Anush S. Pillai DO
Methodist Family Medicine
Residency Program,
Houston, Texas;
Weill Medical College,
Cornell University, New York, NY
aspillai@tmh.tmc.edu

Heejung Bang, PhD
Division of Biostatistics and
Epidemiology,
Dept. of Public Health,
Weill Medical College,
Cornell University, New York, NY

Charles Green, PhD
Center for Clinical Research
and Evidence-Based Medicine,
University of Texas Medical
School at Houston,
Houston, Texas

Metformin & glitazones: Do they really help PCOS patients?

While the use of metformin and thiazolidenediones in treating PCOS patients is fairly common, this review revealed little evidence-based support for the practice

Practice recommendations

• There is no evidence to support the routine use of either metformin or a thiazolidenedione as first-line therapy for treatment of polycystic ovarian syndrome. (**C**)

• Diet and exercise are a better approach to PCOS treatment. A weight reduction of as little as 5% can help regulate the menstrual cycle and improve fertility, decrease insulin resistance, and reduce associated symptoms and comorbidities. (**B**)

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

A 35-year-old woman with no past medical or surgical history presents to your office with complaints consistent with oligomenorrhea. She also reports a 15-pound weight gain over this past year.

Your patient is married and sexually active, but has never been pregnant. Her menarche was at age 12, and she says she has had irregular, infrequent menses over the past year, with 4 to 5 days of medium flow. Her social/family history is unremarkable.

She denies using any drugs, medications, supplements, or herbs. She had a recent TSH, fasting blood glucose, CBC, basic metabolic panel, and Pap smear done by her previous physician during a routine physical and all were normal.

On exam, your patient is clinically obese (abdominal adiposity) and notably hirsute. Her skin exam is also positive for hyperpigmented lichenified plaques around her neck and axilla, consistent with acanthosis nigricans. The rest of her exam is unremarkable.

Her signs and symptoms prompt you to suspect polycystic ovarian syndrome (PCOS), which you confirm after ruling out type 2 diabetes mellitus, thyroid disease, hyperprolactinemia, congenital adrenal hyperplasia, and androgen secreting tumors.

Your next step, of course, is treatment and you consider your options. Would pharmacological treatment with metformin or a thiazolidinedione (TZD) be appropriate?

An answer that may surprise you

There is no evidence to support the routine use of either metformin or a TZD as

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PCOS is associated with features of insulin resistance, hyperandrogenism, and oligomenorrhea leading to anovulatory bleeding and infertility. Many—though not all—PCOS patients have ovarian cysts.

first-line therapy for the treatment of PCOS, based on a meta-analysis of randomized controlled clinical trials (strength of recommendation [SOR]: **C**). Instead, you should individualize your approach to achieve the patient's short- and long-term goals, as well as to minimize complications and comorbidities. A good approach at this time would be to educate your patient on lifestyle changes, such as diet and exercise, since the evidence supports their use (SOR: **B**).[1-4] A weight reduction of as little as 5% can help regulate the menstrual cycle and improve fertility, decrease insulin resistance, and reduce associated symptoms and comorbidities.[4]

Why the shift away from metformin or a TZD?

This recommendation is based on a meta-analysis that we, the authors, recently conducted. The following review provides a more detailed look at our analysis of the evidence to date. But before we get to the study, let's look at the syndrome that sparked our research.

Abstract

Background   Polycystic ovarian syndrome (PCOS) leads to a multitude of clinical and biochemical alterations in patients. Metformin and the thiazolidenediones (TZDs)—which have insulin sensitizing properties—are believed to be effective in minimizing the changes caused by this syndrome.

Objectives   Our goal was to assess the evidence for the use of TZDs or metformin in the treatment of PCOS patients. In addition, we sought to assess and compare the effectiveness of metformin vs TZDs in the clinical and biochemical regression of PCOS based on available randomized controlled trials (RCTs).

Search strategy   We searched Medline (January 1966 to January 2007), PubMed (January 1954 to January 2007), Google Scholar search engine (through January 2007), and reference lists of articles. We also contacted researchers and clinicians in the field.

Selection criteria   We reviewed RCTs involving women diagnosed with PCOS (based on 1990 the National Institutes of Health Criteria) who were treated with either metformin or TZDs. Trials were limited to those that were testing only the effects of either of these agents as their primary endpoint.

Main results   A total of 115 trials were obtained, of which only 33 trials met the inclusion criteria. Ultimately, 31 trials involving total 1892 patients were included in the analysis (23 metformin, 2 rosiglitazone, 1 pioglitazone, 5 troglitazone) with 2 unobtainable trials.

There was insufficient data to compare metformin to the TZDs in any parameter because the literature often contained inadequate quantitative data, or there were too few published trials. As a result, we performed the meta-analysis for metformin only.

Among the outcomes examined, the only statistically significant changes were minimal decreases with metformin in ovulation rates and luteinizing hormone to follicle stimulating hormone ratio (LH/FSH), and an increase in fasting insulin.

There was no clinically significant change with metformin in ovulation rate, pregnancy rate, body mass index, waist-to-hip ratio, hirsutism (F-G score), LH/FSH, fasting insulin, fasting blood glucose, total testosterone, free testosterone, androstenedione, and dehydroepiandrosterone sulfate.

Authors' conclusions   There is a paucity of data from RCTs to compare the effectiveness of metformin vs TZDs as well as the effects of either agent in treating the clinical and biochemical features of PCOS. Further research involving RCTs with larger sample sizes is needed before any recommendation can be made on the usefulness of these agents in the treatment of PCOS.

❚ Background

A syndrome with extensive variability

PCOS (also known as Stein-Leventhal syndrome) is associated with features of insulin resistance (obesity, acanthosis nigricans); hyperandrogenism (hirsutism, elevated androgen levels), and oligomenorrhea leading to anovulatory bleeding and infertility. PCOS has a prevalence of approximately 5% to 10% in women of reproductive age. Patients may have high serum concentrations of androgenic hormones, such as testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS). However, much variation exists clinically and a specific patient may have normal androgen levels.[3] In addition, despite the syndrome's name, not all women with PCOS have ovarian cysts.

The features of peripheral insulin resistance, hyperinsulinemia, oligomenorrhea, and infertility can be magnified in the presence of obesity. Insulin resistance is not due to defects in insulin binding to the insulin receptors; rather, it involves post-binding signaling pathways. The elevated insulin levels may have gonadotropin-augmenting effects on ovarian function.[3]

Numerous comorbidities play a role

There is a great deal of frustration for both physicians and patients regarding the various comorbidities associated with this syndrome. For patients, the problems include androgenic features, menstrual irregularities, and infertility. For clinicians, however, the concerns include cardiovascular risks[4] (obesity, lipid abnormalities, elevated C-reactive protein and leptin levels, blood pressure changes), hyperinsulinemia, insulin resistance, and the theoretical risks for endometrial hyperplasia due to a hyperestrogenic state.

NIH criteria is used for diagnosis in trials

Although there are no definitive consensus criteria for the diagnosis of PCOS, the 1990 National Institutes of Health (NIH) criteria and its revision in 2003, the Rotterdam Criteria, have been used to make the diagnosis in clinical trials. Most trials however use the NIH criteria as there is disagreement regarding the Rotterdam Criteria.

The NIH criteria use the following for the diagnosis of PCOS:

- oligomenorrhea
- hyperandrogenism (clinical or laboratory evidence), and
- absence of other endocrine disorders (congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, and androgen secreting tumors).

In reviewing the literature, most clinicians and researchers have noted that PCOS has been associated with various outcomes such as elevated body mass index (BMI),[5] waist-to-hip ratio,[5,6] fasting blood glucose,[7] insulin levels,[7] testosterone levels,[8] androstenedione levels,[8] DHEAS levels,[9] hirsutism scores,[9] lipids,[5] blood pressure,[9] luteinizing hormone to follicle-stimulating hormone ratio (LH/FSH),[9] C-peptide,[5] and leptin,[6] as well as decreased ovulatory and pregnancy rates.[4,5,10]

Metformin/TZDs are used, but what about the evidence?

Both metformin and the TZDs (glitazones) including troglitazone—which was withdrawn from the market—pioglitazone, and rosiglitazone, are antidiabetic agents that also work as insulin sensitizers. These agents—especially metformin—are widely used by primary care physicians and specialists to treat the clinical and biochemical features of PCOS. However, the evidence-based data supporting this use is lacking. Although much research has been done on this topic, most published trials are of less than ideal quality and involve methodological issues. Often times they are nonrandomized, not controlled, involve a low number of subjects, provide no long-term follow up, and use nonstudy agents or ancillary treatments that were not randomized and could yield confounding results.

❚ Objectives

Our primary objective was to assess whether there is evidence to support the use of metformin or TZDs, as well as to suggest any differences among the drugs. The secondary objective was to ascertain if, and to what extent, the studied drugs affected the studied parameters.

❚ Methods

Search strategy

We searched MD Consult, PubMed, Medline, Ovid, and Google Scholar through January 2007 with the following terms: "PCOS and metformin," "PCOS and Glucophage," "PCOS and troglitazone," "PCOS and pioglitazone," "PCOS and rosiglitazone," "PCOS and thiazolidinediones." These searches were also done by substituting "+" instead of the word "and," as well as by using full form of the abbreviation PCOS—polycystic ovarian syndrome.

The following limits were placed on the search: randomized controlled trials, English language, human, and female subjects. We also searched articles from reference lists and made additional efforts to contact clinicians and researchers in this field.

Selection criteria

Our search resulted in 115 articles. From these articles, we included only those trials that:

- Used the NIH 1990 criteria for the diagnosis of PCOS
- Studied the effect of any of the following drugs: metformin, troglitazone, rosiglitazone, or pioglitazone
- Did not use or advocate adjunctive therapy—ie, diet or exercise
- Were randomized and controlled (based on a review of the methods section).

We also excluded studies that permitted confounding or concomitant treatments if it made it difficult to estimate the true effect of the medications studied.

This criteria resulted in 33 trials and ultimately 31 trials were included in the analysis (23 metformin, 2 rosiglitazone, 1 pioglitazone, 5 troglitazone) with a total of 1892 patients. Two metformin trials were unobtainable.

Outcome measures

We studied the parameters that are needed for the diagnosis of PCOS, as well as parameters that are associated with the syndrome's comorbidities. The measured variables included: ovulation rates, pregnancy rates, BMI, waist-to-hip ratio, lipid panel, blood pressure, fasting insulin levels, fasting blood glucose, C-peptide, glycosylated hemoglobin (Hb A_{1c}), LH/FSH, total testosterone, free testosterone, androstenedione, DHEAS, leptin, C-reactive protein, hirsutism (based on the Ferriman-Gallwey [F-G] score), and weight.

Methods of the review

Each included trial was evaluated in detail regarding how well it met the inclusion and exclusion criteria, the number of participants, the follow-up period, quantitative reporting of the data, and the overall methodology. The principal author rated methodological quality as good, fair, or poor on the basis of an overall assessment of these features. We did not use explicit validity checklists with summary scores because they have not been shown to predict the effect of bias on treatment differences or to provide more reliable assessments of validity.[11,12]

Description of studies

All included studies met the inclusion criteria. However, it is important to note that most of the studies had low numbers of participants (only 4 studies had a sample size [n] >50, 3 studies with n >100). Some of the trials shared the same patients but analyzed different end points so the fundamental "independence" assumption required for most standard statistical analyses, including meta-analysis, was likely violated.
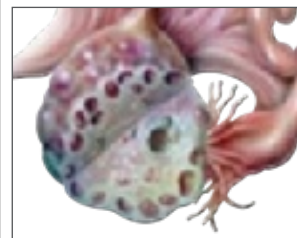
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Metformin and glitazones are widely used to treat PCOS patients, though the evidence is lacking

A few of the trials used another pharmacological agent or invasive procedure as control treatment. Some trials had designs such that in the end, the treatment and control groups both received ovulation induction agents for the patients who failed to ovulate. Even with the strict inclusion and exclusion criteria, many of the included trials still were of less than satisfactory design quality for our purposes.

Data collection/extraction

The principal author reviewed the text, tables, and figures and then collected and extracted the data from relevant publications. The data set was reviewed by the secondary authors for errors in data entry, format, outliers, or implausible values.

Statistical analysis

For each analysis, we converted all data to the same metric based on conversion formulas provided by each individual trial. We also verified the conversion factors online via data provided by standard clinical and reference laboratory values.

Some trials provided standard deviations (SD), while others provided standard error (SE) or standard error of the mean (SEM). We derived pooled variances accordingly. We converted all SDs to SE using the equation SE = SD/square root (N), where N denotes the sample size. We created data sets in the above fashion for each parameter.

Trials that did not report SD, SE, or sample variance for a given parameter were not included in the corresponding meta-analysis. We did not conduct a statistical analysis if only a small number of trials existed (ie, n <5), as it would result in less reliable conclusions.

No article provided individual level data or SD/SE for the "change" in the selected endpoint before and after treatment in the control and treatment arm. Instead, most publications presented the summary statistics separately for before and after treatment.

Since covariance (or correlation) between before and after values was not available and variability of the difference measure could not be estimated from the majority of the trials, it was not possible to perform methodologically sound meta-analysis by addressing the absolute or percent change before and after treatment and comparing this difference measure between 2 competing treatments. This is an inherent problem in many meta-analyses due to limited raw data.

However, as all the trials were randomized, we felt justified in performing the statistical analysis using the mean difference after treatment in the control and intervention arms. Our assumption: the values before treatment should be reasonably balanced between the 2 arms. Thus, we calculated the pooled estimates of treatment effect with 95% confidence intervals (CIs) for the mean differences between the control and intervention arms after treatment. We adopted the random effects model approach.[13]

Next, statistical significance was evaluated for treatment effect and heterogeneity. Publication bias was also examined by two different tests.[14,15] Sensitivity analysis was also performed to assess the impact of the identification of potential hidden studies by the trim and fill method.[16]

A 2-sided hypothesis with type I error of 5% was employed in all statistical testing and CI construction. Statistical analyses were carried out by STATA version 8.2.[17]

❚ Results

Of the 31 trials included for the meta-analysis, we judged that 7 were of good quality, 6 were of fair quality, and 18 were of poor quality.[2,5–10,18–41] (See **TABLE W1** online at www.jfponline.com.)

Not enough data to compare TZD vs metformin

As the TZDs had few trials for each drug (5 troglitazone, 2 rosiglitazone, 1 pioglitazone) and not enough of the TZD

trials reported data on most parameters, it became unrealistic to perform a statistical comparison of the treatment effect between metformin and the TZDs. Moreover, there were not enough data from TZD trials to analyze the effect of TZDs on any studied parameter. Thus, only data from metformin trials were used in the meta-analysis.

Metformin linked to changes in 3 outcomes

Of the outcomes we evaluated, there were statistically significant changes in three: ovulation rate, LH/FSH ratio, and fasting insulin. (For complete details of our findings, see **TABLE**.)

After analyzing the ovulation rate in 9 trials, we found a change of –0.18% (95% CI, –0.35 to –0.01; P=.03) from the control group. Our analysis of the LH/FSH ratio in 7 trials revealed a change in value of –0.21 (–0.30 to –0.13; P<.001). We evaluated the fasting insulin levels in 14 trials and found an increase of 30.4 pmol/L (13.9 to 46.8; P<.001).

Insufficient trials (n ≤5) reported on total cholesterol, triglycerides, HDL, LDL, systolic blood pressure, diastolic blood pressure, C-peptide, C-reactive protein, leptin, and Hb A_{1c}. Thus, we did not conduct a meta-analysis for these outcomes.

We intentionally used type I error of 5% for individual tests, not for overall test. If we had adopted multiple testing adjustments, we would have had more conservative results with much wider CIs, which makes it harder to reject the null hypothesis. Specifically, only 2 comparisons (LH/FSH and fasting insulin) would still be significant after multiple testing adjustments, while all marginally significant results would no longer be significant. A second reason to use type I error of 5% for individual (not overall) test is that endpoints are expected to be correlated, since most data were from the same trials.[42,43]

We did not find any major change in results in the sensitivity analyses we performed. It is worth mentioning, though, that there was significant heterogeneity and variability in the treatment effects from virtually all comparisons we made, though most comparisons revealed no publication bias. When heterogeneity is detected, combining the effects is not always advisable; and when effects are combined, they should be viewed with extreme caution.[44–46]

At a minimum, we failed to find any homogeneous or consistent treatment effects. Our sensitivity analysis offers additional protection against publication bias or file drawer problems.[47]

Findings don't support a common practice

Much has been reported in the literature, as well as by the media, regarding the large role that metformin and the TZDs can play in helping to alleviate the alterations caused by the polycystic ovarian syndrome. However, this systematic review of the literature, focusing on randomized controlled trials, failed to find evidence supporting the claims made in the literature, by the media, or offered anecdotally.

Based on our analysis, there is insufficient evidence to assess a difference in effect sizes between the TZDs and metformin. There is also insufficient evidence to assess if either the TZDs or metformin have an effect on lipids, blood pressure, C-peptide, C-reactive protein, leptin, or Hb A_{1c}.

With regard to the analyzed parameters, there were minimal decreases of statistical significance in ovulation rates and LH/FSH, and minimal increase of statistical significance in fasting insulin with metformin. (We cannot account for the paradoxical and unexpected finding of an increase of fasting insulin with metformin, especially since metformin works as an insulin sensitizer.) There was, however, no clinically significant change with metformin in any of the parameters we studied (ovulation rate, pregnancy rate, body mass index, waist-to-hip ratio, hirsutism score, LH/FSH, total cholesterol,

There was no clinically significant change with metformin in any of the parameters we studied

TABLE

Meta-analysis results by outcome

OUTCOME	NUMBER OF TRIALS	POOLED ESTIMATE OF TREATMENT EFFECT (95% CI)*	P VALUES			SENSITIVITY ANALYSIS**
			TREATMENT EFFECT*	HETERO-GENEITY†	PUBLICATION BIAS‡	
Ovulation rate (%)	9	–0.18 (–0.35 to –0.01)	.03	.001	.92	–0.18/0.03
Pregnancy rate (%)	8	–0.09 (–0.18 to 0.01)	.08	<.001	.90	Unchanged
BMI (kg/m²)	16	0.70 (–0.08 to 1.48)	.08	.05	.01	–0.001/1
Waist-to-hip ratio	13	–0.02 (–0.05 to 0.02)	.38	<.001	.20	–0.03/0.06
Hirsutism (F-G score)	7	–0.26 (–1.64 to 1.12)	.71	.09	.76	Unchanged
LH/FSH	7	–0.21 (–0.30 to –0.13)	<.001	.72	1	–0.22/<0.001
Fasting insulin (pmol/L)	14	30.4 (13.9 to 46.8)	<.001	<.001	.51	Unchanged
FBG (mmol/L)	13	0.21 (–0.10 to 0.52)	.19	<.001	.43	Unchanged
Total testosterone (nmol/L)	13	0.01 (–0.38 to 0.40)	.95	<.001	1	Unchanged
Free testosterone (pg/mL)	8	1.40 (–0.04 to 2.85)	.06	<.001	.71	Unchanged
Androstenedione (nmol/L)	11	0.09 (–0.25 to 0.42)	.60	<.001	.53	Unchanged
DHEAS (µmol/L)	14	–0.48 (-1.20 to 0.24)	.19	.004	.58	–0.91/0.03

*Using Dersimonian and Laird's random effects model, uncorrected for multiple testing.

† Using Cochran's Q statistics.

‡ Using Begg and Mazumdar test.

** Pooled estimate/*P* value, using the trim and fill method.

We did not conduct meta-analysis for endpoints with number of studies ≤5: total cholesterol, triglycerides, HDL, LDL, C-peptide, Hb A$_{1c}$, leptin, C-reactive protein, systolic blood pressure, and diastolic blood pressure.

LH/FSH, luteinizing hormone to follicle-stimulating hormone ratio; FBG, fasting blood glucose; DHEAS, dehydroepiandrosterone sulfate.

fasting insulin, fasting blood glucose, total testosterone, free testosterone, androstenedione, and DHEAS).

This systematic review provides a strong message that many of the trials were not of adequate methodological quality to make a definitive statement for clinical practice. In addition, most trials had a low sample size and used additional treatments with gonadotropins or ovulation induction agents that can yield altered results.

The primary aim of this study was to ascertain the evidence for the use of either TZDs or metformin in the treatment of patients with PCOS. This systematic review with the meta-analysis has found insufficient evidence to support the routine use of either. The secondary aim of this study was to obtain evidence to assess if either agent was superior in clinically reducing the various biochemical and clinical alterations due to this condition. Based on our analysis, we cannot claim either agent as superior.

▋ Limitations
Few trials, sparse data

Any systematic review and meta-analysis will have inherent limitations as data from multiple trials, that might not be directly comparable, are combined to give an overview. Another limitation is that trials published in other languages were not included. We cannot exclude

the possibility of selection or information bias because only one person reviewed all the articles to decide which would be included. However, we set the inclusion/exclusion criteria as well as endpoints very carefully prior to the study and literature search and had independent reviews by other authors during statistical analyses to minimize this problem.

The quality assessment of each trial is also subjective, even though strict inclusion/exclusion criteria were utilized. Assessing the efficacy of the TZDs could not be done as there were very few trials. Moreover, most of the TZD trials did not study or report on all the parameters. It is difficult to assess for publication bias or outliers and to justify combining the results when only a small number of trials are available or the data are sparse. In addition, although 5 trials with good sample size were available for troglitazone, this agent is no longer on the market, thus limiting clinical utility.

As most trials were not truly blinded upon careful review of the article, this may provide some bias. Furthermore, we could not conduct the meta-analysis for the gold standard method based on difference measures (before, after, and between treatment) due to data unavailability. Our alternative choice of analysis is justified based on the assumption that randomization will allow for baseline values in both groups to be approximately similar.

Finally, we used the SD or SE (or SEM) information as the original authors reported. Although SE is a function of sample size, SD is the population parameter so its variability should not be high. However, we found that the SDs varied considerably. It may be that the authors inadvertently used SD and SE interchangeably, thus leading to the heterogeneity of effect size.

❚ Conclusions
Further study is needed
Carefully designed and sufficiently powered PCOS studies with large sample sizes, followed by the proper reporting of the study findings, are warranted. These studies, evaluating drug effects, should be done in a randomized placebo controlled fashion. Such trials should not be interfered with by using hormonal or ovulation induction agents other than the medication being studied. Diet and exercise should not be a part of the study's design as these have been independently validated in similar contexts.[4]

For now, focus on lifestyle, and symptom-based treatment
PCOS encompasses a myriad of clinical and biochemical features, where each component adds to morbidity. The data, as per our study, are not sufficient to support the use of either of the studied agents in altering either the clinical or biochemical changes associated with the condition.

Thus, clinicians should tailor their treatment regimen to the individual patient's short- and long-term goals. Clinicians should also educate patients regarding lifestyle changes, such as diet and exercise, since multiple trials[1–4] have justified their use. Other options include symptom-based treatment, such as oral contraceptives for the regulation of menses or hirsutism.[4] ■

Correspondence
Anush S. Pillai, DO, 424 Hahlo, Houston, TX, 77020; aspillai@tmh.tmc.edu.

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You should educate patients on diet and exercise, since multiple trials have justified their use

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FAST TRACK

Carefully designed and sufficiently powered PCOS studies with large sample sizes are needed

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