Insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials


CRD summary
This well-conducted review assessed insulin sensitisers for the treatment of hirsutism in women. The authors concluded that inconsistent and low-quality evidence suggested that insulin sensitisers provided limited or unimportant benefit for hirsutism treatment. This cautious conclusion was an accurate reflection of the evidence and was likely to be reliable.

Authors' objectives
To assess the evidence for the use of insulin sensitizers including metformin and thiazolidinediones (TZDs) in the treatment of hirsutism.

Searching
MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched without language restrictions from inception to May 2006. Search terms were reported as being available from the authors. Reference lists of identified studies and reviews were checked, and experts were contacted. Only studies reported in full were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) that compared metformin or TZDs – alone or in combination with oral contraceptive pills (OCPs) or anti-androgens – to placebo or OCPs or anti-androgens for the treatment of hirsutism in women aged at least 12 were eligible for inclusion. Studies were required to have a minimum treatment duration of six months and to report hirsutism as an outcome. Both subjective and objective measures of hirsutism were acceptable. Studies enrolling patients with a diagnosis other than polycystic ovary syndrome (PCOS), idiopathic hirsutism or presumed late-onset congenital adrenal hyperplasia were excluded from the review, as were studies using clomiphene, glucocorticoids or GnRH (gonadotropin-releasing hormone) as therapeutics.

Included studies enrolled predominantly young women (median age 27 years) with a diagnosis of PCOS. Approximately half the studies enrolled only overweight or obese women, a quarter only enrolled lean women; a quarter had minimum hirsutism inclusion criteria. Interventions used were metformin at doses between 1,000 mg/day and 2,000 mg/day or the TZDs troglitazone at 600 mg/day or rosiglitazone at 4 mg/day. Anti-androgens used were spironolactone and flutamide. OCPs used involved ethinyl estradiol at 30 micrograms or 35 micrograms and one other agent.

Two reviewers independently assessed the studies for inclusion in the review. Disagreements were resolved through discussion with or arbitration by a third reviewer.

Assessment of study quality
Two reviewers independently assessed study validity using the following criteria: allocation concealment; blinding of participants clinicians and outcome assessors; and loss to follow-up.

Data extraction
Two reviewers independently performed the data extraction using a standardised form. Authors were contacted for outcome data where necessary. Mean differences between control and intervention groups were calculated using end of study or change from baseline data. Data for the latest follow-up at which patients were still exposed to the interventions were used for these calculations.

Methods of synthesis
The studies were combined using a DerSimonian and Laird random-effects meta-analysis to calculate a weighted mean difference (WMD) with 95% confidence interval (CI) for subjective assessment of hirsutism by a healthcare professional. Statistical heterogeneity was assessed using the $I^2$ statistic. Where multiple comparisons were reported the
control group was not included multiple times in the analysis. A priori subgroup analyses were used to assess the impact of aspects of study quality (blinding and attrition), patient population (age, aetiology and baseline hirsutism) and treatment and control interventions (nature, dose and duration). Some additional post hoc comparisons were undertaken on the effect of weight. Interactions between subgroups and treatments were also explored. Patient-assessed and physician-assessed outcome measures were analysed separately.

**Results of the review**

Sixteen RCTs with 22 comparisons were included in the review. Only two studies reported blinded outcome assessment. Only four reported adequate allocation concealment. Seven studies had attrition rates higher than 20 per cent.

Insulin sensitisers versus placebo (nine RCTs). There was a small but statistically significant effect of insulin sensitisers (WMD -1.5, 95% CI: -2.8, -0.2).

Insulin sensitisers versus OCPs (five RCTs). There was no statistically significant difference between the groups.

Metformin versus androgens (three RCTs). There was a statistically significant difference in favour of anti-androgens (WMD - 3.7, 95% CI: -6.8, -0.6).

Metformin combined with other treatments (five RCTs). Metformin plus flutamide was statistically significantly more effective than metformin alone (WMD -4.6, 95% CI: -7.9, -1.3; two RCTs). No significant differences were found between metformin combined with flutamide versus OCP (one RCT) or between metformin plus flutamide versus flutamide alone (two RCTs).

High or moderate levels of statistical heterogeneity were found in all analyses. Results of subgroup analyses were reported extensively. Results for studies using patient self-assessment were also reported.

**Authors' conclusions**

Inconsistent and low quality evidence suggests that insulin sensitizers provide limited or no important benefit for women with hirsutism.

**CRD commentary**

The review question and inclusion criteria were clear and specific. The authors searched some relevant databases and other sources. The lack of restrictions on language or publication status reduced the chances of bias and of relevant studies being excluded. The authors used rigorous methodology throughout the review process and conducted an appropriate validity assessment which was used to inform the synthesis. The use of meta-analysis and the a priori specification of sub-group analyses was appropriate for the exploration of statistical heterogeneity. However, a large number of analyses was proposed, which can raise the issue of multiple comparisons and increasing the likelihood of a significant result being detected. The authors' cautious conclusions reflected the poor quality evidence of the review and were likely to be reliable.

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

**Practice:** The authors referred to accompanying clinical practice guidelines.

**Research:** The authors stated that independently funded large RCTs should be conducted in women with different aetiologies of hirsutism using different types and doses of insulin sensitizers alone and in combination with other interventions (particularly OCPs). These should have long follow-up periods and use a primary outcome of blinded patient-assessment of hirsutism. In particular efficacy in overweight women should be investigated. Trials with biological and mechanical comparators should also be undertaken.

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