Insulin sensitizing drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis

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BACKGROUND: Women of reproductive age, who are overweight or obese, are prone to infertility. Weight loss in these women leads to increased fecundity, higher chances of conception after infertility treatment and improved pregnancy outcome. In spite of the advantages, most patients have difficulty in losing weight and often regain lost weight over time. This review assesses whether treatment with insulin sensitizing drugs contributes to weight loss, compared with diet or a lifestyle modification programme.

METHODS: After a systematic search of the literature, only randomized controlled trials (RCTs), investigating the effect of insulin sensitizing drugs on weight loss compared with placebo and diet and/or a lifestyle modification programme, were included. Subjects were restricted to women of reproductive age. The main outcome measure was change in body mass index (BMI).

RESULTS: Only 14 trials, unintentionally all but two on women with polycystic ovary syndrome (PCOS) only, were included in the analysis. Treatment with metformin showed a statistically significant decrease in BMI compared with placebo (weighted mean difference, −0.68; 95% CI −1.13 to −0.24). There was some indication of greater effect with high-dose metformin (>1500 mg/day) and longer duration of therapy (>8 weeks). Limitations were power, low use of intention-to-treat analysis and heterogeneity of the studies.

CONCLUSION: A structured lifestyle modification programme to achieve weight loss should still be the first line treatment in obese women with or without PCOS. Adequately powered RCTs are required to confirm the findings of this review and to assess whether the addition of high-dose metformin therapy to a structured lifestyle modification programme might contribute to more weight loss.

Key words: BMI / overweight / insulin sensitizing drugs / obesity / weight loss

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Introduction

The rising prevalence of obesity in women worldwide has implications for their reproductive outcome. Obesity is associated with menstrual disorders and anovulation (Hartz et al., 1979; Green et al., 1988; Grodstein et al., 1994; Lake et al., 1997) but fertility is also decreased in women with regular menstrual cycles who are overweight (Jensen et al., 1999; van der Steeg et al., 2005). Furthermore, women, who are overweight or obese while undergoing assisted reproduction, have lower pregnancy rates and higher miscarriage rates (Wang et al., 2000; Lintsen et al., 2005; Maheshwari et al., 2007). During pregnancy, obesity leads to a significant increase in pregnancy complications (Cedergren, 2004; Weiss et al., 2004) and difficulties during labour (Sebire et al., 2001). Infants are at greater risk of congenital abnormalities (Waller et al., 1994; Werler et al., 1996) and intrauterine demise (Stephansson et al., 2001; Nohr et al., 2005) contributing to an increase in perinatal morbidity and mortality.

Obesity is characterized by insulin resistance and consequent hyperinsulinaemia. Hyperinsulinaemia contributes to anovulatory infertility by increased ovarian androgen secretion (Poretsky, 1991; Danaif, 1997). In women with polycystic ovary syndrome (PCOS), insulin enhances intraovarian steroidogenesis by interacting with luteinizing hormone (LH) leading to inappropriate advancement of granulosa cell differentiation and arrest of follicle growth (Franks et al., 1996; Willis et al., 1996).

The cornerstone of the treatment of obesity should be based on lifestyle changes by diet, exercise and behavioural modification (NIH, 1998). In obese women with anovulatory infertility, weight loss leads to spontaneous ovulation and improves the chances of spontaneous conception (Kiddy et al., 1992; Guzick et al., 1994; Clark et al., 1995; Hollmann et al., 1996). In obese women with PCOS, a minimum of 5% loss of abdominal fat is essential for the resumption of spontaneous ovulation (Huber-Buchholz et al., 1999).

An intensive lifestyle modification programme improves the chances of spontaneous conception and conception during fertility treatment (Clark et al., 1998). Pre-pregnancy weight loss can reduce the incidence of gestational diabetes (Glazer et al., 2004).

In view of the low success rate in achieving weight loss and even lower success rate for maintaining this weight loss, drug therapy for obesity in conjunction with the continuation of lifestyle changes is advised according to obesity guidelines (NIH, 1998). According to a randomized controlled trial (RCT), the combination of a lifestyle modification programme with drug therapy, achieves more weight loss than a lifestyle programme alone (Wadden et al., 2005). Orlistat and sibutramine, two approved anti-obesity drugs, should, however, not be used in women who anticipate conception because of lack of safety data on their use during early pregnancy.

Insulin sensitizing drugs are not considered anti-obesity drugs even though some evidence indicates that metformin therapy might contribute to weight loss (Knowler et al., 2002). A systematic review confirming the effectiveness of metformin for ovulation induction in women with PCOS, could not demonstrate that metformin contributes to weight loss (Lord et al., 2003). Another review on the same topic did, however, demonstrate a contribution of metformin to weight loss (Harborne et al., 2000). A recent RCT comparing three ovulation induction modalities (metformin and placebo, metformin and clomiphene, clomiphene and placebo) in women with PCOS also showed more weight loss in women treated with metformin (Legro et al., 2007).

If metformin treatment does contribute to weight loss, treatment of women of reproductive age with obesity and infertility could improve the chances of conception. Data on the safety of metformin use in the first trimester are reassuring (Gilbert et al., 2006; Lilja and Mathiesen, 2006).

The objective of this review was to assess whether treatment of women, of reproductive age who are overweight or obese, with insulin sensitizing agents contributes to weight loss in comparison to placebo and diet and/or a lifestyle modification programme.

Materials and Methods

The following clinical comparisons were assessed: (i) The effectiveness of insulin sensitizing drugs for losing weight compared with placebo, with or without a diet/lifestyle programme. (ii) The side-effects and drop-out rate reported by women taking these drugs. (iii) The most effective insulin sensitizing drug for losing weight, compared with each other, with or without a diet/lifestyle modification programme.

Data sources

Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase were searched up to and including August 2007. Only RCTs were included.

Main keywords used for this search were body weight, BMI, obesity, RCT, diet, insulin sensitizing drugs and weight loss (see Appendix 1 for the full list of keywords).

Hand-searching was performed on the references used in the included studies and relevant review articles were meticulously searched for related articles. Authors were contacted for missing data or questions regarding the methodology.

Study selection

Titles and abstracts identified through the search strategies were independently screened by two reviewers (A. Nieuwenhuis-Ruijbrok, W. Kunenbecker). Articles were discarded if they did not meet the inclusion criteria. Full text articles were obtained of studies for potential inclusion. Independent review of the trials was undertaken by the same two reviewers to assess the quality and characteristics of the studies. Differences in opinion between the reviewers on selected articles were settled by consensus.

The subjects were women of reproductive age who are overweight (Body mass index (BMI), 25–29.9 kg/m²) or obese (BMI ≥ 30 kg/m²) according to accepted diagnostic criteria (NIH, 1998) and who were deemed eligible for weight loss measures. Studies that included prepuberal and postmenopausal women were excluded.

Main intervention

Treatment with insulin sensitizing drugs: metformin, pioglitazone, rosiglitazone or d-chiro-inositol. Treatment with metformin was assessed in two subanalyses according to the daily dosage of ≤1500 mg or >1500 mg. This dosage cut-off for metformin was used because most initial studies used the dosage of 500 mg tablets three times daily (low dose) and later studies using 1000 mg two times daily or 850 mg tablets two to three times daily (high dose).

Comparison interventions

One or more of the following: placebo only or placebo with diet advice or a lifestyle modification programme. The primary outcome measure was change in BMI in kilogram per square metre.
Secondary outcomes were drop-out rates and side-effects caused by the drugs.

Data synthesis and analysis

The effect was measured as weighted mean difference (WMD) and 95% confidence intervals (CIs), using RevMan for the analysis. Data from the 14 trials were stratified over two main interventions, and subanalysis was performed on four co-interventions while still maintaining adequate numbers of patients for analysis.

For statistical analysis, standard deviations (SDs) were required. Hence, for all trials, in which 95% CI or standard error of the means (SEM) were given, these values were converted into SDs. In two trials (Fleming et al., 2002; Kjotrod et al., 2004) more expanded calculations were needed to derive the SDs.

Quality assessment

Trial quality was assessed on minimization of selection bias, performance bias, attrition bias and detection bias. Assessment of the quality of allocation concealment was graded in four categories: adequate (A), unclear (B), inadequate (C) or not given (D). Other trial characteristics assessed were differences in baseline values, non-compliance, standardized outcome measures, drop-out rate, the extent of losses to follow-up, side-effects, blinding methods and whether analysis was by intention to treat.

In the statistical analysis, the WMD was used to express the effect of each continuous outcome. Heterogeneity in the data was noted and cautiously explored using certain characteristics of the study, particularly assessments of quality. In order to examine the stability of the results in relation to a number of factors, sensitivity analyses were performed. These analyses included quality of allocation concealment, blinding, treatment length over eight weeks, high or low dose of metformin, inclusion BMI and ethnicity.

Results

Search results

The search strategy revealed 31 trials eligible for inclusion in this review. After studying these publications, 17 trials were excluded (see separate reference list in Appendix 2) and the data of the remaining 14 trials were analysed. See Table I of included studies for full details of the 14 included trials (extended version of Table I hosted on website of Human Reproduction Update).

The 14 included studies randomized 649 women with 20 subjects in the smallest trials (Pasquali et al., 2000; Gambineri et al., 2004) and 143 in the largest trial (Tang et al., 2006).

Eleven of these trials were stated to be double-blind and two single-blind. One did not state the blinding method (Mitkov et al., 2006).

In three trials, randomization was performed by centre (Nestler and Jakubowicz, 1996; Kjotrod et al., 2004; Tang et al., 2006) and in three trials the randomization was computer generated (Vandermolen et al., 2001; Fleming et al., 2002; Yarali et al., 2002).

Pasquali et al. (2000) packaged drug and placebo and labelled according to subject number. Then randomization was performed in blocks of four.

One trial stated that it 'randomly placed' its subjects (Gambineri et al., 2004), two trials numbered the participants sequentially (Jakubowicz et al., 2001; Kocak et al., 2002). However, Kocak et al. (2002), randomized patients by order of admission, resulting in a quasi-randomized study. Two studies used random number tables (Kilicdag et al., 2005; Ortega-Gonzalez et al., 2005) and two (Crave et al., 1995; Mitkov et al., 2006) did not state the method of randomization.

In four studies, a power calculation was performed (Fleming et al., 2002; Kjotrod et al., 2004; Kilicdag et al., 2005; Tang et al., 2006), while the other nine did not mention a sample size calculation. In three trials, an analysis by intention-to-treat was stated to have been performed (Vandermolen et al., 2001; Fleming et al., 2002; Kjotrod et al., 2004).

The analysis of metformin versus thiazolidinediones was included even though these three trials tested two different thiazolidinediones: rosiglitazone and pioglitazone.

The analysis comparing the duration of trials was included as the effectiveness of the drugs involved might be correlated with the duration of its use.

Five trials were included in the ‘duration ≤8 weeks’ arm (Nestler and Jakubowicz, 1996; Jakubowicz et al., 2001; Vandermolen et al., 2001; Kocak et al., 2002; Yarali et al., 2002), lasting 35 days to 7–8 weeks. Six trials were included in the ‘duration >8 weeks’ arm (Crave et al., 1995; Pasquali et al., 2000; Fleming et al., 2002; Gambineri et al., 2004; Kjotrod et al., 2004; Tang et al., 2006), lasting from 16 weeks to 6 months.

The criteria for diet or no-diet were not very strict. When mention was made of diet or lifestyle adaptations, the trial was coded as diet, even if compliance to diet was not assessed. In seven of the included studies, no mention was made of a diet (Nestler and Jakubowicz, 1996; Jakubowicz et al., 2001; Kocak et al., 2002; Yarali et al., 2002; Kilicdag et al., 2005; Mitkov et al., 2006).

In two trials (Gambineri et al., 2004; Ortega-Gonzalez et al., 2005), the women were instructed not to modify their usual eating or exercise patterns during the study period, these trials were coded as ‘no diet’.

In the other five trials, diet as co-intervention was implemented with a variety of criteria (Crave et al., 1995; Pasquali et al., 2000; Gambineri et al., 2004; Kjotrod et al., 2004; Tang et al., 2006). Pasquali et al. (2000) and Gambineri et al. (2004) placed the women on a standardized hypo caloric diet (1200–1400 kCal daily) for the first month, and continuing dietary treatment for the rest of the study period. Crave et al. (1995) placed the women on a low fat low caloric diet (1500 kCal daily with 30% fat). Kjotrod et al. (2004) mentioned diet and lifestyle modification without specifying the intervention. The patients in the trial of Tang et al. (2006) received standardized dietary advice from a research dietician aiming for a calorie reduction of 500 kCal per day.

In one of the 12 trials, clomiphene citrate (CC) was used as a co-intervention (Vandermolen et al., 2001). In this trial, all participants received CC for the first 5 days of the first cycle. With ovulation, the CC dose did not change, but with persistent anovulation, the dosage of CC was increased by 50 mg/day for the next cycle.

All studies used for this review were fully published in peer-reviewed journals. Ten of the included trials were single centre studies (Crave et al., 1995; Pasquali et al., 2000; Jakubowicz et al., 2001; Fleming et al., 2002; Kocak et al., 2002; Kjotrod et al., 2004; Gambineri et al., 2004; Kilicdag et al., 2005; Ortega-Gonzalez et al., 2005; Mitkov et al., 2006) and four trials were multicentre (Nestler and Jakubowicz, 1996; Vandermolen et al., 2001; Yarali et al., 2002; Tang et al., 2006).
Table I Characteristics of the included studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Methods</th>
<th>Number randomized inclusion criteria</th>
<th>Main intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crave et al. (1995)</td>
<td>Method of randomization: not stated Brining: double blind Intention to treat analysis: no</td>
<td>24 BMI &gt; 25 kg/m², hirsutism</td>
<td>High-dose metformin (n = 12), placebo (n = 12) Duration: 4 months</td>
</tr>
<tr>
<td>Fleming et al. (2002)</td>
<td>Method of randomization: computer generation by pharmacy in blocks of four Brining: double blind Intention to treat analysis: yes</td>
<td>94 Oligomenorrhea, PCO* detected by ultrasound</td>
<td>High-dose metformin (n = 26), placebo (n = 39) Duration: 14 weeks</td>
</tr>
<tr>
<td>Gaminbini et al. (2004)</td>
<td>Method of randomization: randomly placed Brining: single-blind Intention to treat analysis: no</td>
<td>20 (only the data of the metformin and placebo arms were used) BMI &gt; 28 kg/m² and waist hip ratio &gt; 0.8; PCOS: oligomenorrhea or amenorrhea, hyperandrogenism, PCO detected by ultrasound</td>
<td>High-dose metformin (n = 10), placebo (n = 10) Duration: 6 months</td>
</tr>
<tr>
<td>Jakubowicz et al. (2001)</td>
<td>Method of randomization: sequentially numbered, identical containers of identical drugs** Brining: double blind Intention to treat analysis: no</td>
<td>56 Oligomenorrhea, PCO detected by ultrasound, elevated free testosterone, ovulation with clomiphene citrate 150 mg</td>
<td>Low-dose metformin (n = 28), placebo (n = 28) Duration: 7–8 weeks</td>
</tr>
<tr>
<td>Kilidag et al. (2005)</td>
<td>Method of randomization: random number tables and assigned through consecutively numbered opaque, sealed envelopes Brining: double blind Intention to treat analysis: no</td>
<td>30 Oligomenorrhea, hyperandrogenism and/or an elevated serum testosterone level, PCO detected by ultrasound</td>
<td>High-dose metformin (n = 15), rosiglitazone (n = 15) Duration: 3 months</td>
</tr>
<tr>
<td>Kjotrod et al. (2004)</td>
<td>Method of randomization was performed by the hospital pharmacist, performed in blocks of four Brining: double-blind Intention to treat analysis: yes</td>
<td>40 Criteria for overweight: BMI &gt; 28 kg/m², PCO detected by ultrasound, oligomenorrhea or amenorrhea and 1 out of the next 5: high level of testosterone, low SHBG level, high LH/FSH ratio, high level of fasting insulin C, hirsutism NOTE: the baseline valu</td>
<td>High-dose metformin (BMI &gt; 28, n = 19), placebo (BMI &gt; 28, n = 21) Duration: 16 weeks</td>
</tr>
<tr>
<td>Kocak et al. (2002)</td>
<td>Method of randomization: sequential by order of admission Brining: double blind Intention to treat analysis: no</td>
<td>56 Oligomenorrhea with hirsutism, hyperandrogenaemia, or ultrasound findings of PCO.</td>
<td>High-dose metformin (n = 28), placebo (n = 28) Duration: 2 cycles</td>
</tr>
<tr>
<td>Mikov et al. (2006)</td>
<td>Method of randomization: not stated Brining: not stated Intention to treat analysis: no</td>
<td>30 Oligomenorrhea, PCO detected by ultrasound, hyperandrogenaemia</td>
<td>High-dose metformin (n = 15), rosiglitazone, 4 mg/day (n = 15) Duration: 3 months</td>
</tr>
<tr>
<td>Ortega-Gonzalez et al. (2005)</td>
<td>Method of randomization: random number tables Brining: double blind Intention to treat analysis: no</td>
<td>52 Oligomenorrhea, PCO detected by ultrasound, hyperandrogenemia, acanthosis nigricans, fasting hyperinsulinemia and fasting glucose/insulin</td>
<td>High-dose metformin (n = 27), pioglitazone, 30 mg/day (n = 25) Duration: 6 months</td>
</tr>
<tr>
<td>Pasquali et al. (2000)</td>
<td>Method of randomization: generated in blocks of four Brining: double-blind Single centre intention to treat analysis: no</td>
<td>20 (only the data of the PCOS women were used) Obese women with PCOS diagnosed by: oligomenorrhea, hyperandrogenism, PCO detected by ultrasound</td>
<td>High-dose metformin (n = 12), placebo (n = 8) Duration: 6 months</td>
</tr>
<tr>
<td>Tang et al. (2006)</td>
<td>Method of randomization: by means of block-of-four randomization using random tables Brining: double blind Intention to treat analysis: no</td>
<td>143 Desire to conceive, PCOS diagnosed by: oligomenorrhea or amenorrhea, PCO detected by ultrasound. All patients had normal serum prolactin levels and normal thyroid-, liver- and renal function tests.</td>
<td>High-dose metformin (n = 69), placebo (n = 74) Duration: 6 months</td>
</tr>
<tr>
<td>Vandermolen et al. (2001)</td>
<td>Method of randomization: computer-generated in blocks of six Brining: double blind Intention to treat analysis: yes</td>
<td>27 Oligo-ovulation, hyperandrogenism NOTE: all patients received CC (50 mg/d) for ovulation induction as co-intervention after the initial 7 weeks treatment period</td>
<td>Low-dose metformin (n = 12), placebo (n = 15) Duration: 7 weeks</td>
</tr>
</tbody>
</table>

Continued
Unintentionally all studies, except two (Crave et al., 1995; Pasquali et al., 2000), were found to be on women with PCOS. The diagnostic criteria for PCOS broadly followed the National Institute of Health consensus criteria (anovulation and hyperandrogenemia with exclusion of other endocrinopathies) or the diagnostic criteria of the Rotterdam consensus meeting (Rotterdam criteria, 2004). The following criteria for PCOS broadly followed the National Institute of Health, 1990, were found to be on women with PCOS. The diagnostic criteria for PCOS broadly followed the National Institute of Health consensus criteria (anovulation and hyperandrogenemia with exclusion of other endocrinopathies) or the diagnostic criteria of the Rotterdam consensus meeting (Rotterdam criteria, 2004). The following criteria for PCOS broadly followed the National Institute of Health, 1990, were found to be on women with PCOS. The diagnostic criteria for PCOS broadly followed the National Institute of Health consensus criteria (anovulation and hyperandrogenemia with exclusion of other endocrinopathies) or the diagnostic criteria of the Rotterdam consensus meeting (Rotterdam criteria, 2004).

The included trials were performed on different ethnic groups and geographical locations. Trials were performed in Europe, USA, Turkey, Mexico, Bulgaria and Venezuela, and one study was spread over Mexico, Bulgaria and Venezuela, and one study was spread over Mexico, Bulgaria and Venezuela, and one study was spread over Mexico, Bulgaria and Venezuela.

The mean baseline characteristics for BMI can be found in Table II. All women included in the trials were of reproductive age. The duration of the trials varied between 35 days and 6 months. Heterogeneity in this review was assessed for each analysis. Performance bias (blinding) was explored; for each trial binding methods are stated in Table I.

### Analyses

The analysis was structured to address three relevant clinical comparisons as mentioned in the methods section:

(i) the effectiveness of insulin sensitizing drugs for losing weight compared with placebo, with or without a diet/lifestyle programme. In this comparison, there was one main analysis (A) and four subanalyses (B–E).

(A) Metformin versus placebo (BMI) (Fig. 1).

Eleven trials with a total of 537 women compared metformin treatment with placebo (Crave et al., 1995; Nestler and Jakubowicz, 1996; Pasquali et al., 2000; Jakubowicz et al., 2001; Fleming et al., 2002; Yarali et al., 2002; Kocak et al., 2002; Vandermolen et al., 2001; Fleming et al., 2002; Yarali et al., 2002; Kocak et al., 2002; Gambineri et al., 2004; Kjotrod et al., 2004; Tang et al., 2006). Of these 537

### Table I

<table>
<thead>
<tr>
<th>Trial</th>
<th>Methods</th>
<th>Number randomized inclusion criteria</th>
<th>Main intervention</th>
</tr>
</thead>
</table>

*PCO, polycystic ovaries. **Information used from the Lord et al. (2003) review.

### Table II Baseline characteristics, BMI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Type of outcome (BMI in kg/m²)</th>
<th>N metformin group</th>
<th>N placebo/thiazolidinedione group</th>
<th>Placebo/thiazolidinedione group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang et al. (2006)</td>
<td>BMI</td>
<td>69</td>
<td>37.6 ± 5.0</td>
<td>74</td>
<td>38.9 ± 9.5</td>
</tr>
<tr>
<td>Fleming et al. (2002)</td>
<td>BMI</td>
<td>45</td>
<td>34.2 ± 8.0</td>
<td>47</td>
<td>35.0 ± 8.7</td>
</tr>
<tr>
<td>Kocak et al. (2002)</td>
<td>BMI</td>
<td>28</td>
<td>31.9 ± 5.4</td>
<td>28</td>
<td>30.8 ± 4.4</td>
</tr>
<tr>
<td>Jakubowicz et al. (2002)</td>
<td>BMI</td>
<td>26</td>
<td>31.8 ± 1.5</td>
<td>22</td>
<td>31.7 ± 1.4</td>
</tr>
<tr>
<td>Ortega-Gonzalez et al. (2005)</td>
<td>BMI</td>
<td>18</td>
<td>34.1 ± 6.8</td>
<td>17</td>
<td>32.2 ± 4.1</td>
</tr>
<tr>
<td>Kjotrod et al. (2004)</td>
<td>BMI</td>
<td>17</td>
<td>32.0 ± 3.9</td>
<td>19</td>
<td>33.7 ± 3.5</td>
</tr>
<tr>
<td>Yarali et al. (2002)</td>
<td>BMI</td>
<td>16</td>
<td>28.6 ± 4.0</td>
<td>16</td>
<td>29.6 ± 4.8</td>
</tr>
<tr>
<td>Klicicdag et al. (2005)</td>
<td>BMI</td>
<td>15</td>
<td>26.2 ± 5.4</td>
<td>15</td>
<td>29.3 ± 6.2</td>
</tr>
<tr>
<td>Mitkow et al. (2006)</td>
<td>BMI</td>
<td>15</td>
<td>27.9 ± 4.6</td>
<td>15</td>
<td>28.6 ± 4.6</td>
</tr>
<tr>
<td>Crave et al. (1995)</td>
<td>BMI</td>
<td>12</td>
<td>35.2 ± 4.2</td>
<td>12</td>
<td>32.7 ± 5.2</td>
</tr>
<tr>
<td>Pasquali et al. (2000)</td>
<td>BMI</td>
<td>12</td>
<td>39.8 ± 7.9</td>
<td>8</td>
<td>39.6 ± 6.9</td>
</tr>
<tr>
<td>Vandermolen et al. (2001)</td>
<td>BMI</td>
<td>11</td>
<td>37.6 ± 14.3</td>
<td>14</td>
<td>38.4 ± 8.2</td>
</tr>
<tr>
<td>Nestler et al. (1996)</td>
<td>BMI</td>
<td>11</td>
<td>34.1 ± 5.0</td>
<td>13</td>
<td>35.2 ± 4.7</td>
</tr>
<tr>
<td>Gambineri et al. (2004)</td>
<td>BMI</td>
<td>10</td>
<td>37 ± 5.9</td>
<td>10</td>
<td>37.6 ± 4.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. *Baseline values in this trial only include the women who finished the trial.
women, only the 469 women, who completed the trials, were included in the analysis.

Metformin treatment contributed to a significant decrease in BMI (WMD $-0.68$, 95% CI $-1.13$ to $-0.24$, $P = 0.003$).

Test for heterogeneity: $\chi^2 = 9.35$, df = 10 ($P = 0.50$), $I^2 = 0\%$.

(B) High-dose metformin (>1500 mg/day) versus placebo (BMI) (Fig. 1, top part).

Eight trials with a total of 429 women compared high-dose metformin (>1500 mg/day) versus placebo (Crave et al., 1995; Pasquali et al., 2000; Fleming et al., 2002; Kocak et al., 2002; Yarali et al., 2004; Kjotrod et al., 2004; Tang et al., 2006). A total of 57 women did not complete the trial and were not included in the analysis, leaving 372 women for analysis.

High-dose metformin treatment contributed to a significant decrease in BMI (WMD $-0.98$, 95% CI $-1.51$ to $-0.45$, $P = 0.003$).

Test for heterogeneity: $\chi^2 = 4.29$, df = 7 ($P = 0.75$), $I^2 = 0\%$.

(C) Low-dose metformin (≤1500 mg/day) versus placebo (BMI) (Fig. 1, lower part).

Three trials compared low-dose metformin (≤1500 mg/day) versus placebo, with a total of 98 women (Nestler and Jakubowicz, 1996; Jakubowicz et al., 2001; Vandermolen et al., 2001). In this analysis, 97 women were included for analysis, as one did not complete the trial.

There was no evidence of effect on BMI (WMD 0.02, 95% CI $-0.79$ to 0.84, $P = 0.96$).

Test for heterogeneity: $\chi^2 = 0.94$, df = 2 ($P = 0.62$), $I^2 = 0\%$.

(D) High-dose metformin versus placebo, diet/no diet (BMI) (Fig. 2).

Five trials included diet as a co-intervention (Crave et al., 1995; Pasquali et al., 2000; Gambineri et al., 2004; Kjotrod et al., 2004; Tang et al., 2006) randomizing 247 women, of which 222 were included in the analyses, since 25 women did not complete the trials. Three trials in which 182 women were randomized did not include diet as a co-intervention (Fleming et al., 2002; Kocak et al., 2002; Yarali et al., 2002). Thirty women did not complete the trial, hence 143 were left to be analysed.

There was no evidence of effect on BMI in the ‘diet’ group, five trials of 220 women (WMD $-0.84$, 95% CI $-2.20$ to 0.51, $P = 0.22$). In the ‘no diet’, three trials of 152 women, there was, however, a significant decrease in BMI (WMD $-1.01$, 95% CI $-1.59$ to $-0.43$, $P = 0.0006$).

Test for heterogeneity (diet): $\chi^2 = 3.86$, df = 4 ($P = 0.43$), $I^2 = 0\%$.

Test for heterogeneity (no diet): $\chi^2 = 0.38$, df = 2 ($P = 0.83$), $I^2 = 0\%$.

(E) Metformin versus placebo, duration ≤8 weeks/duration >8 weeks (BMI) (Fig. 3).

In the duration of ≤8 weeks arm, five trials were included (Nestler and Jakubowicz, 1996; Jakubowicz et al., 2001; Vandermolen et al., 2001; Kocak et al., 2002; Yarali et al., 2002). In this arm, 186 were randomized, of which 184 women completed the trials and were included in the analysis. In the arm of duration of >8 weeks, six trials were included (Crave et al., 1995; Pasquali et al., 2000; Fleming et al., 2002; Gambineri et al., 2004; Kjotrod et al., 2004; Tang et al., 2006). 341 women were randomized and 287 completed the trials.

There was no evidence of effect on BMI in the ‘duration ≤8 weeks’, but there was evidence of effect in the ‘duration >8 weeks’ sub analyses.

Duration ≤8 weeks: WMD $-0.16$, 95% CI $-0.90$ to 0.58, $P = 0.67$.

Duration >8 weeks: WMD $-0.97$, 95% CI $-1.53$ to $-0.42$, $P = 0.0006$.

Test for heterogeneity (≤8 weeks): $\chi^2 = 2.50$, df = 4 ($P = 0.65$), $I^2 = 0\%$. 

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**Figure 1** Metformin versus placebo; high dose versus low dose (BMI).
Test for heterogeneity (>8 weeks): $\chi^2 = 3.90$, df = 5 ($P = 0.56$), $I^2 = 0\%$.

(ii) The side-effects and drop-out rates reported by women taking these drugs. Owing to the heterogeneous description of side-effects and drop outs in the various studies, we could not perform an analysis on percentages of drop outs and side-effects in the above mentioned comparisons. An overview of the side-effects and drop outs is presented in Table III.

(iii) The most effective insulin sensitizing drug for losing weight compared with each other. High-dose metformin versus thiazolidinedione (BMI). Three trials with a total of 112 women compared high-dose metformin (>1500 mg/day) versus thiazolidinedione (Kilicdag et al., 2005; Ortega-Gonzalez et al., 2005; Mitkov et al., 2006). A total of 95 women completed the trials, only these were included in the analysis. These three trials were the only trials assessing the effect of

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**Figure 2** High-dose metformin versus placebo, diet versus no diet.

**Figure 3** Metformin versus placebo; duration ≤ 8 weeks versus > 8 weeks (BMI).
Table III  Drop outs and side-effects

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants (N=)</th>
<th>Side-effects reported (N=)</th>
<th>Drop outs (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin group</td>
<td>Placebo/thiazolidinedione</td>
<td></td>
</tr>
<tr>
<td>Crave et al. (1995)</td>
<td>12</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Fleming et al. (2002)</td>
<td>45</td>
<td>47</td>
<td>**</td>
</tr>
<tr>
<td>Gabinieri et al. (2004)</td>
<td>10</td>
<td>10</td>
<td>**</td>
</tr>
<tr>
<td>Jakubowicz et al. (2001)</td>
<td>26</td>
<td>22</td>
<td>**</td>
</tr>
<tr>
<td>Kilicdag et al. (2005)</td>
<td>15</td>
<td>15</td>
<td>**</td>
</tr>
<tr>
<td>Kjotrod et al. (2004)</td>
<td>17</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Kocak et al. (2002)</td>
<td>28</td>
<td>28</td>
<td>**</td>
</tr>
<tr>
<td>Mitkov et al. (2006)</td>
<td>15</td>
<td>15</td>
<td>**</td>
</tr>
<tr>
<td>Nestler et al. (1996)</td>
<td>11</td>
<td>13</td>
<td>**</td>
</tr>
<tr>
<td>Ortega-Gonzalez et al. (2005)</td>
<td>27</td>
<td>25</td>
<td>**</td>
</tr>
<tr>
<td>Pasquali et al. (2000)</td>
<td>12</td>
<td>8</td>
<td>**</td>
</tr>
<tr>
<td>Tang et al. (2006)</td>
<td>69</td>
<td>74</td>
<td>**</td>
</tr>
<tr>
<td>Vandermolen et al. (2001)</td>
<td>11</td>
<td>14</td>
<td>**</td>
</tr>
<tr>
<td>Yarali et al. (2002)</td>
<td>16</td>
<td>16</td>
<td>**</td>
</tr>
</tbody>
</table>

*Not stated. **Stated, but number not available. (), number between brackets represents the number of drop outs due to side-effects.
Sensitivity analyses
Sensitivity analyses were performed on the metformin intervention arm to test whether there was an influence from allocation concealment and blinding. Excluding the three trials that were graded ‘B’ (Gambineri et al., 2004; Mitkov et al., 2006) or ‘C’ (Kocak et al., 2002) for allocation concealment did not change the analyses for BMI. When excluding the trials that were single blinded (Nestler and Jakubowicz, 1996; Gambineri et al., 2004) or did not state the blinding method (Crave et al., 1995; Mitkov et al., 2006), no change in the analyses for BMI occurred.

Discussion
The 14 selected RCTs randomized a total of 649 women but only the 554 women who completed the trials were included for analysis. All except two of the studies analysed were on women with PCOS.

This review indicates that metformin treatment of reproductive aged women with PCOS, who are overweight or obese, leads to a significant decrease in BMI when compared with placebo.

Studies assessing the treatment with high-dose metformin (>1500 mg/day) revealed a more pronounced decrease in BMI when compared with the low-dose metformin (≤1500 mg/day) studies. The fact that no significant decrease in BMI was seen in the three trials on low-dose metformin (Nestler and Jakubowicz, 1996; Jakubowicz et al., 2001; Vandermolen et al., 2001) could be attributed to shorter duration of treatment although with only 97 women analysed, this sub-analyses was potentially underpowered to show a significant effect.

Duration of the treatment for ≤8 weeks did not show a significant decrease in BMI even after excluding the three trials on low-dose metformin (Nestler and Jakubowicz, 1996; Jakubowicz et al., 2001; Vandermolen et al., 2001).

The group with ‘diet’ as a co-intervention did not show a significant decrease in BMI. The poor reporting and implementation of diets or a lifestyle programme in the analysed trials could explain this unexpected finding. On the other hand, this finding could also indicate that metformin treatment does not have an additional effect on weight loss in patients, who undergo a diet or lifestyle programme.

Due to inconsistent reporting of the gastrointestinal side-effects of metformin (nausea, abdominal cramps and diarrhoea) in the trials, this review could not assess whether the significant decrease in BMI in the metformin group can be attributed to gastrointestinal side-effects. An RCT comparing different doses of metformin in obese women with PCOS (Harborne et al., 2005), showed that high-dose metformin (2550 mg/day) had a more consistent effect on weight loss compared with low-dose metformin (1500 mg/day) without increased drop-out rates due to gastrointestinal side-effects.

Treatment with metformin did not significantly contribute to a decreased BMI when compared to thiazolidinedione. This finding was unexpected because treatment with thiazolidinedione is known to contribute to weight gain (Kahn et al., 2006; Balas et al., 2007). With only 95 women completing the trials, this analysis was potentially underpowered to show more weight loss in the metformin group.

The most important limitation of this review is that the analysis was only performed on the study subjects completing the trial period. Because only three trials (Vandermolen et al., 2001; Fleming et al., 2002; Kjotrod et al., 2004) used intention to treat analysis and the other trials inconsistently reported baseline BMI values and withdrawal after randomization, sound statistical analysis was not possible using all included patients and a sensitivity analysis including and excluding the withdrawals after randomization and the drop outs was not possible. The second limitation of this review is that most of the 14 included trials were designed for a different primary outcome and clinical question. Heterogeneity of the study populations is another limitation of this review.

What would the clinical relevance be of minimal additional weight loss due to high-dose metformin treatment? With the average women analysed in this review having a BMI of 35 kg/m² and assuming an average height of 1.64 m, treatment with high-dose metformin would have contributed to reach a final BMI of 34.02 kg/m² (WMD, −0.98) and a decrease in weight from 94.2 to 91.5 kg. This decrease of 2.7 kg corresponds to a 2.9% decrease of the initial bodyweight.

Orlistat and sibutramine, two of the registered anti-obesity agents, taken for a period of 1 year, contribute to 2.9 and 4.6% additional weight loss, respectively (Padwal et al., 2003; Padwal and Makumbar, 2007). Considering the lack of safety data, both of these medications should not be taken during conception and early pregnancy while data on the use of metformin during conception and early pregnancy are extensive and reassuring (Gilbert et al., 2006; Lilja and Mathiesen, 2006; Legro et al., 2007).

In overweight or obese women with PCOS, a minimum of 5% weight loss is required for resumption of ovulation and spontaneous conception (Kiddy et al., 1992; Hollmann et al., 1996). In obese women with PCOS, a minimum of 5% loss of abdominal fat is essential for the resumption of spontaneous ovulation (Huber-Buchholz et al., 1999). Minimal weight loss improves the chances of spontaneous conception and conception after fertility treatment in obese women undergoing a lifestyle modification programme (Clark et al., 1998). Modest pre-pregnancy weight loss decreases the incidence of gestational diabetes (Glazer et al., 2004) and prevention of minimal weight gain between pregnancies decreases the chance of pregnancy complications (Villamor and Cnattingius, 2006).

With the abovementioned evidence in mind, the 2.9% additional weight loss achieved when treating women with PCOS who are overweight or obese with high-dose metformin therapy (with a maximum intervention period in this review being 6 months) can be compared with the additional weight loss achieved with orlistat and sibutramine (with an intervention period of 1 year). High-dose metformin therapy can therefore be considered a safe and possibly relevant intervention in women with PCOS who are overweight or obese to achieve additional weight loss.

Conclusion
This review shows that treating women of reproductive age with PCOS who are overweight or obese with metformin leads to a
significant decrease in BMI. Considering the limitations of this review, this conclusion should be interpreted with caution. There is some indication of greater effect with high-dose metformin (>1500 mg/day) and longer duration of therapy (>8 weeks) leading to 2.9% additional weight loss. This is, however, based on subgroup analysis, which was probably underpowered for the low dose and short duration subgroups. According to this review, the addition of a metformin treatment in patients on a diet or lifestyle programme does not contribute to further weight loss.

A structured lifestyle modification programme to achieve weight loss should still be the first line treatment in obese women with or without PCOS. Adequately powered RCTs are required to confirm the findings of this review and to assess whether the addition of high-dose metformin therapy to a structured lifestyle modification programme might contribute to more weight loss.

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Insulin sensitizing drugs for weight loss in women of reproductive age


Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE. Metformin increases the ovariary rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. Fertil Steril 2001;75:310–315.


Appendix I

Full list of key words used in database searches is as follows:

- Body weight
- Weight loss
- Weight reduction
- Diet
- Obesity
- Body mass index/BMI
- Weight gain
- Weight
- Overweight
- Weight cycling
- Waist-to-hip ratio
- Body fat distribution
- Waist circumference
- Central abdominal/subcutaneous/visceral fat
- Insulin sensitizing agents
- Biguanides
- Anti-obesity agents
- Hypoglycemic agents
- Rosiglitazone
Rosiglitazone-metformin combination
Metformin
Pioglitazone
Troglitazone
d-chiro-inositol
d-chiro-inositol-galactosamine
Hyperandrogenism
Hyperinsulinism
Hyperinsulinemia
Randomized controlled trial
Controlled clinical trial
Random allocation
Double-blind
Single-blind
Clinical trial
Placebo

Appendix 2: excluded studies


Malkawi HY, Qublan HS, Hamaideh AH. Medical vs. surgical treatment for clomiphene citrate-resistant women with polycystic ovary syndrome. J Obstet Gynaecol 2003;23:289–293.


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