The effects of metformin on endogenous androgens and SHBG in women: a systematic review and meta-analysis
Barba M, Schunemann HJ, Sperati F, Akl EA, Musicco F, Guyatt G, Muti P

CRD summary
This review assessed whether metformin affected circulating androgens or sex hormone binding globulin levels in women. It found reasonable evidence that metformin induced changes in these surrogate markers in women with or at risk of polycystic ovarian syndrome. The conclusions were well supported by the evidence presented and are likely to be reliable.

Authors' objectives
To evaluate the effects of metformin compared to placebo or no treatment on endogenous androgen levels and sex hormone binding globulin (SHBG) levels in women.

Searching
MEDLINE (from 1966), EMBASE (from 1980) and Cochrane Central Register of Controlled Trials were searched up to March 2007. Search terms were not provided, but were available from the review authors. No language restrictions were applied. PubMed’s related articles feature was used to identify further papers. Reference lists of included studies were screened.

Study selection
Randomised controlled trials (RCTs) of metformin compared with placebo or no treatment in female patients of any age were included. Metformin could be given alone or in combination with other drugs or lifestyle modifications so long as the co-interventions were the same in all groups. Reported co-interventions included oral contraceptives, flutamide, clomiphene citrate, physical exercise and diet. The dosage of metformin ranged from 425mg/day to 1,700mg/day and was at least 1,500mg/day in most trials. Duration of treatment ranged from 21 to 720 days.

Most trials were conducted in adult populations only; three included only children (aged less than 14). Most trials specified a maximum body mass index of 25kg/m² to 30kg/m²; a few included only patients with body mass index above these levels. Studies of pregnant or lactating women were excluded. All bar one of the RCTs in adult patients included only patients with a diagnosis of polycystic ovary syndrome; the trials in children included only those of low birth weight. Populations with different indications for metformin within an RCT were considered separately. Studies published only in abstract form were included if methodological aspects were described.

Primary outcomes were post-treatment measures of the concentration of total testosterone, free testosterone, dehydroepiandrosterone sulphate (DHEAS), androstenedione or SHBG in either blood, urine or saliva. All included trials reported measuring these concentrations in blood only. Secondary outcomes were fasting glycaemia and insulinaemia. Cross-over trials were eligible for inclusion; only results prior to cross-over were included. Trials with a loss to follow-up of greater than 20% were excluded.

Search results were assessed independently by two reviewers; a third reviewer evaluated all titles and abstracts that only one of the reviewers had judged eligible. The degree of agreement between reviewers was assessed using the kappa statistic (K). Full text articles were screened independently by two reviewers with disagreements resolved by discussion with a third reviewer.

Assessment of study quality
Quality assessment criteria included items related to concealment of allocation, blinding, intention to treat analyses and percentage of follow up.

Quality assessment was performed independently by two reviewers. Disagreements were resolved through discussion with a third reviewer.
Data extraction
Pre- and post-treatment measures of androgen or SHBG concentrations were extracted where possible. At least two attempts were made to contact study authors if any data were missing or unclear.

Data extraction was performed independently by two reviewers. Disagreements were resolved through discussion with a third reviewer.

Methods of synthesis
For each outcome, the weighted mean difference (WMD) was estimated using the DerSimonian and Laird random-effects model. The primary analysis was an unadjusted analysis of post-treatment measurements; analysis adjusted for baseline values (comparison of changes from baseline between groups) was considered as a secondary analysis.

Heterogeneity was assessed using the $I^2$ statistic and pre-planned subgroup analyses were used to examine potential causes, namely whether evidence of clinical and/or biochemical hyperandrogenism was required and whether metformin was administered as a single agent or in combination with co-interventions.

A regression analysis was used to investigate whether the use of placebo predicted effect sizes. Publication bias was assessed by visual inspection of funnel plots.

Results of the review
Twenty RCTs (848 women) were included in the review. Reviewer agreement for title and abstract screening was 0.435 (K). Raw agreement for full text eligibility and data extraction was 97%. Overall methodological quality was judged to be acceptable. Fifteen trials reported their randomisation method, 15 reported some form of blinding (two were open label and the remaining three gave no details) and eight reported conducting intention-to-treat analysis.

Primary analyses:
Circulating levels of SHBG were significantly increased (WMD of 5.88nmol/L, 95% CI 2.01 to 9.75, p=0.003; 11 RCTs, n=453). Heterogeneity was moderate ($I^2=60\%$). Where metformin was given as a single agent, heterogeneity decreased ($I^2=28.3\%$) and the observed effect from metformin was increased (WMD 9.04nmol/L, 95% CI 1.05 to 17.03). Metformin had no significant effect on androgen levels.

Secondary analyses:
Metformin decreased the circulating levels of three androgens (total testosterone -0.38nmol/l, 95%CI -0.51 to -0.25, DHEAS -0.50µmol/L, 95% CI -0.83 to -0.16, androstenedione -1.39nmol/L, 95% CI -2.30 to -0.49). Heterogeneity was low ($I^2=9.4\%$ for total testosterone, 0% for DHEAS and 38.6% for androstenedione). Metformin increased circulating levels of SHBG (WMD 6.63nmol/L, 95% CI 2.32 to 10.94). Heterogeneity was significant for SHBG ($I^2=43.6$, p=0.04).

Where metformin was given as a single agent, heterogeneity decreased for trials that evaluated its effect on SHBG ($I^2=0\%$) and the WMD increased to 12.30nmol/L (95%CI 6.30 to 8.30).

Subgroup analyses by the requirement for evidence of hyperandrogenism was also reported to reduce heterogeneity for SHBG, but the results were not reported. A small but statistically significant decrease in the secondary outcome of fasting glycaemia was also reported (-0.02mmol/L, 95% CI -0.03 to -0.01, $I^2=0$). The number of trials and participants for which the secondary analyses could be performed was not reported.

Sensitivity analysis of studies that used placebo were reported to show similar effects to those that did not use a placebo. Funnel plots were reported to be produced for each outcome and to be available from the authors, but were not discussed.

Further post hoc subgroup analyses were conducted in regard to the effect of additional characteristics that might explain study heterogeneity, including diagnosis of polycystic ovary syndrome, body mass index at inclusion.
methodology for measuring circulating androgen and metformin dosage and duration; none were reported to reduce heterogeneity.

Authors’ conclusions
The authors concluded that there was moderate-quality evidence that metformin caused changes in circulating androgens and SHBG levels in women affected by or at risk of developing polycystic ovary syndrome.

CRD commentary
The review addressed a well-focused question and used clearly defined and appropriate inclusion criteria. The electronic search appeared comprehensive and was well documented. No language restrictions were applied. It appeared that no attempts were made to identify unpublished literature, which possibly led to some degree of publication bias. The presence of publication bias was assessed using funnel plots; although these were reported to be available from the authors, they were not included in the paper and were not discussed, so it was not possible to determine whether publication bias was an issue. Comprehensive study details were provided in terms of patient characteristics and details of the interventions. The quality assessment covered important design features that may have affected study validity; these were not tabulated, which made it difficult to determine the quality of individual studies. Reviewer bias and errors were minimised by independent performance of study selection, data extraction and validity assessment. A thorough assessment of the presence of heterogeneity was performed. The use of and approach to statistical synthesis was appropriate. The authors’ conclusions reflected the evidence presented and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice

Research: The authors stated that high-quality RCTs were needed to evaluate whether metformin has effects on surrogate markers and patient-important outcomes (such as those related to the role of androgens as breast cancer promoters or as potential mediators of cardiovascular risk) in healthy premenopausal and in postmenopausal women.

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