Metformin vs thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis

CRD summary
The review found that there was insufficient evidence to determine whether metformin or thiazolidinediones were superior for the treatment of polycystic ovary syndrome. Considering the poor quality of included trials and substantial variation, the authors' cautious conclusions are appropriate and likely to be reliable.

Authors' objectives
To compare the efficacy and safety of insulin-sensitising drugs such as metformin and thiazolidinediones for the treatment of polycystic ovary syndrome.

Searching
MEDLINE (from 1966) and EMBASE (from 1988) were searched up to May 2010 for relevant studies published in English; search terms were reported. Reference lists of retrieved papers were also searched.

Study selection
Parallel-group randomised controlled trials (RCTs) of patients with polycystic ovary syndrome, in which metformin was compared with thiazolidinediones (rosiglitazone or pioglitazone) to assess effects on clinical, hormonal and metabolic outcomes, were eligible for the review.

Clinical outcomes included body mass index, ovulation, pregnancy, hirsutism and menstrual pattern. Hormonal outcomes included serum androstenedione, free testosterone, dehydroepiandrosterone sulphate, luteinising hormone and follicle-stimulating hormone levels. Metabolic outcomes included fasting blood glucose, fasting insulin levels, homeostasis assessment model of insulin resistance, total cholesterol, high-density lipoprotein C, low-density lipoprotein C and triglycerides.

Included trials were undertaken in Turkey, Saudi Arabia, Mexico, Slovenia, Virginia, Bulgaria, and the UK. In included trials, most patients ranged in body mass index (BMI) from the normal range (BMI 22 to 25) to obese (BMI 31 to 36). Participants were mostly insulin resistant, but one trial specifically included non-obese patients with normal insulin sensitivity. Daily doses of metformin ranged from 1,500mg to 2,550mg; daily doses of rosiglitazone were either 4mg or 8mg; daily doses of pioglitazone were either 30mg or 45mg. Treatment duration ranged from three to six months.

Two reviewers independently selected studies for the review, with disagreements resolved by consultation with a third reviewer.

Assessment of study quality
Trials were assessed for quality with criteria including randomisation, blinding, allocation concealment, and intention-to-treat analyses. These criteria were graded as adequate, unclear, inadequate, or not used.

Two reviewers independently assessed studies for quality, without disagreements.

Data extraction
Data were extracted on clinical, hormonal and metabolic outcomes. Safety data were extracted on the side-effects of treatments. Dichotomous outcomes were expressed as odds ratios (ORs) and continuous data as mean differences, with 95% confidence intervals (CIs).

Two reviewers independently extracted data.

Methods of synthesis
Trials were pooled in meta-analyses. Summary effect measures, odds ratios, weighted mean differences (WMDs) or standardised mean differences (SMDs) were calculated, with 95% confidence intervals, using a fixed-effect model.
where the $X^2$ test of heterogeneity indicated statistical homogeneity. The random-effects model was used when unexplained statistical heterogeneity was found. Heterogeneity was also quantified using $I^2$.

Subgroup analyses were undertaken based on treatment duration of three or six months.

**Results of the review**

Ten RCTs (n=459 women) were included in the review. Adequate randomisation was reported in six trials. Allocation concealment was reported in two trials. Double blinding was reported in one trial. Intention-to-treat analysis was reported in one trial. The participant withdrawal rate ranged from zero to 44%.

**Three-month treatment duration** (six RCTs)

Clinical outcomes: Compared with thiazolidinediones, metformin was associated with a significant reduction in body mass index (WMD or SMD -2.47, 95% CI -3.33 to -1.62; $I^2$=55%; five RCTs). No significant differences were found between the treatment groups for the other clinical outcomes.

Hormonal and metabolic outcomes: Compared with metformin, thiazolidinediones were associated with a significant reduction in free testosterone (WMD or SMD 0.36, 95% CI 0.03 to 0.69; $I^2$=0%; three studies) and DHEAs (WMD or SMD 0.49, 95% CI 0.18 to 0.79; $I^2$=0%; four studies) but there were no significant differences reported between the treatment groups for the other hormonal or metabolic outcomes (for many metabolic outcomes there was significant heterogeneity).

**Six-month treatment duration** (four RCTs)

Clinical outcomes: Compared with thiazolidinediones, metformin was associated with a significant reduction in body mass index (WMD or SMD -0.70, 95% CI -0.76 to -0.65; $I^2$=0%; four RCTs). There were no significant differences between groups for pregnancy or hirsutism rate.

Hormonal outcomes: Compared with metformin, there was a non significant trend favouring thiazolidinediones in the reduction of luteinising hormone (WMD or SMD 0.3, 95% CI -0.03 to 0.63; $I^2$=29.3%; three RCTs). No significant differences were found between the treatment groups for the other hormonal outcomes (for many outcomes there was significant heterogeneity).

Metabolic outcomes: Compared with thiazolidinediones, metformin was associated with a significant reduction in triglycerides (WMD or SMD -1.13, 95% CI -1.68 to -0.57; $I^2$=61.4% but heterogeneity test not significant; two RCTs). No significant differences were found between the treatment groups for the other metabolic outcomes (for many outcomes there was significant heterogeneity).

**Side effects**: Compared with thiazolidinediones, metformin was associated with a significant increase in the odds of any side effects at three months (OR 8.88, 95% CI 3.54 to 22.27; $I^2$=20.2%; five RCTs) and at six months (OR 12.22, 95% CI 3.53 to 42.31; $I^2$=0%; three RCTs). Side effects with metformin were mostly gastrointestinal, such as nausea, diarrhoea or abdominal cramping; with thiazolidinediones, they were mostly headaches.

**Authors' conclusions**

There was insufficient evidence to determine whether metformin or thiazolidinediones were superior for the treatment of polycystic ovary syndrome.

**CRD commentary**

The review addressed a clear research question. The inclusion criteria appeared appropriate. A limited search was conducted (two databases and reference lists) for studies published in English, so language and publication bias could not be excluded. Adequate methods were used to select studies, extract data, and assess studies for quality, which minimised the chances of reviewer error and bias.

A suitable assessment tool was used to evaluate the included trials; all the trials were small, with sample sizes less than 100. Most trials had major shortcomings in quality, with lack of allocation concealment, blinding, and intention-to-treat analysis. Two trials had withdrawals of more than 30%. Synthesis in meta-analyses and assessment of heterogeneity
were appropriate, but interpretation of the results was hindered by the lack of clarity in the reporting of the specific summary effect measures (WMD or SMD) used in the measurement of each outcome (reported in tables). There was substantial heterogeneity in many analyses, particularly for the measurement of metabolic outcomes at three or six month treatment duration and hormonal outcomes at six months duration. The authors acknowledged that the follow-up periods in the included trials were of insufficient duration to enable meaningful interpretation of the effects of treatment on several clinical outcomes, such as pregnancy and ovulation rate.

Considering the poor quality of the included trials and substantial heterogeneity, the authors’ cautious conclusions are appropriate and likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that side effects and costs need to be considered in decision making on the suitability of drug options for treatment of polycystic ovary syndrome.

Research: The authors stated that a large scale well-designed RCT was needed to adequately compare metformin with thiazolidinediones. It should also assess cost and quality of life, control for heterogeneity and perform intention-to-treat analysis for the measurement of outcomes.

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