Adverse Effects of the Common Treatments for Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis

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Context: Polycystic ovary syndrome (PCOS) is common among women of childbearing age and the available pharmacological therapies have different side-effect profiles.

Objective: We summarized the evidence about the side effects of oral contraceptive pills, metformin, and anti-androgens in women with PCOS.

Data Source: Sources included Ovid Medline, OVID EMBASE, OVID Cochrane Library, Web of Science, Scopus, PsycInfo, and CINAHL from inception through April 2011.

Study Selection: We included comparative observational studies enrolling women with PCOS who received the agents of choice for at least 6 months and reported adverse effects.

Data Extraction: Using a standardized, piloted, and Web-based data extraction form and working in duplicate, we abstracted data from each study and performed meta-analysis when possible.

Data Synthesis: We found 22 eligible studies of which 20 were randomized. No study reported severe side effects (eg, lactic acidosis, thromboembolic episodes, liver toxicity, cancer incidence, or pregnancy loss). Meta-analysis demonstrated no significant change in weight in oral contraceptive pills or flutamide users. Indirect evidence from populations without PCOS demonstrated no increased risk of lactic acidosis with metformin, only case reports of liver toxicity with flutamide (no comparative evidence), and increased relative risk difference of venous thromboembolism with oral contraceptive pills but very low absolute risk. Evidence on mortality, cardiovascular mortality, and cancer was inconclusive.

Conclusions: Drugs commonly used to treat PCOS appear to be associated with very low risk of severe adverse effects although data are extrapolated from other populations. (J Clin Endocrinol Metab 98: 4646–4654, 2013)

Abbreviations: AA, antiandrogen agents; BMI, body mass index; Mt, metformin; OCP, oral contraceptive pills; PCOS, polycystic ovary syndrome; RCT, randomized controlled trials; VTE, venous thromboembolism; WMD, weighted mean difference.
Poly cystic ovary syndrome (PCOS) affects approximately 6% to 10% of reproductive age women (1,2). It is the most common endocrinopathy and cause of anovulatory infertility in women in the United States. When fully expressed, PCOS patients present with ovulatory dysfunction (oligomenorrhea/amenorrhea, increased risk of endometrial cancer, and infertility) and androgen excess (hirsutism and insulin resistance with or without obesity) (3–7). Women with PCOS have a higher prevalence of risk factors for type 2 diabetes and cardiovascular diseases (8, 9). They also have a 5- to 10-fold increased risk of developing diabetes compared with age- and weight-matched women (10).

The treatment of PCOS depends on the woman’s goal for therapy. Lifestyle modification is often used to treat the metabolic consequences of PCOS (11). Pharmacological agents such as metformin (Mt), oral contraceptive pills (OCPs), and antiandrogen agents (AA) are also frequently used (12). Mt is associated with fatal and nonfatal lactic acidosis even though the incidence ranges from 1 to 17 cases per 100,000 patients-years (13). OCPs have been associated with weight gain (14) and cardiovascular (15) and thromboembolic events (16). AA use has been associated with hepatic toxicity that could be fatal (17). The risk and nature of these side effects must be considered when choosing therapies.

This systematic review and meta-analysis was commissioned by the PCOS Task Force of The Endocrine Society to summarize the existing evidence about the side effects of the most common pharmacological treatments for PCOS.

Materials and Methods

Search and analysis methods, eligibility criteria, and the outcomes of interest were specified in advance in a protocol developed by study investigators and the Endocrine Society.

Eligibility criteria

We sought to include randomized controlled trials (RCTs) and comparative observational studies enrolling women with PCOS who received Mt, OCPs, or AAs for at least 6 months and reported any severe adverse effects. Studies had to include a comparison group of women who had PCOS but received placebo or no treatment.

Search methods

An expert reference librarian (P.J.E.), following the protocol, designed and conducted an electronic search strategy (Supplemental Table 1, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). We searched Ovid Medline, OVID EMBASE, OVID Cochrane Library, Web of Science, Scopus, PsycInfo, and CINAHL from inception through April 2011, without language limitations. To identify additional candidate studies, we reviewed the reference lists of the eligible primary studies, narrative reviews, and systematic reviews and we queried the expert members of the commissioning task force.

Study selection

Two reviewers working independently considered the potential eligibility of each of the abstracts and titles that result from executing the search strategy. Eligible studies were reviewed in full text version. Disagreements were resolved by consensus.

Data extraction and management

Using a standardized, piloted, and Web-based data extraction form and working in duplicate, we abstracted the following descriptive data from each study: full description of participants enrolled (principal baseline characteristics as age, childbearing, weight and body mass index [BMI]), the interventions they received (type, dose, and frequency), the control interventions, the monitoring for efficacy or adherence, the measure of outcome (specifically defined as event or measure and timeframe for the ascertainment of this outcome), and the source of funding. We extracted the outcomes of interest at the longest point of complete follow-up.

Outcomes of interest

The outcomes of interest were 1) for Mt lactic acidosis; 2) for OCPs thromboembolic events (venous or arterial) and other cardiovascular events, overall cancer risk, incidence of diabetes, changes in weight and BMI; and 3) for AA drug-induced liver injury. Metabolic parameters such as blood glucose (fasting blood glucose, postprandial glucose, glucose tolerance test, random glucose, and area under the curve of glucose) and insulin resistance (as glucose-to-insulin ratio, Homeostasis Model of Assessment of Insulin Resistance, Quantitative Insulin Sensitivity Check Index) were extracted and analyzed for AA and OCPs only. We did not evaluate the gastrointestinal side effects of Mt because these patients often abandon therapy promptly and would be underrepresented in the long-term studies we sought to include.

Author contact

We contacted authors of studies in which data were not available or were reported incompletely for our purposes. We used a maximum of two contacts via e-mail, or by postal mail if e-mail was not available, at 2-week intervals.

Assessment of risk of bias in individual included studies

To assess the methodological quality of the included RCTs we used the Cochrane risk of bias assessment tool to evaluate randomization performance and methods, allocation concealment, baseline imbalances, extent of blinding (patients, caregivers, data collectors, outcome assessors, and data analysts), rate of loss to follow-up, and whether adherence was monitored. For observational studies we used the Newcastle and Ottawa quality assessment tool to evaluate how the groups were selected, the comparability between them, whether there was adequate follow-up, and how outcomes/exposure were ascertained.
Meta-analysis

For dichotomous outcomes we estimated the risk ratio and for continuous outcomes we estimated the weighted mean difference (WMD). Random-effects model was chosen a priori to pool effect size across studies (18). The I² statistic was used to measure inconsistency in results across studies. The I² statistic quantifies differences in results between studies that are not attributable to chance, therefore reflecting true inconsistency between different trials. Our analyses were performed using Comprehensive Meta-Analysis version 2.2 (Biostat Inc). Analysis was conducted separately in pregnant and nonpregnant women.

Indirect evidence

Anticipating sparse adverse effect data in studies of women with PCOS, we planned to present the best available evidence simultaneously about adverse effects of the interventions of choice in patients without PCOS (patients with diabetes, healthy women, and women with hirsutism). This indirect evidence may be extrapolated to women with PCOS. We searched for systematic reviews and, if not available, for studies with long-term follow-up as a representative sample of indirect evidence of the adverse effects of the drugs of interest. These data are presented separately as indirect evidence.

Subgroup and sensitivity analysis

We determined a priori a limited number of hypotheses to explore subgroups interactions and potential explanations for inconsistency. Subgroup analyses were based on 1) syndrome severity; 2) methodological quality; 3) patient’s baseline weight (overweight vs non-overweight); 4) daily dose of the medications; 5) length of the intervention. We planned to test the hypotheses of a subgroup effect using a test of interaction (19) and to conduct meta-regression to assess the correlation between the effect size and doses of drugs.

Results

Search results

Literature search identified 1076 potentially eligible articles, of which 22 original studies reported in 25 publications, enrolling 1335 PCOS patients, met the eligibility criteria and were included in the direct evidence part of the systematic review (Supplemental Figure 1). No unpublished relevant studies were available.

All but 2 of the 22 included studies were RCTs published in English (2 of them were crossover studies): 17 evaluated Mt in nonpregnant women, 2 Mt during pregnancy, and 3 used flutamide, the only AA evaluated in this systematic review, in nonpregnant women. Only one prospective cohort study evaluated OCPs. One case-control study evaluated Mt during pregnancy. Agreement for inclusion was substantial (interreviewer agreement beyond chance was 0.71). Six of eight study authors contacted contributed with additional data to the published record.

Study characteristics (Table 1)

The mean age of participants was 28 years (range 12–46). Nineteen studies followed the patients for less than a year. There was apparent heterogeneity in the included studies related to the diagnostic criteria of PCOS, BMI status, medication regimen and doses, and the severity of the disease (infertile women with evident clinical presentation vs fertile subclinical presentations). None of the included studies was designed to evaluate the harms of the interventions and about half of the studies excluded patients from the analysis due to side effects. The participants in general had good health (without diabetes, hypertension, or other comorbidities).

Risk of bias in included studies (Supplemental Table 2)

All of the included RCTs had adequate randomization method and 14 of them preserved randomization by implementing concealed allocation. Eight studies blinded all possible involved parties (including patients, caregivers, data analysts, and data collectors); eight had a double-blind design (patients and caregivers), and four were designed as an open-label RCT. Loss to follow-up was reported in 18 RCTs with a mean of 16.5% (range 0 to 66%). All but two studies did not present any important baseline imbalance between their groups (two RCTs had imbalances in metabolic parameters). Adequate methods for reducing loss to follow-up and for measuring the adherence to the treatment were reported in 12 and 9 of the studies, respectively. The overall risk of bias of the 20 included RCTs was low to moderate, mainly based on a low risk of selection and performance bias and a moderate attrition bias.

The risk of bias in the two observational studies was high due to a brief period of follow-up (less than 9 months in both) and lack of adjustment for confounders.

Direct evidence (studies of women with PCOS)

Mt

No study reported patients who experienced lactic acidosis or pregnancy loss with this agent. The trial by the Cooperative Multicenter Reproductive Medicine Network (20) randomly assigned 626 infertile women with PCOS to receive clomiphene citrate plus placebo, extended-release Mt plus placebo, or a combination of Mt and clomiphene for up to 6 months. The rates of first-trimester pregnancy loss did not differ significantly among the groups but Mt was associated with lower conception rate. Mt had more gastrointestinal side effects and less vaso-motor and ovulatory symptoms than clomiphene. The trial did not have a placebo arm.
None of the included studies reported severe side effects, such as drug-induced liver injury, cancer incidence, thromboembolic events, or any other cardiovascular event.

Flutamide and OCPs (Ethinyl-estradiol 30 µg + Chloromadinone acetate 2 mg and Ethinyl-estradiol 30 µg + Drospirenone 3 mg) did not significantly affect patients’ BMI (Flutamide: BMI WMD = 1.39, 95% CI = -3.22 to 0.44, P = .14, I² = 0, Supplemental Figure 2) and (OCPs: BMI WMD = 0.001, 95% CI = -0.16 to 0.16, P = .99, I² = 0, Supplemental Figure 3). There was no significant effect on weight (Flutamide: WMD = 3.76, 95% CI = -9.91 to 2.39, P = .23, I² = 0, Supplemental Figure 4) and (OCPs: WMD = 0.04, 95% CI = -0.35 to 0.43, P = .84, only reported in one study). OCPs did not affect fasting blood glucose (WMD = 1.18, 95% CI = -6.99 to 4.63; P = .69) and there were no data on the incidence of diabetes. The effect of the AA on blood pressure was not reported in any of the included studies.

Indirect evidence (studies in general population) (Table 2)

Mt
A systematic review published in 2010 (21) evaluated the risk for lactic acidosis in type 2 diabetic patients taking Mt and showed no cases of fatal or nonfatal lactic acidosis in 347 prospective trials and cohort studies with more than 70 490 patient-years of Mt use. The authors concluded that there is no evidence that Mt is associated with an increased risk of lactic acidosis.

Flutamide
Hepatotoxicity. The major concern with flutamide use is its association with severe hepatotoxicity and secondary death. A prospective cohort (22) of 214 hyperandrogenic...
teenagers and young women who took a low dose of flutamide during 1 year showed no cases of hepatotoxicity. Another study (23) evaluating the same design and population found no cases of hepatotoxicity in 190 PCOS patients who were treated with different doses of flutamide (62.5, 125, or 250 mg/d) for 15 months (range 3–54 mo). Two case series reports that evaluated 10 cases (7 of those were hyperandrogenic young women [24] and 9 cases, 1 of those was a hirsute teenager [25]) of severe hepatotoxicity induced by flutamide showed a relation between the treatment length and liver damage. Overall hepatotoxicity due to flutamide is thought to be dependent on the length of treatment and age, but the quality of evidence supporting this association is very low.

OCP

**Venous thromboembolism (VTE)**

OCPs are associated with a three- to six-fold increase of relative risk of VTE (26). An observational study with 142 475 women-years of observation (27) showed an increase of VTE risk from 5/10 000 in never users to 9–10/10 000 in OCPs users. A 15-year Danish historical cohort study followed 1 626 158 nonpregnant women, 15 to 49 years old, with no history of cardiovascular disease (28). This large study reported increased risk of thrombotic stroke and myocardial infarction that ranged across the various different OCPs with relative risks up to 2.5. The absolute risks were very small, consistent with other studies. The risk was increased by a factor of 0.9 to 1.7 with OCPs that included ethinyl estradiol at a dose of 20 μg and by a factor of 1.3 to 2.3 with those that included ethinyl estradiol at a dose of 30 to 40 μg (28). A systematic review of observational data concluded that the third-generation OCPs show a higher risk for VTE than second generation (16). This evidence highlights the fact that clinicians should be aware not only of the general drug class effects but also of the change in the size effect within the generation of these drugs. The VTE risk should be taken into greater consideration when patients have additional risk factors for VTE, such as advanced age, obesity, hypertension, diabetes, smoking, and hypercholesterolemia (29).

**Overall mortality and cardiovascular disease mortality**

A prospective cohort study with more than 378 000 women-years that compared OCPs users against never users found a significantly lower rate of death from any cause and lower rate of death from cardiovascular diseases (30). A systematic review of 20 observational studies found that the association of OCPs with stroke depends on the study design (case control studies found an association and co-
hort studies did not find an association). This suggests that the quality of this evidence is very low and, if an association exists at all, it is weak at best in users of low-dose OCPs (31).

**Overall risk of cancer**

An observational prospective study (32) that compared 23,000 women who were using OCPs against 23,000 women who never used these drugs concluded that, after 744,000 OCPs user-years, the overall risk of cancer was not affected by the drug. Rather, OCPs showed a protective trend.

**Weight gain**

A systematic review that included four RCTs, with placebo or a nonhormonal contraceptive method used in the control group, showed no differences in weight gain at 6 months of use (33). A prospective observational study of 568 women with more than two decades of follow-up (14,200 patients-years) showed no significant difference in weight gain in OCPs users (34).

**Discussion**

**Summary of findings**

We conducted a systematic review and meta-analysis to determine potential side effects of the common treatments available for women with PCOS. No study of women with PCOS reported severe side effects (eg, lactic acidosis, thromboembolic episodes, liver toxicity, cancer incidence, or pregnancy loss). Meta-analysis demonstrated no significant change in weight in OCP or flutamide users.

Indirect evidence from populations without PCOS demonstrated no increased risk of lactic acidosis with Mt, only case reports of liver toxicity with flutamide (no comparative evidence), and increased relative risk of VTE with OCP but very low absolute risk. Evidence on mortality, cardiovascular mortality, and cancer was inconclusive. The quality of evidence supporting the safety of Mt is high considering that women with PCOS would likely use it after the standard contraindications (21). The quality of evidence for the safety of AA and OCPs is likely lower and prescribers should consider other risk factors such as age and smoking status, along with patient preferences, and other considerations. In general, all the available treatments had a low occurrence of side effects and seemed to be well tolerated.

**Limitations and strengths**

The included studies in women with PCOS were not designed to evaluate side effects; thus, particularly in open-label studies, difference in outcome ascertainment and reporting can lead to biased results. The duration of

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Side Effect</th>
<th>Study Name</th>
<th>Study Design</th>
<th>Population</th>
<th>Size Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Lactic Acidosis</td>
<td>Sulperter, 2010 (21)</td>
<td>Systematic Review</td>
<td>Type 2 diabetic patients</td>
<td>69642 metformin users 70490 user-year</td>
<td>No cases of fatal or nonfatal lactic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dikensay, 2009 (22)</td>
<td>Prospective Cohort</td>
<td>Hyperandrogenic women</td>
<td>214 flutamide users 214 user-year</td>
<td>No cases of hepatotoxicity after 1 year of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iffiez, 2005 (63)</td>
<td>PCOS young women</td>
<td></td>
<td>190 flutamide users</td>
<td>No cases of hepatotoxicity in 3 to 54 months of follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brah, 2011 (24)</td>
<td>Case Series</td>
<td>Prostate cancer or hyperandrogenic status</td>
<td>10 cases of severe hepatotoxicity</td>
<td>7/10 cases related with the use of flutamide for hyperandrogenic state</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Garcia-Cortes, 2001 (25)</td>
<td>Case Series</td>
<td>Prostate cancer or hyperandrogenic status</td>
<td>9 cases of severe hepatotoxicity</td>
<td>1/9 cases in a teenage woman with hirsutism</td>
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**Table 2. Indirect Evidence**

<table>
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<tr>
<th>Drugs</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Oral Contraceptive Pills (OCPs)</td>
<td>VTE</td>
<td>Kammeron, 2001 (16)</td>
<td>Systematic Review Observational studies</td>
<td>3rd vs 2nd Gen OCPs</td>
<td>3rd O. 349 2nd O. 787</td>
<td>Third generation OCPs were associated with 1.7 times higher than second generation OCPs. OR (95% CI) = 1.7 (1.4 to 2.0)</td>
</tr>
<tr>
<td>Overall and cardiovascular mortality</td>
<td>WHO, 1995 (26)</td>
<td>Case Control</td>
<td>OCPs Average users vs Non users</td>
<td>1143 VTE cases 2998 controls</td>
<td>OCPs were associated with a three to four times higher risk compared to never OCPs users</td>
<td></td>
</tr>
<tr>
<td>Overall risk of cancer</td>
<td>Hammoned, 2010 (36)</td>
<td>Prospective Cohort</td>
<td>OCPs Average users vs Non users</td>
<td>23,000 OCPs user 819,175 OCPs user-years 379,000 never user-years</td>
<td>OCPs use were associated with lower risk of death from any cause OR 0.88, 95% CI 0.87 to 0.93 and death from cardiovascular diseases (OR 0.86, 95% CI 0.77 to 0.96)</td>
<td></td>
</tr>
<tr>
<td>Weight Gain</td>
<td>Lindh, 2011 (31)</td>
<td>Prospective Cohort</td>
<td>OCPs Average users vs Non users</td>
<td>568 OCPs user 14,020 user-years</td>
<td>There was no significant difference in weight increase between women who had used OCPs and women who had never used OCPs</td>
<td></td>
</tr>
</tbody>
</table>

Indirect evidence from populations without PCOS demonstrated no increased risk of lactic acidosis with Mt, only case reports of liver toxicity with flutamide (no comparative evidence), and increased relative risk of VTE with OCP but very low absolute risk. Evidence on mortality, cardiovascular mortality, and cancer was inconclusive. The quality of evidence supporting the safety of Mt is high considering that women with PCOS would likely use it after the standard contraindications (21). The quality of evidence for the safety of AA and OCPs is likely lower and prescribers should consider other risk factors such as age and smoking status, along with patient preferences, and other considerations. In general, all the available treatments had a low occurrence of side effects and seemed to be well tolerated.
follow-up did not exceed 1 year in most PCOS studies; hence, longer duration of medication use may be associated with adverse effects. In addition, seven studies (with focus on efficacy) excluded patients from the analysis due to side effects without explicit description of these side effects, making the estimation of event rate challenging and restricting the applicability of these results. Therefore, we think that data on side effects are likely better derived from large observational studies (eg, the Danish cohort study by Lidegaard et al [28] that captured the use of OCPs and did not exclude patients with side effects). Last, trials of efficacy enrolled younger women that were selected to have low side-effect profile, making the incidence of side effects very low (eg, thromboembolic events). Therefore, our strategy of summarizing the evidence started by PCOS trials (looking for side effects) and expanded into observational studies with wider inclusion criteria, longer follow-up, and increased focus on safety. The extent to which this evidence remains direct and applicable will be determined by guideline developers.

The strengths of this systematic review relate to the comprehensive nature of the literature search and the measures undertaken to reduce the effect of bias and error (eg, a priori performed protocol, reviewing studies by independent pairs, and contacting original study authors).

Implications for practice
This systematic review is mainly focused on treatment harms. Potential harms reported in studies conducted in other populations without PCOS may also indirectly apply. For example, although we did not find reliable data on thromboembolic events in PCOS, increased risk of these events in OCP users have been reported (35, 36). Individualized risk assessment is paramount. Cardiovascular risk, for example, varies among women with PCOS and should be assessed before and during estroprogestins therapy. Second- and third-generation progestins may be a safe treatment when cardiovascular risk is average (37). In obese patients with normal glucose and lipid profile, second-generation progestins may be associated with lower VTE risk, whereas in women with altered lipid profile or glucose intolerance, third-generation progestins can be considered (37).

Guideline developers will incorporate this information with benefits of treatments and patients’ values and preferences to develop helpful clinical recommendations. The accompanying clinical practice guidelines from the Endocrine Society will provide practical recommendations about the treatment of PCOS.

Implications for research
Future RCTs of PCOS treatments should systematically collect data on side effects and have sufficient follow-up that capture long-term harms. Large, well-designed observational studies will also be essential for evidence of safety because of their larger size, higher statistical power, longer follow-up, and their representation of real world setting.

Conclusions
Drugs commonly used to treat PCOS appear to be associated with low risk of severe adverse effects.

Acknowledgments
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All coauthors have seen and agree with the contents of the review and there is no financial interest to report. We certify that the submission is original, that all statements asserted as facts are based on authors careful investigation and research for accuracy, that the manuscript does not, in whole or part, infringe any copyright or violate any right of privacy or other personal or property right whatsoever, that it has not been published in total or in part, and is not being submitted or considered for publication in total or in part elsewhere.

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