation and perinatal mortality or significantly increase abortion, postpartum haemorrhage and neonatal intraventricular haemorrhage. Subgroup data from 6 trials were also available; however, this did not add significantly to the body of evidence because it was scant and not based on a priori hypotheses related to chronic hypertension. Adverse effects of antihypertensive agents: the methodological quality of research evidence addressing adverse effects of antihypertensive drug therapy in pregnant women is weak. A meta-analysis of 9 randomised trials that evaluated diuretics during pregnancy did not find an increased risk of attendant foetal adverse events, nor did a large cohort study. Neither methyldopa nor hydralazine has been associated with any pattern of foetal anomalies. There was conflicting evidence about the use of beta-blockers. The use of angiotensin-converting enzyme inhibitors showed some risk of foetal renal failure if used in the second or third semester.

Effects of non-pharmacological interventions: no trials comparing non-pharmacological interventions with either pharmacological agents or no intervention were found.

Optimum levels for initiating therapy and risks of elevated blood-pressure (46 case-control and cohort studies): the optimum blood-pressure for initiating and maintaining treatment could not be determined from the included studies. The studies were limited by many confounding factors, but consistently showed that chronic hypertension was associated with approximately three-fold increases in the risk of perinatal mortality and approximately two-fold increases in the risks of abortion. Increased risks of pre-eclampsia and of smaller babies were consistent observations. The risks were higher in women with more severe hypertension, and increased foetal risks were apparent even without superimposed pre-eclampsia.

Special monitoring techniques: no trials assessing the benefits, harms or costs of special foetal monitoring techniques in women with chronic hypertension were identified. The few monitoring studies that limited enrolment to women with chronic hypertension were not considered because of unsuitable research designs, such as case reports or small case series without clinical outcomes.
Authors' conclusions
This review shows that the ten research 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 the available studies typically have small numbers of participants and low power to detect moderate or sometimes large effects for important outcomes. The 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 the selection of foetal monitoring strategies in pregnant women with chronic hypertension.

CRD commentary
The authors have clearly stated the research questions and the inclusion and exclusion criteria for each of the ten questions in the review. The literature search was extensive and covered several databases, and was not restricted to English language publications. The search terms were stated and there were attempts to find unpublished or grey literature, and possible publication bias.

The quality of the included studies was assessed. The authors used the quality assessment results in the discussion of the methodological strengths and weaknesses of the grouped studies. Reporting of the conduct of the review was good with some details given on who performed the study selection and data extraction processes, although not for the quality assessment.

The data extraction was reported in tables in the review, along with definitions and outcomes used in the review. However, it was not possible to work out the total number of participants from these data. Narrative and statistical syntheses of the data were presented, depending on the heterogeneity found, and this was appropriate given the format and variety of the individual study results. The authors' conclusions and recommendations appear to follow from the results presented. However, the output of this review was very mixed regarding the results, so there is not a lot of information to guide practice.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that advancement of clinical knowledge regarding management of chronic hypertension during pregnancy requires a multipronged approach. This should address the following.

1. A better understanding of current practice.
2. The benefits and harms of commonly used, but unproven therapies in appropriately sized trials.
3. The need for therapies to be compared early in pregnancy with placebo.
4. The incidences and risks of adverse events.
5. The most appropriate and cost-effective methods of monitoring women with chronic hypertension during pregnancy.

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Bibliographic details
Original Paper URL
http://www.ahrq.gov/clinic/epcsums/pregsum.htm

Other publications of related interest
This additional published commentary may also be of interest. Atallah IN. Review: evidence is sparse and inconclusive for treating and monitoring chronic mild to moderate hypertension in pregnancy. Evid Based Med 2001;6:108.

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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.