Metformin versus Orlistat in the Treatment of Overweight and Obese Women with Polycystic Ovary Syndrome (PCOS): A Systematic Review and Meta-analysis

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Objectives: To compare the effects of metformin and orlistat in terms of reduction in weight or BMI, and improvement of ovulation rates, endocrinologic and lipid profiles, and occurrence of adverse events among overweight or obese women diagnosed with PCOS.
Search methods: We searched Medline, OVID, HERDIN, EMBASE, Cochrane Library and ClinicalTrials.gov. for head to head clinical trials of metformin versus orlistat for the treatment of overweight and obese women with PCOS. We also contacted the pharmaceutical companies and did hand-searching to look for related studies.
Selection criteria: Only randomized controlled trials comparing metformin and orlistat as treatment for overweight and obese PCOS women were included. Other inclusion criteria included: trial period of at least 3 months duration, participants, of any ethnicity, 18-40 years old, who are overweight or obese, and studies with or without non-pharmacologic interventions as part of the treatment regimen.
Data collection and analysis: Titles and abstracts identified through the search strategies were screened by two reviewers. Two authors extracted data on population characteristics, inclusion and exclusion criteria, intervention and co-intervention, primary and secondary outcomes, and details of study design. Two authors assessed the quality and risk of bias of each RCT based on:random sequence generation, allocation concealment, blinding of participants, caregivers, and assessors, attrition bias, incomplete outcome data, selective reporting, and publication bias.
Main results: We included 5 RCTs (n= 221). Overall, treatment effects of orlistat and metformin showed no significant difference in the following outcomes: ovulation rates (RR 0.78; 95% CI 0.41,1.49), reduction of BMI (MD -0.47; 95%CI:-1.53,0.59), serum testosterone levels (MD -2.15;95% CI -9.64, 5.33), free androgen index (MD 3.26; 95% CI -7.91, 14.43), homeostatic model assessment-insulin resistance (3.70; 95% CI -6.74, 14.15), fasting insulin (MD 7.86; 95% CI -3.09,18.81), HDL-C (MD -1.19 ; 95% CI -4.78, 7.16) and triglyerides (MD -1.95; 95% CI -8.81, 4.90). Orlistat was significantly better than metformin in reducing total cholesterol (MD -6.60; 95% CI -10.79, -2.41), and LDL (MD -5.04; 95% CI -9.99, -0.09), and had less adverse events (RR 0.37, 95% CI 0.14,0.96).
Authors' conclusions: Metformin and Orlistat have similar effects on weight loss, ovulation rates, and endocrinologic profiles of obese women with PCOS. Orlistat is more effective than metformin in decreasing total cholesterol and LDL-C levels, and has less adverse events than metformin. Therefore, we may recommend orlistat to overweight or obese women with PCOS who also have dyslipidemia. However, caution is given to our interpretations since small sample sizes, low quality of RCTs, and the wide confidence intervals of pooled estimates significantly influence interpretation and recommendations. RCTs with adequately powered study populations are recommended to confirm findings of this review.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive-aged women affecting 5-10% worldwide.[1] Nearly 30-75% of women with PCOS are either overweight or obese, and majority develop insulin resistance and metabolic syndrome.[2] The increased body mass index (BMI) and resultant increase in visceral adiposity exacerbates the endocrinologic and metabolic imbalance in PCOS, thereby exerting an additive, synergistic effect on the manifestations of PCOS[3], resulting to more severe menstrual dysfunction or anovulation, infertility, hyperandrogenism, hyperinsulinemia, and cardiometabolic disorders.[4] Weight reduction is an initial critical step to treatment of obese women with PCOS. A 5-10% reduction in the initial body weight may improve ovulation and conception, and reduce clinical hyperandrogenemia and insulin resistance.[5] Several studies have shown that supplementing obese PCOS patients with either insulin sensitizing drugs such as metformin, or a lipase inhibitor orlistat, alone or in addition to a hypocaloric diet, significantly achieves more beneficial effects in terms of weight loss and improvement of metabolic syndrome, glycemic control, and insulin resistance.[6,7,8].

Metformin, a biguanide insulin sensitizer, is commonly used by many clinicians to treat PCOS, since it is widely believed to target the central etiology of PCOS. The benefits of metformin treatment are believed to target cardiometabolic, hyperandrogenic and reproductive abnormalities that characterize the syndrome, as well as induce weight loss. Metformin is effective in the treatment of PCOS-related anovulation and infertility. A Cochrane metaanalysis found metformin to improve clinical pregnancy rates among women diagnosed with PCOS.[9] Metformin also induces cardioprotective effects by improving serum lipids as well as plasminogen activator inhibitor (PAI)-1 levels and may decrease the risk of development of type 2 diabetes by improving insulin resistance.[10] Metformin has also been observed to reduce body weight as a side effect, but the precise cellular mechanism of action for metformin in weight loss remains unclear. It is surmised, however, that weight loss is supported by metformin-modulated reduction of hepatic glucose production, reduction of intestinal absorption of glucose and increase of peripheral glucose uptake and utilization.[11] Metformin also centrally decreases appetite and food intake through prolongation of postprandial fall in serum ghrelin concentrations[12] and regulating the hypothalamic neuropeptide Y signalling pathway.[13] Seifarth et al[14] found that metformin significantly reduces body weight among overweight and obese patients, in a randomized controlled trial involving 154 obese participants. A systematic review and metaanalysis by Nieuwenhuis-Ruifrok et al[15] also found that treatment of obese women with metformin showed a statistically significant decrease in BMI compared with placebo. Metformin was also proven to improve lipid metabolism in patients with metabolic syndrome and diabetes via reducing levels of LDL-C, total cholesterol and triglycerides and by increasing levels of HDL-C.[16]

Orlistat, on the other hand, is a cholesterol reductase antagonist that blocks cholesterol absorption at the intestinal villi. Orlistat binds irreversibly to gastric and pancreatic lipases, inhibiting the digestion of triglycerides. This decrease in dietary lipid absorption has been shown to produce sustained weight loss, resulting in significant improvements in the lipid profile and glycemic control. [17] Although it does not target the central etiology of PCOS which is insulin resistance, orlistat's effectivity as an anti-obesity drug makes it a good alternative to metformin in the treatment of obese PCOS patients to safely induce weight loss, and thereby cascade an improvement in endocrinologic and lipid profile and possibly ovulation rates. It has also been shown to irreversibly bind to gastric and pancreatic lipases to inhibit triglyceride digestion.[17] Orlistat, together with lifestyle changes was also shown to reduce the incidence of diabetes among obese Swedes[18]. A systematic review and metaanalysis by Rucker, et al.[19] found that orlistat signifiantly reduced weight, reduced the incidence of diabetes and improved concentrations of total cholesterol and LDL-C, blood pressure, and glycaemic control, compared to placebo.

We performed a systematic review and meta-analysis to compare the effectiveness of orlistat and metformin. We estimated the differences in effect in terms of reduction in weight or BMI,and improvement of ovulation rates, and endocrinologic and lipid profiles. We also compared the frequency of adverse events with the use of each drug.

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Materials and Methods

A. Criteria for considering studies for this review

Only RCTs with head to head comparison between metformin and orlistat as treatment for overweight and obese PCOS women were considered for inclusion. We refined the search to the following criteria: a. adult, reproductive-aged women 18-40 years old; b. Women with PCOS who are overweight (WHO: BMI>25-29.9kg/m^2; Asian BMI>23) or obese (WHO:BMI>=30kg/ m2; Asian BMI=25); c. all races/ethnicities included. We included studies with trial periods of at least 3 months duration, with or without run-in period or non-pharamacolgic and lifestyle modifications as co-interventions.

B. Search methods for identification of studies

We performed the search from February to April 2015. We searched Medline, OVID, HERDIN, EMBASE and the Cochrane Library. We also searched ClinicalTrials.gov. for any current or completed trials regarding metformin and orlistat for obese PCOS patients. We contacted pharmaceutical companies for orlistat and metformin through electronic mail to ask about any ongoing or unpublished trials they may have. We also searched pharmaceutical companies' websites for any ongoing clinical trials. Meticulous hand-searching was also performed on the references used in the included studies for any related articles.

Titles and abstracts were reviewed independently by the two authors, Both authors further evaluated the eligibility of retrieved materials, and disagreements were solved by consulting a third party. Authors tried to correspond with study investigators to clarify study eligibility when needed, or when data are missing. Searches were not limited by language, publication date, or publication status.

C. Data Collection

Two review authors extracted data from included trials and entered results into the RevMan 5.3 program. Data extraction included the following items: a) Population: age, BMI, diagnistic criteria used, study setting (country, race), inclusion and exclusion criteria; b). Intervention: dose, duration, an co-intervention such as exercise and diet; c) outcomes: for dichotomous outcomes: number of women who ovulated (ovulation rates) and experienced adverse events per treatment arm; for continuous data: percent decrease (or increase) in weight (kg), BMI, total and free testosterone, free androgen index (FAI),Dehydroandrostendione, 17-hydroxyprogesterone, homeostatic model assessment for insulin resistance or HOMA-IR, fasting insulin, fasting blood sugar, or 75 grams oral glucose tolerance test; d) Design: method of randomization, presence of run-in period, study design (parallel, cross-over); and e) Funding sources: pharmaceutical companies, university research grants.

We contacted the trial investigators for data on primary and secondary outcomes in the individual trials when the information was inadequate or not explicity stated or clear. One author entered data into the Review Manager, and a second author verified the data entry.

Two authors independently assessed the quality and risk of bias of each RCT using the Cochrane Guidelines.. Trial quality for each article was assessed on the following parameters: random sequence generation, allocation concealment,

blinding of participants and caregivers, blinding of outcome assessors, attrition bias, selective reporting, and publication bias.

D. Measures of treatment effect

We calculated the risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes, such as ovulation rates and adverse events. We calculated the differences in means for continuous outcomes such as BMI or weight reduction in kilograms (kg), lipid profile, and endocrinologic profile.

We converted the data from studies that used standard error of the means (SEM) in reporting outcomes to standard deviation, for our analysis.

E. Assessment of heterogeneity

We assessed clinical heterogeneity by checking the quality or risk of bias of each study, and also checking possible differences in the following: the setting where the studies were conducted, the characteristics of the study group, and the primary and secondary outcomes. We also checked for possible variations in the dosing of the intervention, cut-offs for BMI, criteria used to diagnose PCOS, and the criteria used for inclusion and exclusion of the participants. We assessed statistical heterogeneity based on the Chi^2 test (α 0.10), I^2 statistic and the overlap of CI's in the Forest plots. We label the studies as having "high heterogeneity" when the I^2 statistic was greater than 50%. Poor overlap likewise suggests the presence of significant heterogeneity.

F. Data synthesis

We pooled data for dichotomous and continuous outcomes using a fixed effects model. We used random effects model for pooled trial results with high heterogeneity. We considered a statistically significant difference between active treatment and control when 95% confidence interval does not cross 1 (for RR in dichotomous outcomes) or 0 (for mean difference in continuous outcomes).

Results

A. Description of studies

Results of the search

The initial electronic searches returned 65 titles and abstracts. We identified 2 additional eligible RCTs through handsearching of abstracts and searching through list of references from published studies. We screened the titles and abstracts of these records, and selected 11 potentially relevant RCTs. On review of full text reports, we included 5 RCTs which passed our inclusion criteria, and discarded the remaining 6 studies. See "search and selection flow diagram". Figure 1

We included 5 RCTs, summarized in table 1. The 5 RCTs included a total of 221 obese women diagnosed with PCOS. All participants were of reproductive age (18-40 years old), and identified as obese or overweight, either using WHO criteria or Asia-Pacific standards. Three RCTs enrolled Caucasian women (Jayagopal 2005, Metwally 2009, Cho 2009) all from the United Kingdom, while 2 RCTs were done on Asian women from India (Kumar 2014) and Iran (Ghandi 2011). All 5 RCTs used the Rotterdam criteria to diagnose PCOS.

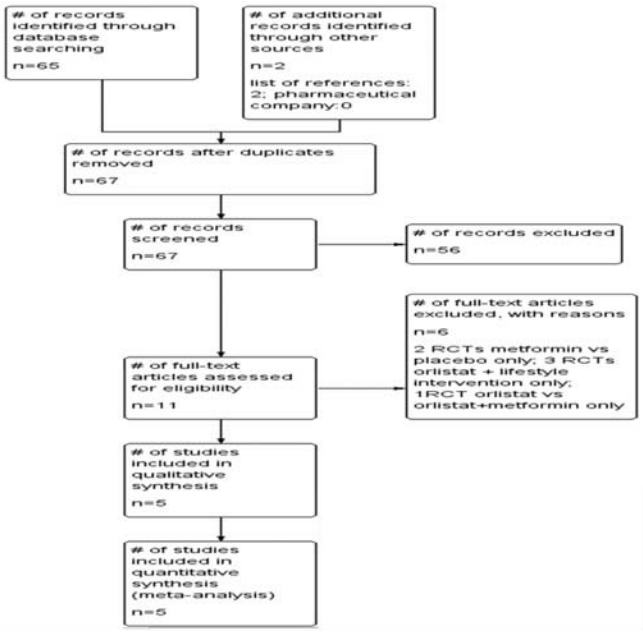

Figure 1. Search and selction flow diagram.

Table 1. Characteristics of the 5 RCTs included in the sytematic review.

Study	Population	BMI range	Comparison	Population characteristic	Attrition rate	Co-intervention	Relevant Outcomes
Jayagopal 2005[4]	21	≥30 kg/m^2	Orlistat 10mg tid vs Metformin in increasing doses	Caucasian	None	8 week run-in period with dietary advice; all patients maintained on diet: fat 30%, CHO 50%, CHON 20%	percent change in weight, percent change in testosterone, percent change in HOMA-IR, percent change in cholesterol
Metwally 2009[19]	40	≥30 kg/m^2	Orlistat 120mg bid vs Metformin in increasing doses	Caucasian	None	None	ovulation rate, percent change in BMI
Cho 2009[19]	30	≥36 kg/m^2	Orlistat 120mg tid vs Metformin in increasing doses	Cucasian	None	8 week run-in period with dietary advice;; Third arm: pioglitazone	percent change in BMI, percent change in SHBG, percent change in HOMA-IR, percent change in fasting insulin
Ghandi 2011[19]	80	≥30 kg/m^2	Orlistat 120mg tid vs Metformin in increasing doses	Asian	None	None	ovulation rate, percent change in weight, percent change in BMI, percent change in testosterone, percent change in cholesterol
Kumar 2014[19]	60	≥23 kg/m^2	Orlistat 10mg bid vs Metformin in increasing doses	Asian	None	all patients placed on a hypocaloric diet: 1,200-1,800 kcal/d, fat25%, CHON 15%, CHO 55%	ovulation rate, percent change in weight, percent change in BMI, percent change in testosterone, percent change in SHBG, percent change in HOMA-IR, percent change in fasting insulin, percent change in cholesterol

Risk of bias in included studies

Figure 2 summarizes the "Risk of Bias" assessments for all 5 included studies.

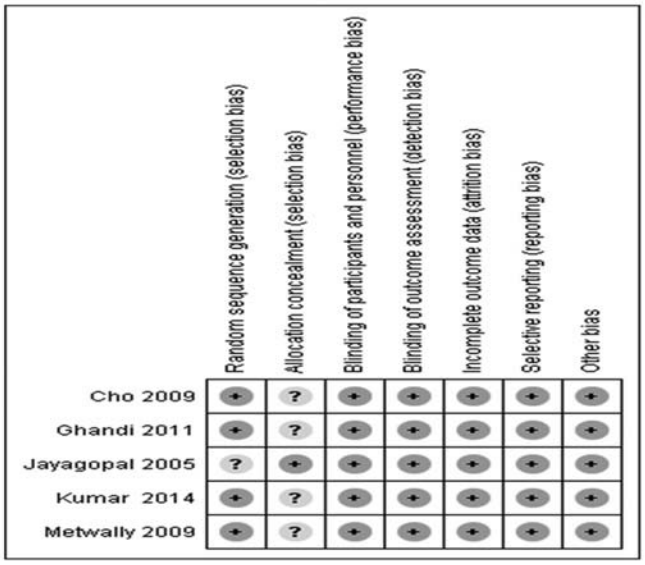

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

B. Effects of interventions

Primary Outcomes

1. Ovulation Rates: Three of the five RCTs (n=180), measured ovulation rates as outcome. The pooled RR is 0.78, favoring metformin (95% CI 0.41,1.49), but with no significant difference. However, the wide confidence interval makes the result inconclusive. Heterogeneity (I^2) is at 39%. Figure 3

2. Change in Weight (kg): Three out of five studies (n= 161) reported percent change in weight (kg) as one of the outcomes. The pooled mean difference of -1.29 (95% CI:-3.03,0.46) in the combined RCTs favor orlistat, but did not reach statistical significance. However, the wide confidence interval makes the results inconclusive. Heterogeneity (I^2) is quite high at 55%. Figure 4

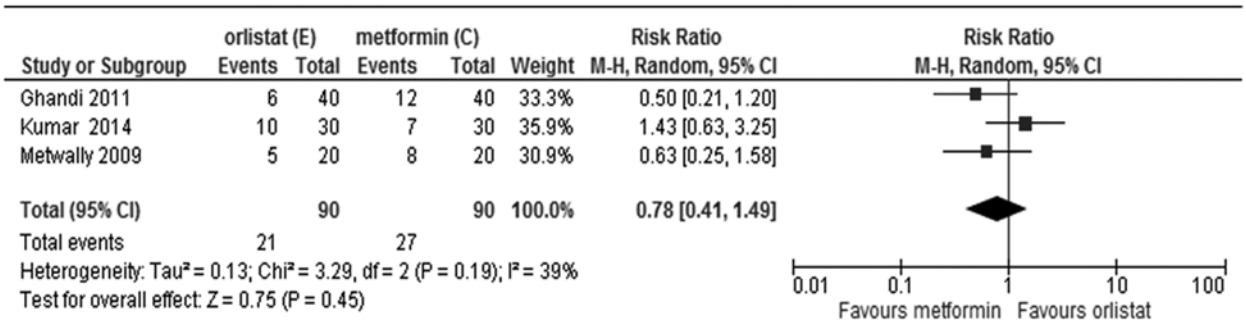

Figure 3. Forest plot of RR for ovulation rates, metformin (C) vs orlistat (E).

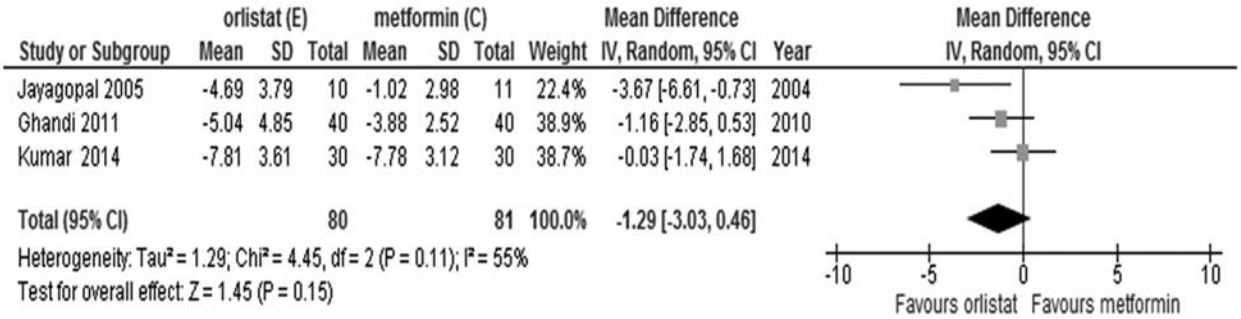

Figure 4. Forest plot of mean difference in percent change in weight (kg), orlistat vs metformin.

3. Change in BMI: Four out of the five RCTs (n=200) reported percent change in BMI as an outcome. Consistent with results from above, the pooled mean difference of -0.47 (95%CI:-1.53,0.59) favors orlistat, but did not reach statistical significance. Again, the wide confidence interval for this outcome makes the result inconclusive. Heterogeneity (I^2) is quite low, only at 7%. Figure 5

Secondary Outcomes

1. Endocrinologic Profile: Only serum total testosterone, free androgen index (FAI), fasting insulin and HOMA-IR were reported by at least 2 of the included RCTs. Only 1 RCT (Metwally 2009) reported percent change in DHEAS and Androstenedione levels and only 1 RCT (Ghandi 2011) reported percent change in Lutenizing hormone (LH) levels and 17-hydroxyprogesterone, so these outcomes were not included. Figure 6

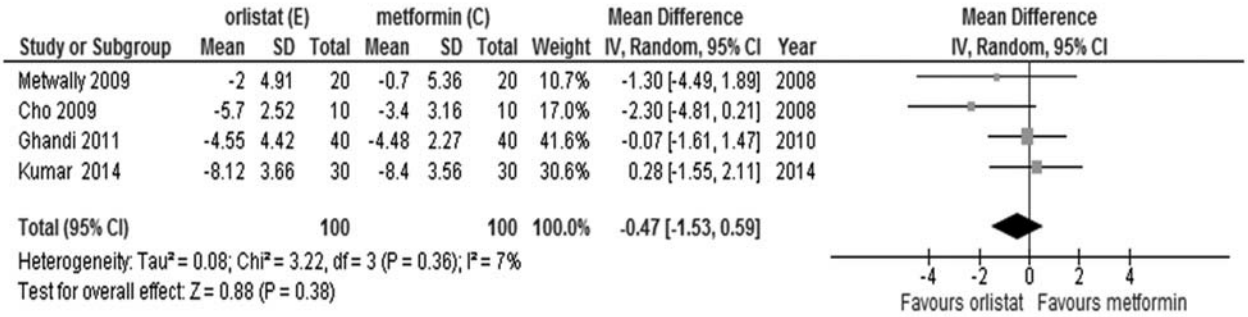

Figure 5. Forest plot of mean difference of percent change in BMI, orlistat vs metformin.

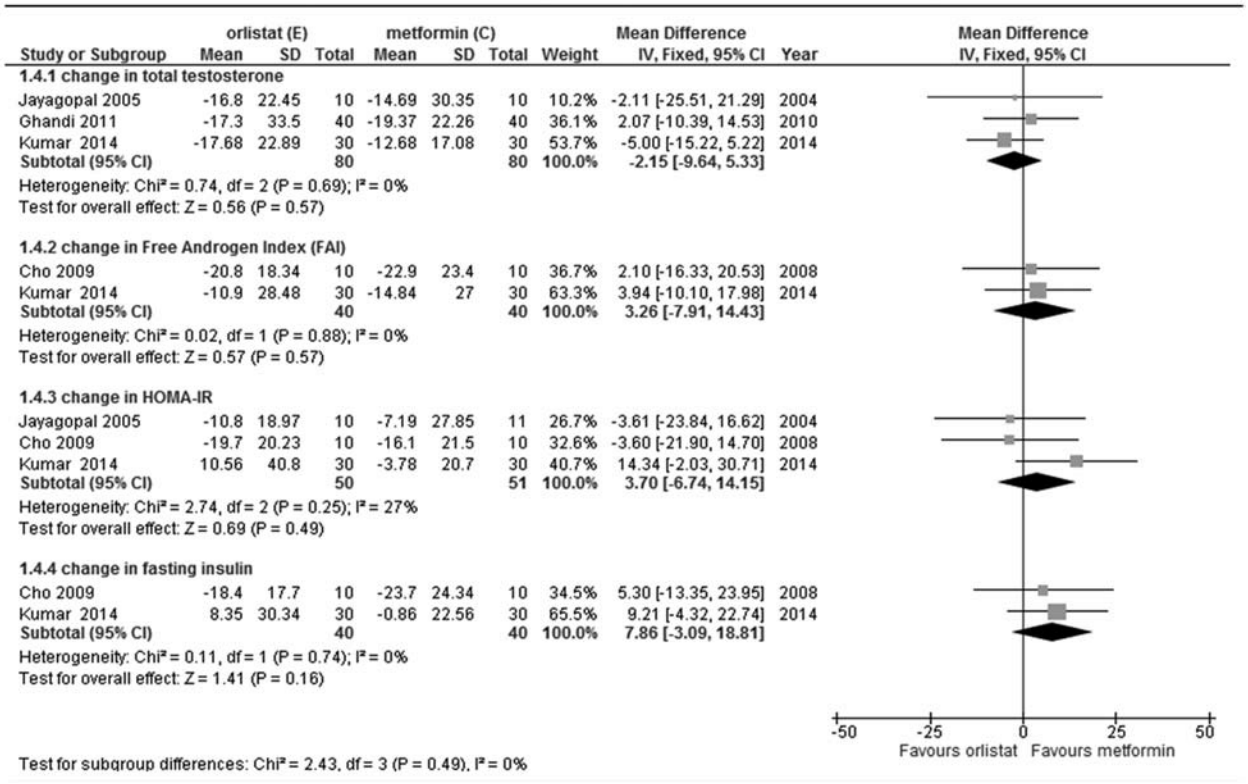

Figure 6. Forest plot of mean difference in percent change in endocrine profile components, orlistat vs metformin.

- Percent change in total testosterone: Pooled result showed a non-signficant mean difference of -2.15 (95% CI -9.64, 5.33), favoring orlistat.
- Percent change in FAI: Pooled result showed a non-signficant mean difference of 3.26 (95% CI -7.91, 14.43), favoring metformin.
- Percent change in fasting insulin: Pooled result showed a non-signficant mean difference of 7.86 (95% CI -3.09, 18.81), favoring metformin
- Percent change in HOMA-IR: Pooled result showed a non-signficant mean difference of 3.70 (95% CI -6.74, 14.15), s favoring metformin.

Only HOMA-IR showed heterogeneity, with $I^2 = 27\%$.

Overall, due to the very wide confidence intervals of the pooled estimates, we found inconclusive evidence in the treatment effects between metformin and orlistat in terms of improvement of androgen levels (total testosterone and free androgen index), and insulin resistance (HOMA-IR and fasting insulin).

2. Lipid Profile: Orlistat is more effective in decreasing levels of total cholesterol and LDL, than metformin. However, we found that orlistat and metformin have no significant differences in treatment effect for HDL and triglyceride levels. Figure 7
   - Percent change in total cholesterol: Pooled result showed statistically signficant mean difference of -6.60 (95% CI -10.79, -2.41), favoring orlistat.
   - Percent change in LDL-C:Pooled result showed a statistically signficant mean difference of -5.04 (95% CI -9.99, -0.09), again favoring orlistat.
   - Percent change in HDL-C: Pooled result showed a non-signficant mean difference of -1.19 (95% CI -4.78, 7.16), favoring orlistat

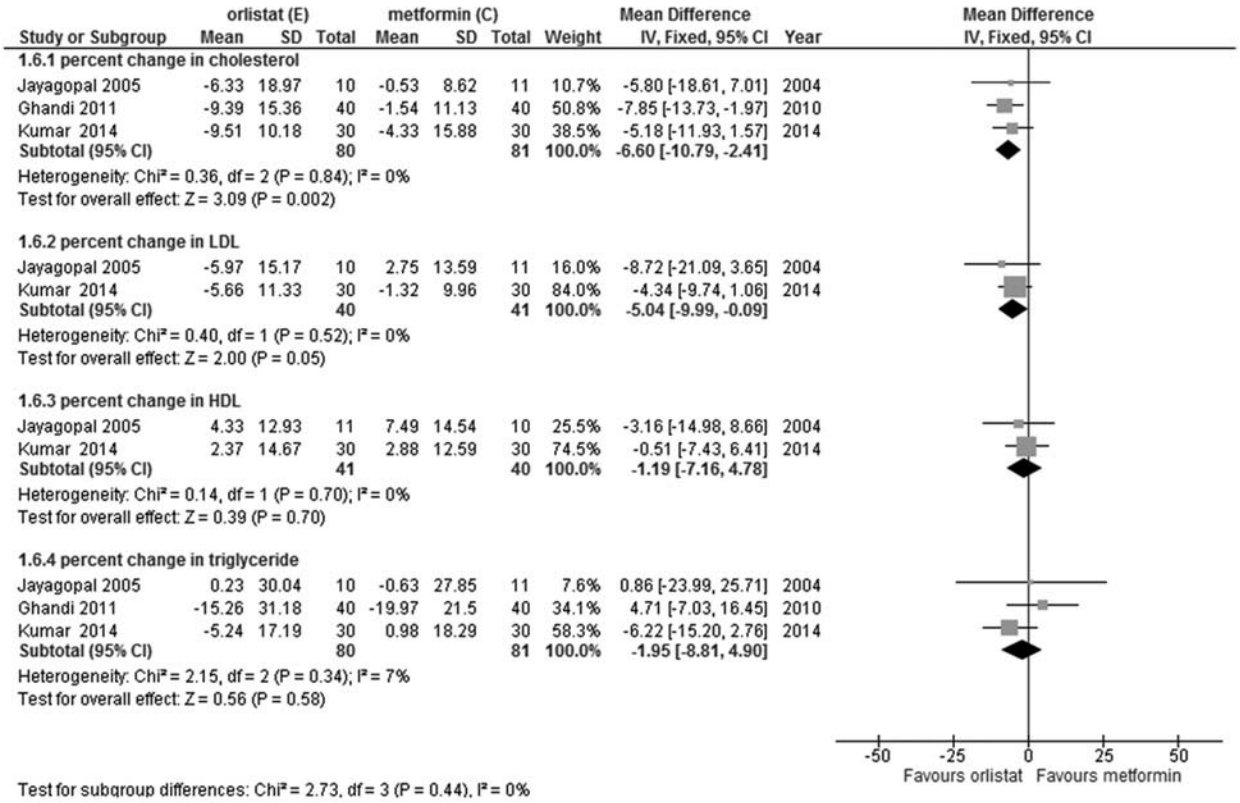

Figure 7. Forest plot of mean difference in percent change in lipid profile components, orlistat vs metformin.

- Percent change in triglycerides: Pooled result showed a non-signficant mean difference of -1.95 (95% CI -8.81, 4.90), favoring orlistat.

No heterogeneity was found for all 4 components under lipid profile.

The wide confidence intervals for HDL-C and triglycerides make the results inconclusive.

3. Adverse Events: Four RCTs reported adverse effects as an outcome. We found that the incidence of adverse events are significantly higher for the metformin treatment arm, than orlistat (pooled RR 0.37, 95% CI 0.14,0.96). Figure 8

C. Subgroup analysis

We performed subgroup analysis based on race (Asians versus Caucasians) and dose of orlistat (BID vs TID) for primary outcomes.

Percent change in BMI: Percent change in BMI favored orlistat over metformin, given either at BID or TID dose, but with no significant difference. Figure 9. Pooled mean difference for percent change in BMI favored metformin for Asian women, but favored orlistat among Caucasian women, but with no significant difference. Figure 10

Ovulation rates: Pooled RR for ovulation rates favored metformin over orlistat, given either at BID or TID dose, or when given to either Asian or Caucasian women, but with no significant differences. Figure 11 and Figure 12

Results of the subgroup analysis strengthened main results for primary outcome.

Discussion

A. Summary of main results

Based on this review, orlistat and metformin generally showed no significant difference in inducing ovulation, reducing weight or BMI, and improving endocrinologic profiles of obese women with PCOS. Orlistat, however, is more effective than metformin in reducing total cholesterol and LDL levels, and has fewer adverse effects.

Three RCTs (Jayagopal 2005, Metwally 2009, Cho 2009) enrolled Caucasian women mainly from the United Kingdom, while the other 2 studies (Ghandi 2011, Kumar 2014) were performed on Asian women (India and Iran). All trials measured outcome measures after 3 months of follow-up period.

We assessed the quality of evidence for all outcomes as "low quality" using the GRADEPRO, mainly due to the following reasons: method of allocation concealment not specified (risk of bias), small sample sizes (precision), wide confidence intervals and inconsistent results. Table 2

The investigators of the pioneering trial (Jayagopal 2005) reported a significantly higher reduction in weight after treatment with orlistat compared to metformin, but found similar effect for both drugs in reducing serum total testosterone levels.

Three trials reported ovulation rates as outcome (Metwally 2009, Ghandi 2011 and Kumar 2014), and their pooled RR favored metformin, although with no statistically signficant difference. This

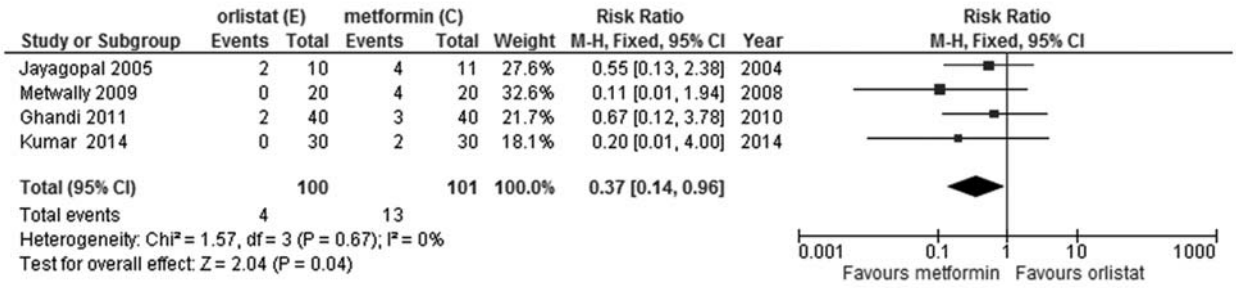

Figure 8. Forest plot of RR of Incidence of adverse effects, orlistat vs metformin.

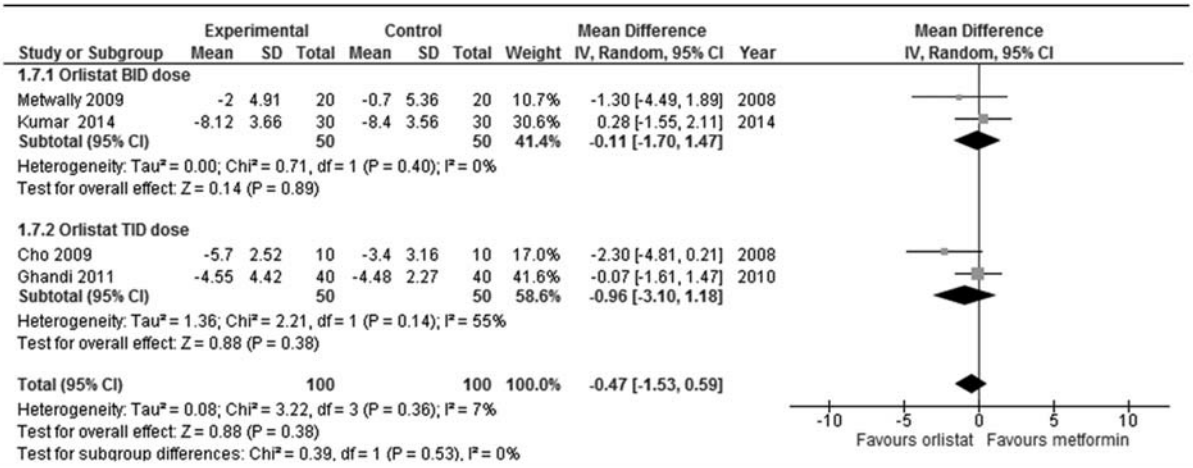

Figure 9. Forest plot of subgroup analysis: percent change in BMI by orlistat dose, metformin vs orlistat.

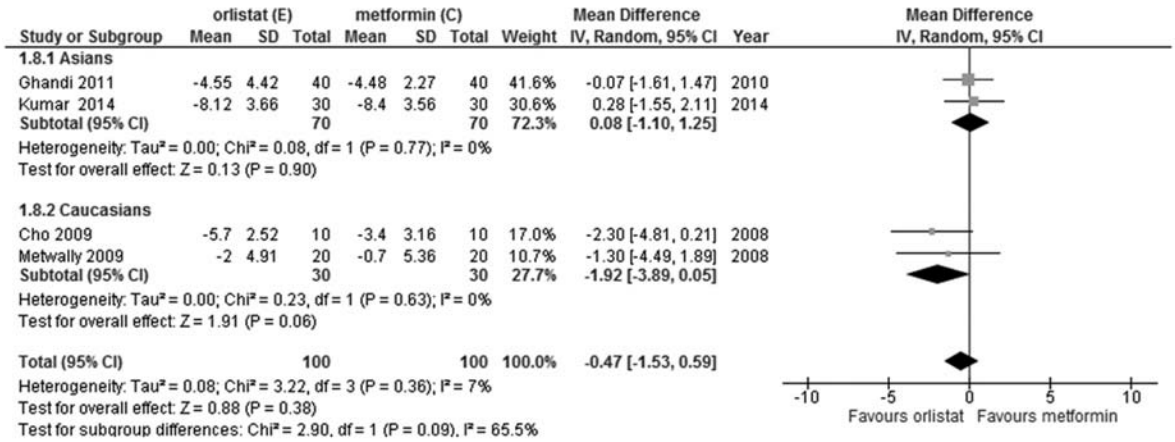

Figure 10. Forest plot of subgroup analysis: percent change in BMI by race, metformin vs orlistat.

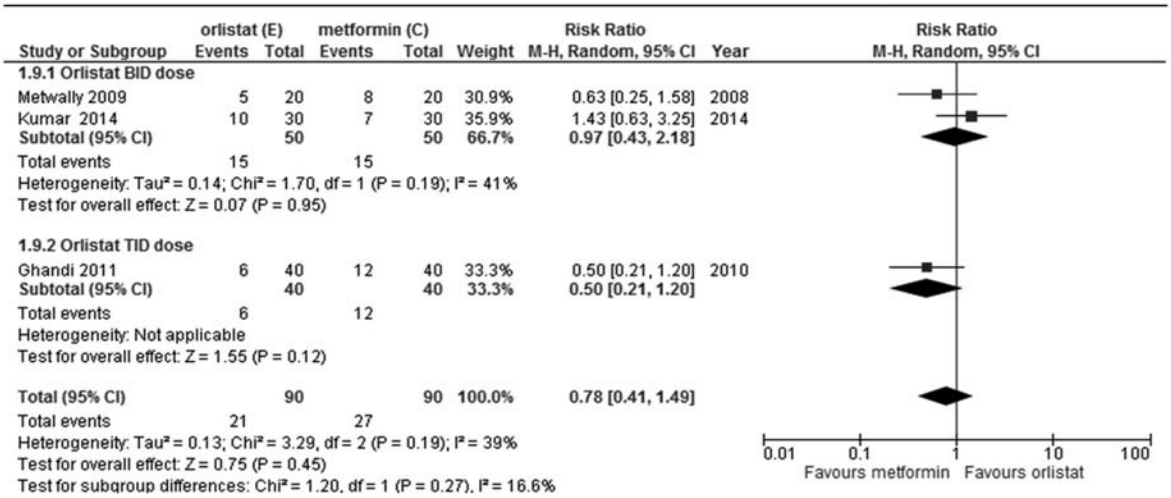

Figure 11. Forest plot of subgroup analysis: ovulation by orlistat dose. metformin vs orlistat

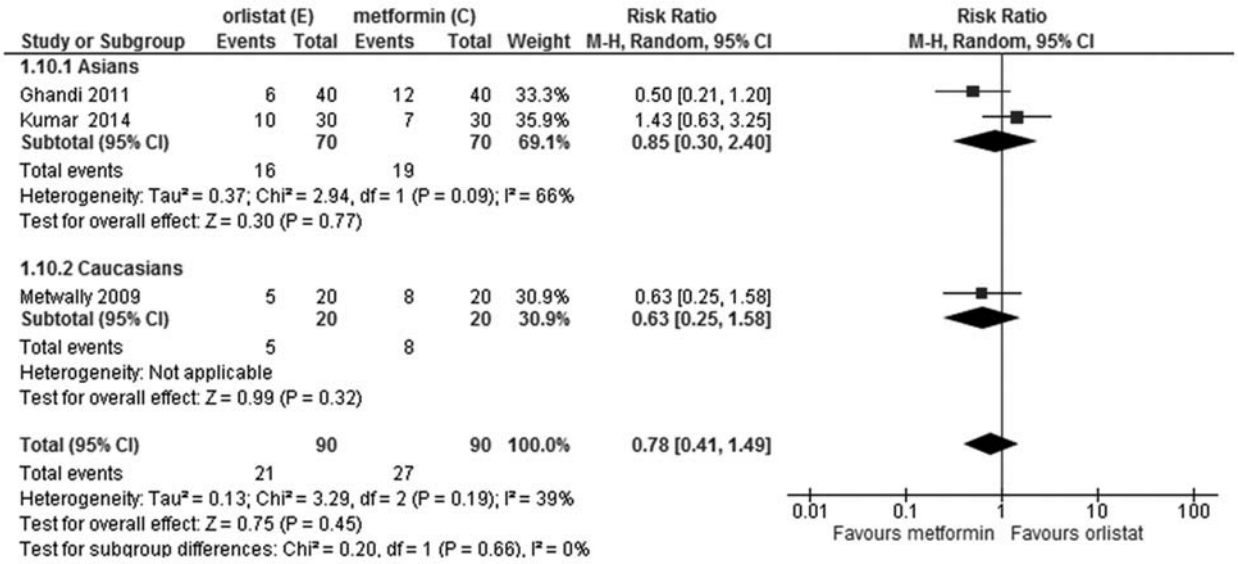

Figure 12. Forest plot of subgroup analysis: ovulation by race, metformin vs orlistat

treatment effect is generally expected since metformin basically targets the central etiology of PCOS (insulin resistance). Lowering insulin resistance leads to a decreased hyperandrogenic milieu in the ovarian stroma, that eventually favors better ovulatory rates.

Three trials reported percent change in weight (Jayagopal 2005, Ghandi 2011, Kumar 2014) while 4 trials reported percent change in BMI (Metwally 2009, Cho 2009, Ghandi 2011, Kumar 2014), as outcomes. Pooled mean difference for both outcomes favored orlistat, but with no statistically signficant difference. These results are generally expected, since orlistat is a lipase inhibitor, which directly inhibits absorption of fats at the level of the intestinal villi. Because of this, we expect orlistat to produce better weight loss outcomes, over metformin. A longer treatment trial and follow-up period could possibly result in better, more significant results favoring orlistat over metformin.

For the endocrinologic profile, pooled estimates for free androgen index, fasting insulin and homeostatic model assessment insulin resistance (HOMA-iR) all favored metformin, but with no statistically significant differences. Again, this is an expected result, as metformin is an insulin sensitizer, and is therefore expected to produce better improvement in terms of insulin resistance. For the lipid profile, pooled mean differences for all 4 parameters all favored orlistat, with orlistat showing significantly better improvement for total cholesterol and LDL-C, over metformin. These results are expected, since orlistat is a cholesterol/ lipase inhibitor. Since orlistat showed signifcant results in lowering serum total cholesterol and LDL-C, we can now recommend that orlistat be given for obese PCOS women with concomittant dyslipidemia or increased cardiometabolic risk factors.

Four trials reported adverse events as outcome. Pooled RR showed that frequency of adverse events are significantly lower for orlistat compared to metformin. This connotes better tolerability and puts orlistat in an advantage over metformin.

B. Overall completeness and applicability of evidence

We noted the adequacy of the studies in terms of the selection of participants, the delivery of interventions, and outcomes investigated. The 5

Table 2. Asssessment of quality of evidence using GRADEPRO
Orlistat compared to Metformin for overweight and obese women with PCOS
Patient or population: overweight and obese women with PCOS
Intervention: Orlistat
Comparison: Metformin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Metformin	Corresponding risk Orlistat				
Ovulation rates follow up: 3 months	Study population 300 per 1000	234 per 1000 (123 to 447)	RR 0.78 (0.41 to 1.49)	180 (3 RCTs)	⊕⊕⊖⊖ LOW[1,2]	risk of bias: method of allocation concealment not specified; precision: small sample sizes and wide CI; inconsistent results
percent change in weight (kg); follow-up: 3 months	The mean percent change in weight (kg) in the control group was -4.23 percent	The mean percent change in weight (kg) in the intervention group was 1.29 lower (3.03 lower to 0.46 higher)	-	161 (3 RCTs)	⊕⊕⊖⊖ LOW[2,3]	method of allocation concealment not specified; small sample sizes and wide CI
Percent change in BMI; follow-up: 3 months	The mean percent change in BMI in the control group was -4.26 percent	The mean percent change in BMI in the intervention group was 0.47 lower (1.53 lower to 0.59 higher)	-	200 (4 RCTs)	⊕⊕⊖⊖ LOW[2]	method of allocation concealment not specified; small sample sizes, wide CI
Percent change in testosterone; follow-up: 3 months	The mean percent change in testosterone in the control group was -15.58 percent	The mean percent change in testosterone in the intervention group was 2.15 lower (9.64 lower to 5.33 higher)	-	160 (3 RCTs)	⊕⊕⊖⊖ LOW[2]	method of allocation concealment not specified' small sample sizes; wide CI
Percent change in FAI; follow-up: 3 months	The mean percent change in FAI in the control group was -18.87 percent	The mean percent change in FAI in the intervention group was 3.26 higher (7.91 lower to 14.43 higher)	-	80 (2 RCTs)	⊕⊕⊖⊖ LOW[2]	method of allocation concalment not specified; small sample sizes; wide CI
Percent change in fasting insulin follow-up: 3 months	The mean percent change in fasting insulin in the control group was -12.28 percent	The mean percent change in fasting insulin in the intervention group was 7.86 higher (3.09 lower to 18.81 higher)	-	80 (2 RCTs)	⊕⊕⊖⊖ LOW[2]	method of allocation concealment not specified; small sample sizes; wide CI

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Metformin	Corresponding risk Orlistat				
Percent change in HOMA-IR follow-up: 3 months	The mean percent change in HOMA-IR in the control group was -9.02 percent	The mean percent change in HOMA-IR in the intervention group was 3 higher (6.74 lower to 14.15 higher)	-	101 (3 RCTs)	⊕⊕⊖⊖ LOW[2]	inconsistent results, small sample sizes, wide CI
Percent change in total cholesterol follow-up: 3 months	The mean percent change in total cholesterol in the control group was -4.75 percent	The mean percent change in total cholesterol in the intervention group was 0.38 lower (10.33 lower to 9.58 higher)	-	161 (3 RCTs)	⊕⊕⊖⊖ LOW[2]	inconsistent results, small sample size, wide CI
Percent change in LDL follow-up: 3 months	The mean percent change in LDL in the control group was 0.72 percent	The mean percent change in LDL in the intervention group was 0.16 higher (15.1 lower to 15.41 higher)	-	81 (2 RCTs)	⊕⊕⊖⊖ LOW[2]	inconsistent results
Percent change in HDL follow-up: 3 months	The mean percent change in HDL in the control group was 3.35 percent	The mean percent change in HDL in the intervention group was 1.19 higher (4.78 lower to 7.16 higher)	-	81 (2 RCTs)	⊕⊕⊖⊖ LOW[2]	
Percent change in triglycerides follow-up: 3 months	The mean percent change in triglycerides in the control group was -5.20 percent	The mean percent change in triglycerides in the intervention group was 5.17 lower (12.02 lower to 1.69 higher)	-	161 (3 RCTs)	⊕⊕⊖⊖ LOW[2]	
Adverse events follow up: 3 months	Study population 129 per 1000	48 per 1000 (18 to 124)	RR 0.37 (0.14 to 0.96)	201 (4 RCTs)	⊕⊕⊖⊖ LOW[2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[1]method of allocation concealment not specified; imprecise because confidence intervals are wide; small sample size; inconsistent because 2 studies favor metformin, while 1 study favor orlistat; [2]No explanation was provided; [3]method of allocation concealment not specified; large CIs, small sample sizes

RCTs, however, are insufficient to adequately answer conclusively all our objectives primarily due to their over-all low quality.

Pregnancy rate would have been the ideal hard outcome to measure effectiveness in improving reproductive function, instead of using a surrogate marker in the form of ovulation rates. However, only 1 RCT reported pregnancy rates as a primary outcome (Metwally 2009), and this particular study controlled only for male factor infertlity.

We purposely did not include pregnancy rate as one of our primary outcomes because infertility is largely a mutifactorial condition that is very difficult to control for a well-designed RCT.

We purposely did not set any limit for the year of publication in our electronic and hand searches, in order to capture all relevant studies regarding our clinical question.

Since manifestations of PCOS differ across races, more RCTs are needed to study the effect of both active drugs on different ethnicities. This problem was partially addressed by this metaanalysis, where 3 out of the 5 studies were done among Caucasian (European) women, and the other 2 RCTs were conducted on Asian women. All 5 RCTs used the same diagnostic criteria to diagnose PCOS among its participants. Further research should include Africans (or American-Africans), Southeast Asians and East Asians who may possibly produce different results due to their different PCOS phenotype.

For a more complete endocrinologic profiling of women with PCOS, laboratory exams should ideally include other components such as androstenedione, Luteinizing hormone (LH), follicle stimulating hormone (FSH), Dehydroepiandrostendione (DHEAS), 17-hydroxyprogesterone (17-OHP) and sex hormone binding globulin (SHBG). However, not all studies reported such outcomes, possibly due to funding limitations.

All 5 studies involved only short course treatments and follow-up period (3 months), which is a reasonable amount of time most reproductive endocrinologists give their patients to lose enough weight prior to treatment of infertility. However, it would be interesting to note if results will significantly differ if treatment period were extended beyond 3 months, i.e, long-course treatments such as 6 or 12 months. Results of this review show that both orlistat and metformin show no significant difference in reducing patients' weight and improving ovulation rates and hormonal profile, given a short course of treatment (3 months).

In clinical practice, especially in the field of Reproductive Endocrinology and Infertility, we could possibly recommend either orlistat or metformin for our obese PCOS patients to induce weight loss and ovulation, and improve their hormonal profile. In order to help physicians (and patients) decide which appropriate drug to choose, other factors must now be factored in, such as frequency of adverse events, and the presence of cardiometabolic risk factors in the individual patients. Based on the results of this review, orlistat would be a better drug over metformin in patients with concommitant dyslipidemia. It also has potentially better drug tolerability, due to the significcantly lower adverse events noted in this review.

C. Quality of the evidence

We have included a total of 5 RCTs with a pooled total number of participants, n= 221. We consider the current evidence for our primary and secondary outcomes to be of low quality, using the GRADEPRO (table 2), as most are downgraded mainly due to the following reasons: method of allocation concealment not specified (risk of bias), small sample sizes (precision), wide confidence intervals and inconsistent results. Further studies are likely to have an important impact on our confidence in the estimates of effects, or may even change the estimates. Random sequence generation was adequately performed and specified in 4 out of the 5 trials, but was not explicitly stated in 1 RCT. Likewise, the specific method of allocation concealment used was also unclear (not specified) in 4 out of 5 RCTs. Unfortunately, corresponding authors did not reply to our inquiries. Masking of participants, personnel and outcome assessors was deemed unnecessary, as all outcomes were measured objectively, and therefore unlikely to

be biased. All 5 RCTs reported complete outcome data, and performed an intention to treat analysis.

Conclusion

Based on our current data available, orlistat may be an alternative for management of women with PCOS who are overweight or obese.There is no statistically significant difference between orlistat and metformin on ovulation rates and weight loss. There is also no statistically signficant difference noted between the two drugs on their effect on improvement of androgen profile and insulin resistance. Orlistat is more effective than metformin in decreasing serum total cholesterol and LDL levels. Orlistat also had significantly less adverse events than metformin. Therefore, we may recommend orlistat to overweight or obese women with PCOS who have concommitant dyslipidemia and cardiometabolic risk factors. However, caution is given to our interpretations since small sample sizes, low quality of RCTs, and the wide confidence intervals of pooled estimates significantly influence our interpretation and recommendations.

More randomized controlled trials with adequately powered study populations are recommended to confirm findings of this review. We also recommend that the studies extend treatment period and follow-up period beyond three months to determine long-term sustainability of weight loss.

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