The effects of Diane-35 and metformin in treatment of polycystic ovary syndrome: an updated systematic review

CRD summary
This review assessed whether Diane-35 could improve the treatment for polycystic ovary syndrome, with and without metformin. The authors concluded that Diane-35 was superior to metformin in reducing androgens, but was inferior in reducing insulin and did not improve hirsutism. There was no evidence of improved outcome for Diane-35 combined with metformin. The authors' conclusions appear to be reliable.

Authors' objectives
To assess the efficacy and safety of Diane-35 in the treatment of polycystic ovary syndrome in combination with and without metformin.

Searching
MEDLINE (1950-February 2008), the Cochrane Central Register of Controlled Trials (February 2008) and the Chinese National Knowledge Infrastructure (February 2008) were searched. The search terms were reported. The bibliographies of retrieved articles and relevant conference reports were manually searched for additional studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that investigated Diane-35 (35 μg ethinyl oestradiol plus 2 mg cyproterone acetate) and metformin in the treatment of polycystic ovary syndrome were eligible for inclusion. Three intervention groups were included: Diane-35 versus metformin; Diane-35 versus Diane-35 combined with metformin; and metformin versus metformin combined with Diane-35.

The primary outcome was hirsutism (measured by the Ferriman-Gallwey score). Secondary outcomes were also listed; these were grouped into clinical, hormonal and metabolic parameters. Severe adverse reactions requiring stopping of medication were also assessed. RCTs without detailed numerical data for outcomes were excluded from the meta-analysis but included in the review. Patient populations described in more than one publication, with the same outcome criteria, were reported from the study with the most detailed data. Studies were excluded if there was no evidence of randomisation.

The duration of interventions ranged from three to 12 months, this led to subgroup analysis during meta-analysis. The dosages of metformin ranged from 250 to 1,000 mg. Where stated, patients had a body mass index of approximately 25 to 31 kg/m² and ranged in age from 16 to 36 years.

Three reviewers selected studies by analysing the titles, abstracts and keywords of retrieved articles for the inclusion criteria. Eligibility for inclusion was resolved by discussion.

Assessment of study quality
Study quality was assessed in terms of randomisation, allocation concealment, blinding and study withdrawals. Each was scored as ‘adequate’, ‘unclear’ or ‘inadequate’ or ‘not used’. The authors did not state how these criteria were applied.

Two reviewers assessed validity.

Data extraction
Data on the occurrence of each outcome was extracted from each study and used to calculate an odds ratio or weighted mean difference for dichotomous or continuous data respectively. Associated 95% confidence intervals were calculated.
Data extraction was carried out by two independent reviewers and checked for accuracy.

Methods of synthesis
The pooled odds ratios and corresponding 95% confidence intervals were calculated using a fixed-effects meta-analysis. Summary data were calculated separately for comparisons of Diane-35 versus metformin (with subgroups based on treatment duration) and Diane-35 versus Diane-35 combined with metformin. Statistical heterogeneity was assessed using the $I^2$ and the $\chi^2$ tests. Subgroup analysis was performed on the country of the trial origin.

Results of the review
Twelve randomised controlled trials (RCTs) met the inclusion criteria (n=582 patients). Trials investigated the effects of Diane-35 versus metformin (nine RCTs), Diane-35 versus Diane-35 plus metformin (two RCTs) and metformin versus metformin plus Diane-35 (one RCT). Four trials reported adequate randomisation and two trials reported adequate allocation concealment. Three trials reported adequate levels of blinding. Only one trial reported using intention-to-treat analysis. Drop-out rates ranged from 0 to 43.75%, and were not found to be statistically different between control and intervention groups. Publication bias was not reported.

Diane-35 versus metformin (three months): Diane-35 did not improve hirsutism in comparison to the use of metformin (odds ratio -2.12, 95% confidence interval (CI): -4.78 to 0.53; two RCTs, n= 42 patients) or other clinical outcomes. Trials with no heterogeneity showed that Diane-35 was superior to metformin in reducing serum levels of androgens (odds ratio -0.41, 95% CI: -0.58 to -0.24; four RCTs, n=99 patients), luteinizing hormone (odds ratio -1.97, 95% CI: -3.16 to -0.77; four RCTs, n=99 patients), dehydroepiandrosterone sulphate (odds ratio -3.23, 95% CI: -5.10 to -1.37; two RCTs, n=42 patients) and increasing sex hormone binding globulin (odds ratio 127.39, 95% CI: 105.04 to 149.74; two RCTs, n=42 patients). Diane-35 showed no improvement for lipid or insulin metabolism in trials with no heterogeneity. Diane-35 did not significantly affect the reporting of severe side effects in one trial.

Diane-35 versus metformin (six months): The effects of Diane-35 were identical to those for three months for clinical, hormonal and metabolic outcomes. However, glucose metabolic abnormalities increased (odds ratio 3.5, 95% CI: 1.18 to 10.35; three RCTs, n=83 patients) and fasting insulin increased (odds ratio 3.51, 95% CI: 1.53 to 5.49; three RCTs, n=69 patients). More studies could not be combined due to heterogeneity; the authors discussed possible sources for this. Side effects were reported as being identical to those at three months.

Diane-35 versus Diane-35 plus metformin: Trials demonstrating no heterogeneity found that Diane-35 did not significantly affect clinical, or lipid metabolic outcomes in comparison to Diane-35 plus metformin. Diane-35 significantly reduced sex hormone binding globulin levels in comparison to Diane 35 plus metformin (odds ratio -31.05, 95% CI: -42.58 to -19.58; two RCTs, n=90 patients) and increased fasting blood glucose (odds ratio 0.34, 95% CI: 0.12 to 0.56; two RCTs, n=90 patients) and fasting insulin levels (odds ratio 6.62, 95% CI: 3.87 to 9.38; two RCTs, n=90 patients). No severe side effects were found.

Metformin versus Diane-35 plus metformin: One trial was included, hirsutism outcomes were not reported. Secondary outcomes were presented. No severe side effects were found.

Subgroup analyses were also presented.

Authors’ conclusions
Diane-35 was superior to metformin in reducing androgens and increasing sex hormone binding globulin. Diane-35 was inferior to metformin in reducing insulin. It remained unclear whether Diane-35 deteriorated lipid metabolism and insulin resistance. There was no statistical evidence that combining Diane-35 with metformin improved the primary outcome of hirsutism.

CRD commentary
The review question was clearly stated. The inclusion criteria was clear. Exclusion criteria were less clear and trials that reported unclear randomisation were not excluded. The search covered a broad range of printed and electronic material. Foreign language papers and unpublished data were sought. This reduced the potential for language and publication...
bias, although bias was not tested. Study selection was conducted triplicate and data extraction conducted in duplicate, to avoid bias. The methodological quality of the trials was assessed by two reviewers. Some analyses had limited trials. This was a generally well-conducted review, with advantages and limitations discussed. The authors' conclusions reflect the evidence provided.

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

**Practice:** The authors stated that Diane-35 can reduce androgen levels and increase sex hormone binding globulin. There was some evidence to indicate that metformin protects polycystic ovary syndrome patients against glucose metabolic abnormalities if used for more than six months. There was no evidence to indicate that the use of Diane-35 plus metformin was safer or more effective than either treatment alone. Diane-35 was not found to improve hirsutism over metformin. Metformin should be administered during or after a meal to avoid gastrointestinal side effects and Diane-35 should be monitored for side effects.

**Research:** The authors recommended that clear reporting of quality control methods and intention to treat analysis in studies with withdrawals should be applied in future studies.

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