Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials


Authors' objectives
To examine the benefits and risks of beta-blockers for pregnancy hypertension.

Searching
The following potential sources were searched for English or French language publications: MEDLINE, from 1966 to December 1997, using the keywords 'adrenergic beta-antagonists', 'maternal mortality', 'pregnancy', 'pregnancy complications', 'perinatology', 'neonatology', 'infant newborn diseases', 'infant' and 'infant mortality'; Excerpta Medica, from 1989 to 1992, to identify papers from Clinical and Experimental Hypertension which was handsearched from 1992 to 1997; Science Citation Index, from 1990 to 1994; bibliographies of retrieved papers; and a standard toxicology text. Abstracts without companion publications were included only in a sensitivity analysis.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCT) were eligible. Studies with clearly inadequate methods of randomisation were included only in a sensitivity analysis.

Specific interventions included in the review
Comparisons of beta-blockers, including labetolol versus non-beta-blocker or no therapy were eligible. Trials of beta-blockers for indications other than pregnancy hypertension were included only in the evaluation of perinatal mortality and morbidity. Trials of single drug administration were accepted if beta-blockers could be expected to be in the maternal-fetal bloodstream at delivery and affect neonatal health. Short-term treatments were excluded from analysis of end point they could not theoretically impact.

Drug therapies were beta-blockers (atenolol, labetolol, pindolol, oxprenolol, metoprolol, acebutolol, and propranolol) with and without hydralazine compared to the following control interventions: placebo; no treatment; hydralazine; methyldopa; nicardipine; and diazoxide. Oral and intravenous (iv) therapies were included. Drugs were used in standard therapeutic doses.

Participants included in the review
Women with pregnancy hypertension were eligible. Participants included those with mild, moderate and severe chronic hypertension or 'late-onset' hypertension.

Outcomes assessed in the review
Maternal outcomes were severe hypertension, additional antihypertensive therapy, admission to hospital prior to delivery, development of preeclampsia or proteinuria, Caesarean section, placental abruption, and the need for patient to discontinue their randomised drug due to maternal side-effects. Perinatal outcomes were perinatal mortality, prematurity, small for gestational age (SGA) infants, admission to special care baby units (SCN)(for trials not practising routine admission) and neonatal bradycardia, hypoglycaemia, hypotension, hypothermia, low Apgar scores, respiratory distress syndrome (RDS). Outcomes classified as apnoea, asphyxia or respiratory distress were excluded. Definitions of outcomes used in different studies were reported in the review.

How were decisions on the relevance of primary studies made?
Titles, abstracts, and/or photocopies of the methods of retrieved papers were screened independently by two reviewers who corroborated their findings.

Assessment of study quality
Validity was not formally assessed although blinding was considered in the results tables. Two reviewers who corroborated their findings assessed validity.

**Data extraction**

Tables reported in the review included the following information: author; sample size; type and severity of hypertension; drug route; intervention; duration; outcome blinding; and fall in MAP. Two reviewers independently abstracted data and corroborated their findings. Abstracted data were entered into 2x2 tables using a statistical package. The most up-to-date data were extracted from duplicate publications.

**Methods of synthesis**

*How were the studies combined?*

Trials were grouped as follows according to the nature of the hypertensive process:

1. Those that enrolled and treated with oral beta-blockers only pregnant women with mild-to-moderate chronic hypertension.

2. Those that enrolled and treated with oral beta-blockers women with mild-to-moderate hypertension presenting later in pregnancy.

3. Those enrolling patients with severe hypertension requiring parenteral therapy.

Groups 1 and 2 were sub-divided according to whether beta-blockers were compared with placebo/no therapy or other antihypertensive therapy.

A summary odds ratio (OR) was calculated using the fixed-effect model of Mantel Haenzsel with the Robins-Breslow-Greenland confidence interval (CI) (see Other Publications of Related Interest nos.1-2). Exact methods were used when data were sparse. Significant results were also expressed in terms of absolute risk reduction (RR) using the number-needed-to-treat (NNT) and 95% CI. Publication bias was investigated for each outcome by calculating the fail-safe N and by plotting ln (OR) against sample size.

*How were differences between studies investigated?*

The null hypothesis (of no between-trial variation) was not rejected if the asymptotic p-value for the Breslow-Day test for homogeneity was less than 0.05.

When exact methods were used the Zelen test for homogeneity was employed.

Outcomes definitions that were not standardised were documented at data abstraction and considered as potential sources of between-study variation.

The following were considered as explanatory variables for each grouping of trials: characteristics of hypertension (severity of hypertension); intervention (route of administration, type of beta-blocker); therapy of controls; goal and duration of treatment; fall in mean arterial pressure (MAP); and outcome definitions. The relationship between ln (OR) and continuous explanatory variables was assessed by weighted least-squares regression using weights from the fixed-effect model. Pearsons R-squared > 20% was taken to suggest a relationship between ln (OR) and a trial characteristic. Details were given of methods used to assess the relationship between ln (OR) and categorical variables.

**Results of the review**

Thirty-four trials in forty publications were included (2324 women with pregnancy hypertension).

The median sample size was 22 patients per group (range: 3 to 97 women).

Methodological flaws included: no description of randomisation method (70% of studies), no allocation blinding (61%) and no blinding of the outcome assessment (67%).
Mean fall in MAP was 6.3 mm lower among labetolol-treated patients than among the comparison group.

There was no association between beta-blocker type and outcome.

Mild chronic hypertension (2 RCTs, 205 women).

Maternal.

No significant effect was found for beta-blockers on the following maternal outcomes: additional therapy (2 RCTs), developed proteinuria (1 RCT), Caesarean section (1 RCT) and placental abruption (1 RCT).

Perinatal.

SGA infants: inconsistent effects were found. The only demonstrated effect on perinatal outcomes was an increased incidence of SGA infants in one RCT but this was not found in a second RCT. No statistically significant effect was found on the following perinatal outcomes: perinatal mortality (2 RCTs), prematurity (1 RCT), neonatal hypoglycaemia (1 RCT) and low Apgar scores (1 RCT).

Mild-to-moderate 'late-onset' pregnancy hypertension.

1. Oral beta-blockers versus placebo/no therapy (8 RCTs, 891 women).

Maternal.

Severe hypertension (6 RCTs): beta-blockers significantly decreased the incidence of severe hypertension. The pooled OR was 0.27 (95% CI: 0.16, 0.45). No significant heterogeneity was found (p=0.62).

Additional therapy (6 RCTs): beta-blockers significantly decreased the incidence of additional therapy. The pooled OR was 0.32 (95% CI: 0.21, 0.50). No significant heterogeneity was found (p=0.73).

Admitted prior to delivery (3 RCTs): beta-blockers significantly decreased the incidence of admission. The pooled OR was 0.52 (95% CI: 0.33, 0.83). Significant heterogeneity was found (p=0.0006).

No significant effect was found for beta-blockers on the following maternal outcomes: developed proteinuria (7 RCTs), Caesarean section (6 RCTs), placental abruption (2 RCTs) and drugs changed because of maternal side-effects (6 RCTs). No significant heterogeneity was found.

Perinatal.

RDS: beta-blockers significantly decreased the incidence of RDS. The pooled OR was 0.33 (95% CI: 0.13, 0.85). No significant heterogeneity was found (p=0.93).

No significant effect was found for beta-blockers on the following perinatal outcomes: perinatal mortality (9 RCTs), prematurity (5 RCTs), admission to SCN (4 RCTs), neonatal bradycardia (3 RCTs), neonatal hypoglycaemia (3 RCTs) and low Apgar scores (3 RCTs).

2. Oral beta-blockers versus other drugs (15 RCTs, 959 women).

No significant effect was found for beta-blockers on maternal or perinatal outcomes compared with other drugs.

Severe 'late-onset' pregnancy hypertension (labetolol versus hydralazine or diazoxide, 5 RCTs, 171 women).

Maternal.

Maternal hypotension (4 RCTs): labetolol was associated with significantly less hypotension than other drugs. The pooled OR was 0.13 (95% CI: 0.03, 0.71). No significant heterogeneity was found (p=0.98).
Caesarean section (5 RCTs): labetolol was associated with a significantly lower section rate than other drugs. The pooled OR was 0.28 (95% CI: 0.13, 0.63). No significant heterogeneity was found (p=0.98).

No significant difference was found for beta-blockers versus other drugs on severe hypertension (4 RCTs) or additional therapy (3 RCTs). Data were not suitable for an assessment of other maternal outcomes.

Perinatal.

No significant difference was found for beta-blockers versus other drugs on perinatal mortality (7 RCTs), admission to SCN (2 RCTs), neonatal hypoglycaemia (5 RCTs), neonatal hypothermia (1 RCT), low Apgar scores (5 RCTs) or RDS (3 RCTs). Significant heterogeneity was found for low Apgar scores (p=0.018). This was attributed to one small study. Data were not suitable for an assessment of other perinatal outcomes.

There was no association between beta-blocker type and outcome (results not presented).

No effect of methodological quality, as assessed by allocation blinding on outcome (no results presented), was seen.

Outcome definitions varied considerably, but only for neonatal bradycardia did outcome definition have an impact on treatment effect.

Overall, beta-blocker-induced falls in MAP were associated with less severe hypertension and a borderline increase in SGA infants. No effect on proteinuria was seen.

Authors' conclusions
It is not clear that the benefits outweigh the risks when beta-blockers are used to treat mild to moderate chronic or pregnancy induced hypertension, given the unknown overall effect on perinatal outcomes. For severe 'late-onset' pregnancy hypertension, intravenous labetalol is safer than intravenous hydralazine or diazoxide.

CRD commentary
The aims were stated and inclusion criteria defined in terms of study design, participants, intervention and outcomes. Several relevant databases were searched, though by restricting studies to those published in the English language, other relevant articles may have been omitted. No attempt was made to locate unpublished material, thus raising the possibility of publication bias, a possibility that was acknowledged by the authors. Methods used to select studies were described. Whilst studies were limited to randomised controlled trials, no formal validity was carried out, although blinding was discussed. Some relevant details of the primary studies were presented in tabular format and methods used to extract data were described. Heterogeneity was assessed, results were reported and, when heterogeneity was significant, potential causes were investigated. The discussion includes consideration of some of the limitations of the review.

The conclusion that labetolol is safer than hydralazine or diazoxide was not supported by the evidence in terms of perinatal outcome. No perinatal outcome showed any statistical difference between intervention groups and the number of events was small (ranging from 2 to 14 per outcome assessed).

Implications of the review for practice and research
Practice: The authors state that for mild-to-moderate 'late-onset' pregnancy hypertension, consideration should be given to treat only severe hypertension with beta-blockers until the relative risks and benefits of mother and foetus are better defined; for severe 'late-onset' pregnancy hypertension, the review provides more justification for the use of labetalol (rather than hydralazine) when parenteral therapy is used to control severe hypertension and no contraindications to beta-blockers exist.

Research: The authors do not state any implications for research.
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