Authors' objectives
To investigate the relationship between foetoplacental growth and the use of oral antihypertensive medication to treat mild-to-moderate pregnancy hypertension.

Searching
MEDLINE was searched for trials published between 1966 to 1997 using the following keywords: 'antihypertensive agents', 'bedrest', 'hospitalisation', 'plasma volume expansion', 'plasma substitutes', 'maternal mortality', 'pregnancy', 'pregnancy complications', 'perinatology', 'neonatology', 'infant newborn diseases', 'infant' and 'infant mortality'. Excerpta Medica (from 1989 to 1992) was examined to identify articles in Clinical and Experimental Hypertension in Pregnancy (now Hypertension in Pregnancy), which was subsequently handsearched from 1992 to 1997. The references of retrieved papers and a standard toxicology text (see Other Publications of Related Interest no.1) were also searched for relevant papers. Studies were restricted to those published in English or French.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included. Trials that appeared to have inadequate methods of randomisation, e.g. randomisation by alternate allocation, were included because most reports failed to describe the method of randomisation adequately.

Specific interventions included in the review
Orally administered drug or non-drug therapy for mild-to-moderate pregnancy hypertension. Trials that administered either placebo, no therapy or antihypertensive therapy to controls were included.

The drugs used were: methyldopa; beta-blockers such as acebutolol, atenolol, labetalol, metoprolol, oxprenolol, pindolol and propranolol; thiazide diuretics such as bendrofluazide, chlorothiazide and hydrochlorothiazide; ketanserin; hydralazine; calcium-channel blockers such as isradipine, nicardipine, nifedipine and verapamil; and clonidine. For drug versus drug trials, beta-blockers were always the experimental intervention and methyldopa was always the control.

Participants included in the review
Pregnant women were included.

Outcomes assessed in the review
Studies that assessed the effectiveness of maternal antihypertensive treatment, in terms of a treatment-induced change in mean arterial pressure (MAP) or perinatal risk, or both, were included. Foetal outcomes of interest were: gestational age at delivery, small-for-gestational-age (SGA) infants (definition recorded), mean crude birth weight and mean placental birth weight.

How were decisions on the relevance of primary studies made?
The retrieved papers were screened independently by two reviewers who resolved any disagreements through discussion.

Assessment of study quality
A published validity checklist was not used, but the authors examined whether allocation concealment was adequate, whether randomisation was successful (balanced baseline maternal characteristics between groups), and whether there was adequate outcome assessment masking. The authors do not state how the papers were assessed for validity, or how
many of the reviewers performed the validity assessment.

**Data extraction**
The data extraction was conducted independently by two reviewers, and any disagreements were resolved through discussion. The most up-to-date data were abstracted from duplicate publications.

When MAP, defined as diastolic blood-pressure plus one third of the pulse pressure, was not reported directly it was calculated from reported systolic and diastolic blood-pressure. The validity of this value was checked by the use of data from studies that reported all three measurements, i.e. MAP, systolic and diastolic blood-pressure. For each trial, the change in MAP from trial entry to the last record in pregnancy was calculated from the treatment values; this defined mean differences in MAP for each trial. Therefore a positive difference in MAP reflected a greater fall in the treatment group than in the control group. The severity of hypertension was defined by the mean value at enrolment: mild (MAP 107 to 113 mmHg), moderate (MAP 114 to 129 mmHg) or severe (MAP greater than or equal to 130 mmHg). Both the dose and duration of therapy were abstracted for the groups of treated women and controls.

**Methods of synthesis**

How were the studies combined?

The studies were combined by a meta-analysis using the Peto odds ratio (OR; see Other Publications of Related Interest no.2). Calculations were based on the fixed-effect model.

The primary aim of the meta-regression was to estimate the association of treatment-induced difference in MAP with measures of foetoplacental growth, i.e. SGA infants, birth weight and placental weight, by use of summary data from each trial. Other risk factors for poor foetoplacental growth such as type of hypertension, type of antihypertensive therapy, and difference between groups in treatment duration were of secondary interest; these could not be included in the regression because of the limited number of trials that reported these end points. Before the meta-regression, the co-linearity between the difference in MAP and each of these factors was assessed by non-parametric methods, i.e. Spearman's, Mann-Whitney U test or Kruskall-Wallis test, as appropriate. Lack of evidence for co-linearity was taken as support that the coefficient for difference in MAP in the regression model would remain essentially the same, irrespective of what else was included in the model.

The meta-regression was performed using weighted least-squares regression. The relationship between the difference in MAP and each of the measures of foetoplacental growth was estimated by Pearson’s correlation coefficient ($r^2$). A p-value of less than 0.05 was considered to be significant. For the SGA outcome, the natural logarithm of the OR for a given trial was used as the dependent variable in the regression. For continuous outcomes, i.e. birth weight and placental weight, the mean difference between treatment groups was used. Each study in the meta-regression was weighted to account for trial size, and therefore, study-specific effect measures (natural logarithm of the OR or mean differences) were not all measured with equal precision. The weights were determined as the inverse of the variance of the study-specific outcome variable. Each data point was multiplied by both the independent (i.e. difference in MAP) and the dependent (e.g. natural logarithm of the OR for a given trial) variable by the square root of the weight.

How were differences between studies investigated?

The authors did not report attempts to investigate sources of heterogeneity.

One trial was omitted from the primary analysis because it was identified as a statistical outlier by the current reviewers (and others). A sensitivity analysis was conducted in which data from this paper were included, and both non-parametric (Spearman’s) and parametric (Pearson’s r) methods were used. Secondary analysis included the relation between other risk factors for poor foetoplacental growth and measures of that growth.

**Results of the review**

Forty-five RCTs (41 publications) were identified that randomly allocated 3,773 women with mild-to-moderate pregnancy hypertension to oral antihypertensive treatment. Seven trials (6 publications) randomised women with chronic hypertension to therapy or either placebo or no therapy. A further 38 trials randomly allocated women with late-onset hypertension to antihypertensive therapy or either placebo or no therapy (15 trials; 15 publications) or other
antihypertensive therapy (23 trials; 20 publications).

In terms of quality, 12 (27%) of the 45 RCTs described adequate allocation concealment, 40 (89%) described successful randomisation by balanced maternal characteristics between groups, and 13 (29%) described adequate outcome assessment masking. The authors note that there was no apparent impact of these factors on trial outcomes.

A greater mean difference in MAP with antihypertensive therapy was associated with the birth of a higher proportion of SGA infants (slope 0.09, standard deviation, SD=0.03, r²=0.48, p=0.006; 14 trials) and lower mean birth weight (slope -14.49, SD=6.98, r²=0.16, p=0.049; 27 trials); this was found to be significant after exclusion of a paper regarded as an extreme statistical outlier. Over the range of the reported mean difference in MAP, a 10 mmHg fall in MAP was associated with a 145 g decrease in birth weight. Only 16% of the variation in mean birth weight between groups could be explained by the differential fall in MAP between treatment and control groups. Inclusion of one outlier (and exclusion of another) showed that this relationship was dependent on omitting this trial (slope -3.84, SD=6.54, p-values were 0.14 and 0.56 using non-parametric and parametric methods respectively). The authors state that there were no methodological problems in this trial that could explain the marked disparity in its results.

No significant relationship was observed between the mean difference in MAP and mean placental weight (slope -2.01, SD=1.62, r²=0.15, p=0.25; 11 trials).

Authors’ conclusions
Treatment-induced falls in maternal blood-pressure may adversely affect foetal growth. Given the small maternal benefits that are likely to be derived from therapy, new data are urgently needed to elucidate the relative maternal and foetal benefits, and the risks of oral antihypertensive drug treatment for mild-to-moderate pregnancy hypertension.

CRD commentary
The review question and inclusion criteria were clearly stated.

The search was adequate, although there was no attempt to identify unpublished literature, which means that publication bias cannot be ruled out. In addition, only papers that were published in English or French were included. The validity of included studies was assessed, but the number of authors who performed the validity assessment was not stated. Details of the primary studies were not provided. Tests for heterogeneity were not conducted before the studies were combined by meta-analysis.

The authors’ conclusions follow from the results, but should be viewed with caution given that tests for heterogeneity were not conducted before the data were combined.

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

Research: The authors state that new data from clinical trials are needed because, at present, we cannot be sure of the impact that antihypertensive treatment for mild-to-moderate pregnancy hypertension may have on perinatal outcomes.

Funding
Physicians’ Services Inc.; Mount Sinai Hospital, Department of Medicine.

Bibliographic details

PubMedID
10675164
Other publications of related interest


This additional published commentary may also be of interest. Ray J. Review: treatment induced blood pressure reductions in pregnancy may be associated with decreased fetal growth. Evid Based Med 2000;5:141.

Indexing Status

Subject indexing assigned by NLM

MeSH

Antihypertensive Agents /therapeutic use; Birth Weight /drug effects; Female; Humans; Hypertension /drug therapy; Infant, Newborn; Infant, Small for Gestational Age; Pregnancy; Pregnancy Complications, Cardiovascular /drug therapy; Regression Analysis

AccessionNumber

12000008014

Date bibliographic record published

28/02/2002

Date abstract record published

28/02/2002

Record Status

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