Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis

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CRD summary
This review found no significant differences between oral hypoglycaemic agents and insulin in glycaemic control or pregnancy outcomes in women with gestational diabetes. Patient satisfaction was higher with the oral agents because of ease of administration. The small numbers of included studies mostly with small sample sizes and of poor quality should be considered when interpreting the results

Authors' objectives
To compare the effects of oral hypoglycaemic agents (OHA) to insulin treatment in pregnant women with gestational diabetes

Searching
MEDLINE, EMBASE, National Health Service Library and The Cochrane Library were searched without language restrictions; search terms were reported. No dates for the searches were specified. References from editorials, letters, text books and retrieved studies were checked to identify additional references. Experts from the Royal College of Obstetricians and Gynaecologists were consulted about the literature search.

Study selection
Randomised controlled trials (RCTs) of patients with gestational diabetes in which insulin was compared with the oral hypoglycaemic agents of metformin or glyburide were eligible for inclusion. Studies had to measure one or more of maternal glycaemic control, neonatal and/or maternal hypoglycaemia, birthweight outcomes, neonatal intensive care unit admissions, intrauterine foetal deaths, congenital abnormalities, ketoacidosis, incidence of caesarean section, side effects of treatment and maternal satisfaction/quality of life outcomes. Duplicates studies and studies that were only published as abstracts, included patients with pre-existing diabetes and only provided preliminary information were excluded from the review.

The OHAs used in the trials were metformin and glyburide. Criteria for diagnosis of gestational diabetes included loading sugar from 75g to 100g and fasting glucose of 95mg/dL to 110mg/dL.

Two reviewers independently performed the study selection; any disagreements regarding eligibility were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed methodological quality by assessment of reporting of selection criteria, methods of randomisation, allocation concealment, comparability of treatment groups, blinding of outcome assessors, use of intention-to-treat analyses and treatment of losses to follow-up. The final data were reviewed by all the authors.

Data extraction
Data were extracted by two independent reviewers to calculate odds ratios (OR) for dichotomous outcomes and weighted mean differences (WMD) for continuous variables, with corresponding 95% confidence intervals (CI). The results were reviewed by all the review authors.

Methods of synthesis
Pooled odds ratios, weighted mean differences and 95% CIs were calculated using a DerSimonian and Laird random-effects model. Statistical heterogeneity was evaluated using the Woolf Q-statistic for dichotomous variables and Cochran's Q-statistic for continuous variables. Homogeneity across studies was assessed by qualitative visual appraisal of forest and L’Abbe plots.
**Results of the review**

Six RCTs (n=1,388 participants) were included in the review. Sample size ranged between 23 and 733 patients. The treatment and insulin groups were comparable in four trials, although in one trial body mass index was higher in the group that received oral hypoglycaemic agents and in another trial gestational age was more in the OHA group. Allocation concealment was adequately reported in two RCTs. There were no trials with assessor blinding. Doses of insulin and OHA were not reported in most studies. Intention-to-treat analyses were used in four trials. Losses to follow-up were less than 10% or not significant in five trials.

There were no significant differences observed between insulin and OHA for glycaemic control (WMD 1.31, 95% CI -0.81 to 3.43; five RCTs), neonatal hypoglycaemia (OR 1.59, 95% CI 0.70 to 3.62; five RCTs), birthweight (WMD 56.11, 95% CI -42.62 to 154.84; six RCTs), incidence of large-for-gestational age-babies (OR 1.01, 95% CI 0.61 to 1.68; four RCTs). Other outcomes in which no significant differences were found between treatments were admission to neonatal intensive care units, neonatal respiratory distress and birth injuries, incidence of small-for-gestational-age babies, preterm births, intrauterine foetal death, congenital abnormalities and maternal hypoglycaemia. The authors reported statistically significant heterogeneity across the results for all complications.

There was a statistically significant higher level of patients satisfaction found with OHA treatment with metformin compared to the group that received insulin (76.6% compared to 27.2%, one RCT) which was attributed to the greater ease of administration of the OHA.

The proportions of patients allocated to receive OHA who also required insulin treatment ranged from "low" to 46.3%, with a higher conversion rate observed in the studies that used metformin.

**Authors' conclusions**

Oral hypoglycaemic agents are credible and safe alternatives to insulin for the first-line treatment of gestational diabetes. In selected cases, these agents may be used as adjunctive treatments to insulin in the management of gestational diabetes.

**CRD commentary**

The review addressed a clear question. Criteria for the inclusion of studies were defined. Appropriate electronic databases were used to identify relevant studies. There were no language restrictions. The review appeared to be restricted to published studies, so there was some risk of publication bias. Steps were taken by the reviewers to minimise errors and bias at all parts of the review process. Pooling results may not have been justified given the presence of statistical heterogeneity identified across all the studies, most of which were small and of poor quality. Little information was presented about dosages of OHA and insulin in the trials, which precluded conclusions about the optimal dose regimen for patients with gestational diabetes. The authors acknowledged some weaknesses of the review concerning the possible presence of publication bias.

In general the review was well conducted, but the small numbers of included studies mostly with small sample sizes and of poor quality should be considered when interpreting the results.

**Implications of the review for practice and research**

**Practice:** The authors stated that oral hypoglycaemic agents were suitable for use in gestational diabetes because of satisfactory glycaemic control, maternal and perinatal outcomes that were comparable with insulin treatment. Use of these agents was associated with higher patient satisfaction, convenience and less patient instruction at initiation of treatment.

**Research:** The authors stated that further research was required to confirm the side-effect profile found in the results of one trial which suggested that treatment of gestational diabetes with metformin was not associated with long-term complications.

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