

Polycystic Ovarian Syndrome: Metformin or Thiazolidinediones for Cardiovascular Risk Reduction?

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Abstract

Objective. The purpose of this article is to explore the relationships among polycystic ovarian syndrome (PCOS), diabetes, and cardiovascular (CV) risk and review the use of metformin and thiazolidinediones (TZDs) in reducing CV risk in women with PCOS.

Methods. The authors conducted a search for and reviewed reports of clinical trials, meta-analyses, and controlled trials published from January 1998 to December 2012 included in the PubMed, Cochrane Collaborative, and Health and Psychosocial Instruments databases. Search terms included PCOS, polycystic ovary/ovarian syndrome, diabetes mellitus, hyperglycemia, cardiovascular, metformin, TZDs, thiazolidinediones, rosiglitazone, and pioglitazone.

Results. The articles provided evidence that PCOS is associated with both metabolic syndrome and

diabetes in women. Metformin is an effective treatment for diabetes with favorable effects on lipid abnormalities to reduce CV risk. TZDs demonstrate some benefit on clinical markers associated with PCOS. However, there is no evidence that TZDs provide a greater benefit than metformin in reducing CV risk in women with PCOS and diabetes. Additionally, there is concern that TZDs may increase patients' risk of adverse events.

Conclusions. Based on evidence linking PCOS to diabetes and increased CV risks, clinicians should systematically screen women with diabetes for PCOS and direct appropriate treatment at minimizing related risks. Treatment with metformin appears to be more beneficial than TZDs and has been shown to lower triglycerides, increase HDL cholesterol, and favorably influence serum insulin levels.

Polycystic ovarian syndrome (PCOS) is the most common endocrine disease in women of reproductive age, with a 6–14% prevalence across different populations around the world.^{1–3} It is a disorder characterized by excessive secretion of androgens (male sex hormones) by the ovaries, oligomenorrhea (infrequent menstrual periods), and insulin resistance. Clinical features are multifactorial and may include hirsutism, alopecia, and acne (from hyperandrogenism), as well as irregular menstrual cycles and polycystic ovaries (from menstrual or ovulatory dysfunction).³

PCOS increases a woman's risk of infertility, dysfunctional

bleeding, endometrial carcinoma, obesity, and depression, as well as insulin resistance, dyslipidemia, and hypertension (all risk factors for cardiovascular disease [CVD]), and possibly CVD itself.^{3,4} The potential increased risk of CVD may be related to the higher incidence of metabolic syndrome in this population.^{5,6}

There are several approaches to treating PCOS, including strategies to improve hyperandrogenic symptoms (hirsutism, irregular menstrual cycles, persistent acne, and obesity), induce ovulation, treat depression,⁴ prevent complications of CVD, and prevent the onset of type 2 diabetes.¹ Treatment includes both pharmacological agents and

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Table 1. Treatment of Clinical Symptoms for Patients With PCOS Alone or in Conjunction With Insulin Resistance

| Clinical Symptom | PCOS | PCOS + Insulin Resistance | Reference |
|------------------------|--|---|---|
| Hirsutism | Eflornithine Spironolactone Oral contraceptive | Eflornithine Spironolactone Oral contraceptive Metformin TZDs | Goodzari et al. ¹ Pfeifer and Kives ⁷ Rosenfield et al ⁸ |
| Acne | Oral contraceptive | Oral contraceptive | Rosenfield et al ⁸ |
| Menstrual irregularity | Spironolactone Oral contraceptive | Spironolactone Oral contraceptives Metformin TZDs | Goodzari et al. ¹ Pfeifer and Kives ⁷ |
| Oligomenorrhea | Clomiphene | Clomiphene | Goodzari et al. ¹ Pfeifer and Kives ⁷ |
| Insulin resistance | | Metformin TZDs | Goodzari et al. ¹ Pfeifer and Kives ⁷ |
| Weight loss | | Metformin | Goodzari et al. ¹ |

lifestyle modifications. Drug therapy is targeted to specific clinical manifestations of the disease (Table 1).^{1,7,8} Lifestyle modifications (exercise and weight reduction) are recommended to reduce insulin resistance,⁹ dyslipidemia, type 2 diabetes,^{8,10} CVD risk factors,¹⁰ and depression and to improve quality of life.¹¹

This review provides an update on PCOS and its relationship to hyperglycemia, insulin resistance, and diabetes and reviews the use of the pharmacological agents metformin and thiazolidinediones (TZDs), both of which have been used in the management of PCOS as well as diabetes.

The criteria for the diagnosis of PCOS are controversial. Currently, there are three definitions of PCOS as shown in Table 2.^{1,3} Prevalence of

PCOS is dependent on the broadness of the definition used, with National Institutes of Health (NIH) criteria being the most stringent and criteria from the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (known as the Rotterdam criteria) being the most inclusive.^{1,3,12}

As evidenced by the criteria, the presence of polycystic ovaries is not essential for a diagnosis of the syndrome. Genetic background and environmental factors, including increased caloric consumption and obesity, both of which are linked to diabetes, are also associated with an increased risk of developing PCOS.^{5,6,13} There are no generally accepted guidelines for routine screening of PCOS.

Review Methods

We conducted a review of clinical trials, meta-analyses, and controlled trials published since 1998 and identified through a search of the Pubmed, Cochrane Collaborative, and Health and Psychosocial Instruments databases. The search included articles published in English using a combination of search terms including PCOS, polycystic ovary/ovarian syndrome, diabetes mellitus, hyperglycemia, cardiovascular, metformin, TZDs, thiazolidinediones, rosiglitazone, and pioglitazone. After the initial database searches, we cross-referenced to ensure inclusion of all recent trials, target key author publications, and assess review articles for additional references.

Table 2. PCOS Diagnostic Criteria

| | NIH, 1990 ^{1,3} | Rotterdam, 2003 ^{1,3} | Androgen Excess and PCOS Society, 2009 ³ |
|-----------------------|--|---|--|
| Diagnosis requirement | Two of two criteria | Two of three criteria | Three of three criteria |
| Criteria | <ol style="list-style-type: none"> Chronic anovulation Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies | <ol style="list-style-type: none"> Oligovulation or anovulation Clinical and/or biochemical signs of hyperandrogenism Polycystic ovaries and exclusion of other etiologies | <ol style="list-style-type: none"> Hyperandrogenism (hirsutism and/or hyperandrogenemia) Ovarian dysfunction (oligovulation or anovulation and/or polycystic ovaries) Exclusion of other androgen excess or related disorders |

Review Results

Associations between PCOS, hyperglycemia, insulin resistance, and diabetes

The association between PCOS and diabetes has been explored in several studies. PCOS is identified as an independent risk factor for impaired glucose tolerance (IGT) and insulin resistance, both conditions known to increase the risk of type 2 diabetes.^{14,15} In fact, both IGT and type 2 diabetes occur more often in women with PCOS,^{5,16–18} validating the association of PCOS with diabetes. Although this association has been supported by multiple short-term studies, long-term studies of women with PCOS focusing on age-related changes in insulin sensitivity and insulin secretion are lacking.¹⁸

One long-term study (> 8 years) by Hudecova et al.¹⁷ involved 84 middle-aged women with PCOS and 87 age-matched, healthy control subjects without PCOS. It found that 18 (21.4%) of the women with PCOS and four (4.5%) of the women without PCOS developed type 1 or type 2 diabetes or IGT at the follow-up ($P < 0.05$). The findings suggest that insulin resistance increases with PCOS regardless of age, and the risk of developing type 2 diabetes may not diminish with age. This study used the insulinogenic index, which monitors insulin resistance by measuring early-phase insulin secretion. One major limitation of the study was that the control group was not matched for weight.

Although PCOS characteristics align closely with those of metabolic syndrome and type 2 diabetes, PCOS is also associated with type 1 diabetes. Women with type 1 diabetes who experience pubertal delay, menstrual disturbances, and hyperandrogenism¹⁹ may also be at risk for PCOS.²⁰ The prevalence may be as high as 31%, depending on the diagnostic criteria used.¹⁹

Hyperandrogenism in type 1 diabetes is theoretically associated with the use of exogenous insulin and its effect on ovaries and adrenal glands.^{19,20} Treatment for hyperandrogenism in women with type 1 diabetes is an area that needs further research.

Association between PCOS and CVD

It is unknown whether there is a causal association of PCOS with CVD or whether the higher incidence of metabolic syndrome in women with PCOS represents the primary risk for CVD.^{5,6} PCOS and metabolic syndrome share overlapping features of dyslipidemia, obesity, insulin resistance, and hypertension, which are also risk factors for CVD.^{10,21} Metabolic syndrome is associated with an increased risk of developing both diabetes and CVD.^{21,22}

Glueck et al.²³ demonstrated a higher incidence of metabolic syndrome in women with PCOS. In this study, metabolic syndrome was compared in 138 oligo- or amenorrheic white women with PCOS (31 ± 9 years of age) versus 1,887 healthy white women in the National Health and Nutrition Examination Survey (NHANES) III cohort.²³ The National Cholesterol Education Program Adult Treatment Panel III definition²³ of metabolic syndrome was used for analysis. Metabolic syndrome was defined as having ≥ 3 of the following criteria: waist circumference > 88 cm, fasting serum triglycerides ≥ 150 mg/dl, HDL cholesterol < 50 mg/dl, blood pressure ≥ 130/85 mmHg, or serum glucose ≥ 110 mg/dl.

Age-matched study results showed that twice as many women with PCOS as healthy women in the NHANES III cohort had metabolic syndrome (46.4 ± 4.2 vs. 22.8 ± 1.1%). The study was limited in that the authors did not control for obesity in their study design or through statistical tests. Therefore, it is unknown whether obesity was a confounder for developing metabolic syndrome irrespective of the presence or absence of PCOS.

The increased risk for metabolic syndrome and diabetes in women with PCOS may predispose them to CVD because all three conditions share risk factors. Because of the prospect of higher prevalence of CVD, the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society recommends assessing CVD risk in women with PCOS. The AE-PCOS Society also

recommends prevention strategies, including lifestyle modification, the use of insulin sensitizers, and the treatment of risk factors such as dyslipidemia when present.^{10,21,22}

Use of metformin in women with PCOS

Metformin has demonstrated multiple beneficial effects in women with PCOS, including improvement in menstrual cycle regularity, rate of ovulation, fertility, hirsutism, and weight.²⁴ In individuals with diabetes, metformin's main benefit lies in its ability to suppress hepatic glucose output, reduce fatty acid oxidation, enhance splanchnic glucose turnover, and increase insulin-mediated glucose utilization.²⁵ Along with its demonstrated benefit in improving glucose control, it may also decrease the CV risks associated with diabetes, a potential benefit in women with PCOS, as well.^{6,13,26–29}

Studies published in the past 5 years on the use of metformin in women with PCOS are focused on its gynecological and fertility benefits. Although no studies have evaluated metformin specifically in women with PCOS and diabetes, the effects of metformin on lipid reduction (Table 3),^{28,30–36} insulin levels, and insulin sensitivity (Table 4)^{16,28,31–37} have been evaluated as secondary endpoints in women with PCOS.

In a 2011 meta-analysis³⁸ comparing metformin to TZDs for treatment of clinical, hormonal, and metabolic characteristics of PCOS, lipid reduction was evaluated with the use of metformin in two of the studies.^{34,39} The study published by Jensterle et al.³⁹ did not find significant change in HDL cholesterol, LDL cholesterol, or triglycerides. In contrast, the study published by Ortega-González et al.³⁴ found a slight decrease in serum triglycerides from a mean baseline of 158 mg/dl to 143 mg/dl after 6 months. Both of these studies were in individuals with PCOS using metformin, although the prevalence of diabetes in this study population was not noted.

Overall, the meta-analysis found metformin to be superior compared to TZDs in reducing triglycerides ($P < 0.0001$). However, it did not identify any significant differences

Table 3. PCOS Treatment Effect of Metformin and TZDs on Lipids

| | Study | Treatment | Insulin Effect | Limitations |
|-----------|--|--|---|--|
| Metformin | Hadziomerovic-Pekic et al. ³⁰ | Metformin, naltrexone, or prednisolone + oral contraceptive | Triglycerides decreased 10 mg/dl Mean age 25 years | Small sample size Pilot study Short study period |
| | Fruzzetti et al. ³¹ | Oral contraceptive versus oral contraceptive + metformin versus oral contraceptive + cyproterone acetate | No change in triglycerides, LDL cholesterol, or total cholesterol Increase in HDL cholesterol ($P < 0.05$) | Small sample size Short study period (8 months) Mean age 24 years |
| | Saxena et al. ²⁸ | Metformin | No change in LDL cholesterol, HDL cholesterol, or total cholesterol Decrease in triglycerides ($P < 0.001$) | Small sample size Observational study Short study period (6 months) |
| | Banaszewska et al. ³² | Metformin, simvastatin, or both | No change in triglycerides, LDL cholesterol, HDL cholesterol, or total cholesterol Mean age 24 years | Short study period (3 months) |
| | Oppelt et al. ³³ | Metformin for 2 years | No change in triglycerides or LDL cholesterol HDL cholesterol increased 7.08 mg/dl ($P = 0.003$) Total cholesterol decreased 25.42 mg/dl ($P = 0.007$) Mean age 26 years | Small sample size No comparator |
| | Ortega-González et al. ³⁴ | Pioglitazone and metformin | No change in LDL cholesterol, HDL cholesterol, or total cholesterol Triglycerides decreased ($P = 0.05$) Mean age 29 years | Small sample size Short study period (24 weeks) Obese patients with acanthosis nigricans |
| | Naka et al. ³⁵ | Pioglitazone, metformin, and control (placebo) | No change in triglycerides, HDL cholesterol, or total cholesterol LDL cholesterol; decreased ($P = 0.05$) Mean age 24 years | Small sample size Short study period (26 weeks) |
| | Kilicdag et al. ³⁶ | Rosiglitazone and metformin | No change in triglycerides, LDL cholesterol, HDL cholesterol, or total cholesterol Mean age 25 years | Small sample size Short study period (3 months) |

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Table 3. PCOS Treatment Effect of Metformin and TZDs on Lipids, *continued from p. 232*

| | Study | Treatment | Insulin Effect | Limitations |
|------|--------------------------------------|--|--|--|
| TZDs | Ortega-González et al. ³⁴ | Pioglitazone and metformin | No change in triglycerides, LDL cholesterol, HDL cholesterol, or total cholesterol Mean age 29 years | Small sample size Short study period (24 weeks) Obese patients with acanthosis nigricans |
| | Naka et al. ³⁵ | Pioglitazone, metformin, and control (placebo) | No change in triglycerides or LDL cholesterol HDL cholesterol and total cholesterol increased ($P = 0.009$) Mean age 24 years | Small sample size Short study period (26 weeks) |
| | Kilicdag et al. ³⁶ | Rosiglitazone and metformin | No change in triglycerides LDL cholesterol decreased ($P = 0.021$) HDL cholesterol decreased ($P = 0.005$) Total cholesterol decreased ($P = 0.026$) Mean age 25 years | Small sample size Short study period (3 months) |

in reduction of total cholesterol or LDL cholesterol and found no difference in increases in HDL cholesterol between TZDs and metformin.³⁸

The studies included in this meta-analysis that evaluated lipid control were of limited duration (3 months [$n = 6$] to 6 months [$n = 4$]) and included patients with BMIs of 29–34 kg/m². In addition, it did not assess medication history, which may have had a bearing on changes in lipid levels.

A 2009 article³² found similar effects on lipid reduction when metformin was used in combination with simvastatin compared to the statin alone. The short-term studies presented in the meta-analysis³⁸ and in the 2009 article on metformin use in PCOS³² found reductions in triglycerides but did not find any change in HDL cholesterol, LDL cholesterol, or total cholesterol.

Unlike these short-term studies, a long-term (2-year) study³³ of metformin monotherapy in women with PCOS resulted in reductions in total cholesterol ($P = 0.007$) and HDL cholesterol ($P = 0.003$). Similarly, reductions in serum triglycerides ($P < 0.001$) and total cholesterol (by 10 mg/dl) and increases in HDL cholesterol ($P < 0.05$) were seen in three separate studies that included

lipid profiles as secondary endpoints in women with PCOS.^{28,30,31} Lipid effects have been achieved with doses from 1,500 to 2,550 mg metformin.^{31,32,38} These findings indicate that metformin has a lipid-lowering effect in women with PCOS that appears to increase with longer use from > 6 months to up to 2 years.

Metformin has also been evaluated for its influence on insulin levels and insulin resistance in women with PCOS. A 2011 meta-analysis³⁸ that compared metformin to TZDs in the treatment of PCOS did not show metformin to influence fasting serum insulin or insulin sensitivity among the 10 randomized, controlled trials included in the analysis. However, this finding was in the presence of statistically significant heterogeneity among the included studies ($P < 0.0001$).

In comparison, an evaluation of 2-hour post-glucose insulin levels published by Fruzzetti et al.³¹ demonstrated that metformin at doses of up to 1,000 mg every 12 hours reduced post-glucose serum insulin ($P < 0.0001$). Furthermore, decreases in fasting insulin and 2-hour oral glucose tolerance test results were seen by Oppelt et al.³³ in patients treated with metformin for 2 years. However, insulin resistance

was not changed when metformin was used for 8 weeks compared to pioglitazone.¹⁶ Finally, three studies indicated no statistically significant change in fasting blood glucose after metformin treatment.^{31–33} As with its lipid effects, metformin's positive effect on insulin levels has been seen at doses from 500 mg three times daily^{16,31} to 1,000 mg twice daily²⁸ and at a duration of treatment > 8 weeks.³³

Despite its list of benefits, metformin is poorly tolerated in some patients because of its side effects of gastrointestinal disturbance, diarrhea, and nausea. Slowly titrating metformin to the target dose allows patients to avoid these side effects.⁴⁰

Overall, metformin's ability to improve lipid profiles and reduce serum insulin concentrations and insulin resistance make it a potentially important treatment for controlling diabetes or hyperglycemia and reducing CV risks in women with PCOS.²⁴

Use of TZDs in women with PCOS

Although the efficacy of metformin for PCOS management has been well validated,^{29,38} there is less evidence in support of a benefit from TZDs related to CV risk reduction in women with PCOS. Indeed,

Table 4. PCOS Treatment Effects of Metformin and TZDs on Insulin Levels and Insulin Sensitivity

| | Study | Treatment | Insulin Effect | Limitations |
|-----------|--------------------------------------|--|--|--|
| Metformin | Fruzzetti et al. ³¹ | Oral contraceptive versus oral contraceptive + metformin versus oral contraceptive + cyproterone acetate | Fasting and stimulated glucose level: no change compared to oral contraceptive alone Insulin sensitivity: improved but no significant change with oral contraceptive ± metformin Mean age 24 years | Small sample size Short study period (8 months) |
| | Saxena et al. ²⁸ | Metformin | Post-glucose serum insulin decreased ($P < 0.001$) Mean age 30 years | Small sample size Observational study Short study period (6 months) |
| | Cho et al. ¹⁶ | Metformin, orlistat, and pioglitazone | No significant change in insulin resistance Mean age 26 years | Short study period Open-label design |
| | Banaszewska et al. ³² | Metformin, simvastatin, or both | No significant change in fasting blood glucose or fasting insulin Mean age 24 years | Short study period (3 months) |
| | Oppelt et al. ³³ | Metformin for 2 years | No significant change in fasting blood glucose or insulin resistance Fasting plasma insulin decreased ($P = 0.04$) Mean age 26 years | Small sample size No comparator arm |
| | Ortega-González et al. ³⁴ | Pioglitazone and metformin | Fasting serum insulin and insulin resistance decreased ($P < 0.001$) Mean age 29 years | Small sample size Short study period (24 weeks) Obese patients with acanthosis nigricans |
| | Kilicdag et al. ³⁶ | Rosiglitazone and metformin | No significant change in insulin resistance Mean age 25 years | Small sample size Short study period (3 months) |
| | Naka et al. ³⁵ | Pioglitazone, metformin, and control (placebo) | No significant change in blood glucose or serum insulin Mean age 24 years | Small sample size Short study period (26 weeks) |
| | Cho et al. ¹⁶ | Metformin, orlistat, and pioglitazone | Insulin resistance decreased ($P = 0.013$) Mean age 26 years | Short study period Open-label design |

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the safety of TZDs has come into question in recent years because of concerns that they may actually increase CV risks.⁴¹

Initial studies demonstrating the efficacy of troglitazone, the first TZD to become available for use in type 2 diabetes, focused on the role

of this drug class in the management of oligomenorrhea and infertility.⁴² Troglitazone was later removed from the market because of its association with serious, life-threatening hepatic toxicity. Evidence validating the efficacy and safety of the currently available TZDs—rosiglitazone

and pioglitazone—for treatment of PCOS in women with type 2 diabetes is limited and focuses primarily on fertility, menstrual cycle regularity, and biomarkers associated with CV risk (e.g., endothelial dysfunction, insulin resistance, and elevated homocysteine).

Table 4. PCOS Treatment Effects of Metformin and TZDs on Insulin Levels and Insulin Sensitivity, continued from p. 234

| | Study | Treatment | Insulin Effect | Limitations |
|------|--------------------------------------|--|--|--|
| TZDs | Ortega-González et al. ³⁴ | Pioglitazone and metformin | Fasting serum insulin and insulin resistance decreased ($P < 0.001$) Mean age 29 years | Small sample size Short study period (24 weeks) Obese patients with acanthosis nigricans |
| | Naka et al. ³⁵ | Pioglitazone, metformin, and control (placebo) | No significant change in blood glucose Serum insulin decreased ($P = 0.002$) Mean age 24 years | Small sample size Short study period (26 weeks) |
| | Kilicdag et al. ³⁶ | Rosiglitazone and metformin | No significant change in insulin resistance Mean age 25 years | Small sample size Short study period (3 months) |
| | Brettenhaler et al. ³⁷ | Pioglitazone and placebo | Fasting serum insulin decreased ($P < 0.02$) Insulin resistance decreased ($P < 0.05$) Mean age 30 years | Small sample size Short study period (3 months) |

In 2005, Kilicdag et al.³⁶ demonstrated significant increases in plasma homocysteine levels ($P = 0.01$) and reductions in total cholesterol (from 161 to 150 mg/dl, $P = 0.026$), HDL cholesterol (from 43 to 39 mg/dl, $P = 0.005$), and LDL cholesterol (from 93.8 to 80.7 mg/dl, $P = 0.021$) in 15 women taking 4 mg rosiglitazone daily for 3 months compared to baseline. In this study (see Table 3), a diabetes diagnosis was not established. However, insulin resistance was measured at baseline, with mean scores in the abnormal range. There was no change in insulin resistance as measured by the homeostasis model assessment or the quantitative insulin sensitivity check index or in BMI or weight as a result of the treatment. The authors concluded that, although rosiglitazone treatment worsened levels of biomarkers such as homocysteine, corresponding changes did not occur in parameters that could result in increased CV risk such as BMI and insulin resistance.³⁶

Another study³⁷ examined the effects of pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in 35 women with PCOS (see Table 4). Although patients with diabetes were excluded from the study, those with IGT were

included. Findings demonstrated a reduction in fasting serum insulin levels and area under the insulin response curve ($P < 0.02$) after an oral glucose load. This represented an increase in insulin sensitivity and a decrease in insulin secretion ($P < 0.05$) for the pioglitazone group. Additionally, free androgen index scores were decreased compared to placebo, and ovulation rates improved for the subjects taking pioglitazone.

TZDs demonstrate some benefit on biological and clinical markers associated with PCOS. However, there is no evidence to support a greater benefit from TZDs than from metformin in the management of PCOS in women with or without diabetes. Additionally, there is some concern that the TZDs may pose greater risks of adverse events (e.g., weight gain or increased CV risk including worsening of heart failure), and their use is contraindicated in individuals with PCOS who are trying to become pregnant.⁴³ The ability to draw conclusions from available data on TZDs is limited because the presence of diabetes or its risks (e.g., IGT) was not a specific objective of the available studies in women with PCOS.

Conclusions

PCOS affects up to 14% of women of reproductive age worldwide, increasing their risk of infertility, diabetes, and CVD. With early diagnosis and treatment, it is possible to improve PCOS-related symptoms and change the course of patients' risk for these conditions.

Based on evidence linking PCOS and diabetes to CV risks, it is prudent for clinicians to systematically screen women with diabetes for PCOS and to direct appropriate treatment at minimizing related risks.

Treatment with metformin is likely more beneficial than TZDs for improving biomarkers of CV risk. It has demonstrated benefits in lowering triglycerides in 6 months, increasing HDL cholesterol over 2 years, and favorably influencing serum insulin levels when used for > 8 weeks. Limited studies with TZDs (pioglitazone) have shown that it results in some improvement in insulin sensitivity, reduction in insulin secretion, decreased androgen production, and improved ovulation. However, TZDs have not been shown to have a greater benefit on lipid reduction than metformin alone, and indeed they may increase CV risk or worsen heart failure. Furthermore, their use is contraindi-

cated in women seeking pregnancy, a common scenario among women with PCOS. In light of these considerations and the need for further study of the clinical benefit and safety of TZDs in this setting, metformin has emerged as the primary agent for reducing CV risk in women with PCOS.

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