

Drug Insight: insulin-sensitizing drugs in the treatment of polycystic ovary syndrome—a reappraisal

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SUMMARY

The recognition that insulin resistance has a pivotal role in the pathogenesis of polycystic ovary syndrome (PCOS) revolutionized our understanding of this complex disorder. PCOS causes major metabolic and reproductive morbidities, including substantially increased risk for type 2 diabetes mellitus and the metabolic syndrome. Insulin-sensitizing drugs (ISDs) ameliorate reproductive abnormalities, restore ovulation and regular menses, increase pregnancy rates and reduce androgenic symptoms in affected women with PCOS. Accordingly, ISDs, specifically metformin, have been widely adopted as therapy for this condition. A recent, large, randomized, multicenter, clinical trial that assessed live-birth rates rather than surrogate end points suggested that metformin alone is inferior to clomiphene citrate in treating infertility associated with PCOS. There is, furthermore, no evidence to support the use of metformin during pregnancy to prevent spontaneous abortions or gestational diabetes mellitus in women with PCOS. Renewed safety concerns about thiazolidinediones followed recent studies that reported increased cardiovascular morbidity with these agents. These concerns might preclude thiazolidinedione use in otherwise healthy women with PCOS. Finally, although ISDs improve insulin action and cardiovascular disease risk, there is no evidence that they provide long-term health benefits in PCOS. This article discusses the role of ISDs in PCOS in light of these new data.

KEYWORDS infertility, insulin resistance, metformin, polycystic ovary syndrome, thiazolidinediones

REVIEW CRITERIA

MEDLINE and EMBASE databases were searched with the following keywords: “polycystic ovary syndrome”, “metformin”, “thiazolidinediones”, “rosiglitazone”, “pioglitazone”, “troglitazone”, and “D-chiro-inositol”. The earliest publication that reported a possible association between polycystic ovary syndrome and insulin resistance is from 1980; hence, the effective time period of the search was 1980–2007. The reference sections of articles obtained were also searched by hand.

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Specify criteria used to diagnose polycystic ovary syndrome (PCOS).
- 2 Describe the metabolic effects of insulin-sensitizing drugs among women with PCOS.
- 3 Describe the effects of insulin-sensitizing drugs on fertility and pregnancy among women with PCOS.
- 4 Identify adverse effects of insulin-sensitizing drugs.

Competing interests

The author and the managing editor R Ashton declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders in women of reproductive age, and affects ~7% of this population.^{1–3} PCOS was originally identified as a reproductive disorder characterized by enlarged, sclerocystic ovaries, menstrual disturbances, obesity, infertility and hirsutism.^{4,5} This syndrome is the leading cause of anovulatory infertility.¹ Over the past 25 years or so,⁶ research has shown that PCOS is an important metabolic disorder that is associated with a substantially increased risk for type 2 diabetes mellitus (T2DM) as well as for the metabolic syndrome^{7,8}—a constellation of cardiovascular risk factors associated with insulin resistance.⁹ Reproductive morbidities associated with insulin resistance, such as gestational diabetes mellitus

(GDM) and pre-eclampsia, are also more common in affected women.^{10,11}

As would be expected from the presence of these cardiovascular disease risk factors, affected women have an increased prevalence of atherosclerosis.¹² Nevertheless, no increase in cardiovascular events has yet been demonstrated, because there have been no prospective, long-term studies that have followed affected women until ages where such events become common.^{7,12} Women with PCOS have defects in both insulin action and secretion.¹³ These defects are independent of obesity, although it substantially worsens these parameters.¹³ The molecular mechanisms of insulin resistance in PCOS differ from those in other common insulin-resistant states, such as obesity and T2DM.^{13,14}

Numerous studies have documented that hyperinsulinemia and insulin resistance not only amplify the reproductive abnormalities of PCOS, but also have key roles in the pathogenesis of the metabolic defects.^{7,13} This insight has led to development of a major new therapeutic strategy based on insulin-sensitizing drugs (ISDs), particularly metformin. This article reviews the effects of ISDs on the reproductive and metabolic components of PCOS with particular attention to randomized, controlled trials (RCTs).

DIAGNOSIS OF POLYCYSTIC OVARY SYNDROME

The 1990 NIH-NICHD (National Institute of Child Health and Human Development) conference on PCOS proposed what have become known as the NIH diagnostic criteria: hyperandrogenism (clinical and/or biochemical) and chronic anovulation with the exclusion of specific disorders of the ovary, adrenal, thyroid and pituitary glands (Box 1).¹³ The presence of polycystic ovaries (PCO), with morphology assessed by ultrasound, was not included as a diagnostic criterion because of the lack of specificity of this finding.¹⁵ PCO can be present in women with normal ovulation and sex-hormone levels, whereas women with all the endocrine features of PCOS can occasionally have normal ovarian morphology as assessed by ultrasound examination.^{15,16}

In 2003, an international conference in Rotterdam¹⁷ proposed revised criteria for PCOS that included PCO. The Rotterdam criteria require the presence of two of the three

Box 1 Diagnostic criteria for polycystic ovary syndrome.^a

NIH-NICHD criteria

Both hyperandrogenism and chronic anovulation

Rotterdam criteria

Two of the following conditions: hyperandrogenism; chronic anovulation; polycystic ovaries

Androgen Excess Society criteria

Hyperandrogenism and ovarian dysfunction (including infrequent or irregular ovulation or anovulation) and/or polycystic ovaries

^aAll criteria require exclusion of other disorders: hyperprolactinemia, nonclassical congenital adrenal hyperplasia, thyroid dysfunction, androgen-secreting neoplasms, and Cushing's syndrome.²² Abbreviation: NICHD, National Institute of Child Health and Human Development.

following findings: hyperandrogenism; chronic anovulation; and PCO (Box 1). All women considered to have PCOS according to the NIH criteria would also be identified by use of the Rotterdam criteria; however, the Rotterdam criteria also include women with PCO who would be excluded by the NIH criteria: those with PCO, hyperandrogenism and ovulatory cycles, and those with PCO, chronic anovulation and normal androgen levels.

Ovulatory women with PCO seem to be less insulin-resistant than anovulatory women with PCO;^{18–20} further, a study published in 2007²¹ suggests that women with PCO, chronic anovulation and normal androgen levels are not insulin-resistant. These observations limit the usefulness of the Rotterdam criteria, and accordingly an expert panel of the Androgen Excess Society (AES) recommended that PCOS should be considered a disorder of androgen excess and that the NIH diagnostic criteria should be used (Box 1).²² The AES also recommended that women with hyperandrogenism, PCO and ovulatory cycles should be considered to have a PCOS phenotype; thus, hyperandrogenism and infrequent or irregular ovulation, as well as hyperandrogenism, regular ovulation and PCO, also fulfill AES criteria for PCOS (Box 1). This Review is, however, limited to PCOS as defined by the NIH, since the majority of published studies used these diagnostic criteria; moreover, only women who fulfill the NIH criteria have been demonstrated to be at high risk for metabolic sequelae of PCOS, such as glucose intolerance⁷ and the metabolic syndrome.⁸

Table 1 Insulin-sensitizing agents used in polycystic ovary syndrome.

Agent	Dose	Currently marketed?
Immediate-release metformin	1 g twice daily or 500–850 mg three times daily	Yes
Extended-release metformin	1 g twice daily or 2 g once daily	Yes
Troglitazone	150–600 mg daily	No
Pioglitazone	30–45 mg daily	Yes
Rosiglitazone	4 mg once or twice daily	Yes
D-Chiro-inositol	1.2 g daily	No

INSULIN-SENSITIZING DRUGS

The biguanide, metformin, and the thiazolidinediones troglitazone (which is no longer available), pioglitazone, and rosiglitazone, are all antidiabetic drugs that act by improving the sensitivity of peripheral tissues to insulin,²³ which results in decreased circulating insulin levels. Metformin inhibits hepatic glucose production through multiple effects on glucose metabolism, and it also increases glucose uptake in peripheral tissues and reduces fatty acid oxidation.²⁴ One mechanism for these pleiotropic actions seems to be the activation of 5'-AMP-activated protein kinase,²⁵ mediated by action on a proximal kinase—serine–threonine protein kinase 11 (previously termed LKB1).²⁶ Thiazolidinediones increase peripheral glucose uptake more potently than metformin does.²⁷ They also decrease hepatic glucose production but to a lesser degree than metformin.^{27,28}

Thiazolidinediones are ligands for peroxisome proliferator-activated receptor γ (PPAR γ),²³ which is part of the superfamily of nuclear receptors. PPAR γ receptors are essential for adipocyte differentiation and growth, and thiazolidinediones actually increase the number of subcutaneous adipocytes.²³ This increase in adipose mass might contribute to their beneficial effects on glucose homeostasis since it is hypothesized that triglycerides can be partitioned into these newly differentiated subcutaneous adipocytes from muscle and liver, which decreases the adverse effects of lipids on insulin action, so-called lipotoxicity.²⁹ Thiazolidinediones also improve insulin signaling and glucose uptake.²³ In addition, thiazolidinediones have a number of other effects on lipid metabolism, inflammatory pathways and vascular biology.²³ A direct result of thiazolidinediones' mechanism of action is an increase in subcutaneous adipose mass, often accompanied by weight gain.²³

D-Chiro-inositol is a naturally occurring substance that is postulated to improve insulin sensitivity by enhancing signal transduction via an alternative pathway for insulin action, mediated by inositolphosphoglycans.^{30,31} It has never been approved for clinical use in diabetes and is mentioned only since there are several studies showing efficacy of this agent as a treatment for PCOS.

INSULIN-SENSITIZING DRUGS IN POLYCYSTIC OVARY SYNDROME

ISDs were first used in women with PCOS in 1994, to investigate the role of insulin resistance in the pathogenesis of the syndrome. In the original report by Velazquez and colleagues,³² menses became more regular with metformin use and there was a significant reduction in circulating androgen levels. There were, however, also significant decreases in body weight so that it was not possible to conclude that these benefits were accounted for solely by improvements in insulin sensitivity. In 1996, studies in which women with PCOS received troglitazone demonstrated that this treatment decreased androgen levels in parallel with decreases in insulin levels and improvements in insulin sensitivity without changes in body weight.³³

There have been numerous subsequent studies of the reproductive and metabolic effects of ISDs in PCOS (Table 1) that are summarized in a meta-analysis of RCTs³⁴ published in 2003; however, only metformin had multiple placebo-controlled trials suitable for analysis. There were 14 such RCTs and all were fairly small: in the treatment arm, the median number of patients was 16 (range 10–45); in the placebo arm there was a median of 15 women (range 8–62). There was one large RCT of troglitazone with approximately 150 individuals per arm among the additional studies included in the meta-analysis.

Metformin and thiazolidinediones had similar metabolic effects in PCOS to their effects in T2DM. Compared with placebo, metformin therapy resulted in significant decreases in fasting glucose and insulin levels as well as in area under the curve (AUC; i.e. the curve of concentration versus time) for insulin levels after oral glucose administration in the meta-analysis.³⁴ Mechanistic studies have shown that metformin improves insulin-mediated glucose disposal in women with PCOS.³⁵ Thiazolidinediones also decrease fasting glucose and insulin levels, AUCs for glucose and insulin levels, and glycosylated hemoglobin levels compared with placebo in women with PCOS.^{36,37} Mechanistic studies have shown that troglitazone improves insulin-mediated glucose disposal³⁸ as well as insulin-secretory defects³⁹ in women with PCOS.

In general, the beneficial effects of ISDs on reproductive parameters are seen only in association with a reduction in circulating insulin levels, consistent with the hypothesis that this reduction is the mechanism for their beneficial effects in PCOS.⁴⁰ Thiazolidinediones do, however, seem to have direct effects on steroidogenesis that could contribute to these changes.^{41,42} Controversy exists as to whether metformin has direct effects on steroidogenesis.^{41,43} Part of the efficacy of thiazolidinediones and metformin in PCOS might, therefore, be related to direct actions on steroidogenesis as well as to their insulin-sensitizing effects.

REPRODUCTIVE ACTIONS OF INSULIN-SENSITIZING DRUGS

Hyperandrogenism

Decreases in free testosterone levels are seen almost universally when studies of metformin and thiazolidinedione are considered together because hyperinsulinemia downregulates circulating levels of sex-hormone-binding globulin.⁴⁴ Changes in total androgen levels are seen less consistently with ISD therapy. Metformin significantly decreased circulating levels of total testosterone, androstenedione and the adrenal androgen, dehydroepiandrosterone sulfate, in the meta-analysis of RCTs.³⁴ Some studies have suggested that metformin is less effective in obese women with PCOS,^{39,45,46} however, an RCT published in 2005 that directly investigated this issue found that metformin had similar androgen-lowering efficacy in both obese and morbidly obese women with PCOS.⁴⁷ Total

testosterone levels have been unchanged by thiazolidinediones in the majority of studies, including a large RCT of troglitazone,³⁶ whereas significant decreases in circulating levels of androstenedione and dehydroepiandrosterone sulfate have been observed.^{33,48}

Significant improvements in hirsutism were noted, both in the meta-analysis with metformin therapy and in the limited number of studies of thiazolidinediones in which this end point was evaluated with a study design of adequate duration.^{34,36,48} The limited data available suggest that the thiazolidinediones that are still FDA-approved—pioglitazone and rosiglitazone—have similar efficacy to troglitazone to reduce androgen levels, particularly free testosterone levels, and to ameliorate hirsutism in women with PCOS.

Anovulation and infertility

Metformin has gained wide acceptance for the treatment of infertility in PCOS on the basis of its efficacy in inducing ovulation. Treatment, either with metformin alone compared with placebo, or with metformin plus clomiphene citrate compared with clomiphene alone, was significantly superior for ovulation induction in the meta-analysis of RCTs.³⁴ This action of metformin probably results from its insulin-sensitizing effects, since thiazolidinediones also significantly increase the number of ovulatory menstrual cycles. The troglitazone RCT showed that this drug was significantly more effective than placebo in promoting ovulation in a dose-dependent manner in women with PCOS.³⁶ Smaller studies with the currently available thiazolidinediones—pioglitazone and rosiglitazone—suggest that they have similar efficacy for ovulation induction to that of troglitazone.^{37,49,50} It has also been suggested that metformin used in conjunction with gonadotropin therapy for ovulation induction improves unifollicular development^{51,52} and conception rates, and reduces ovarian hyperstimulation syndrome.⁵³

When clinical pregnancy rates were assessed rather than ovulation rates in the meta-analysis of ISDs,³⁴ only metformin in combination with clomiphene was significantly more effective than clomiphene alone. By contrast, metformin alone was no more effective than placebo with regard to clinical pregnancy rates. Since the publication of the aforementioned meta-analysis, there have been three RCTs of metformin compared with clomiphene alone or in combination that

Table 2 Summary of recent randomized, placebo-controlled trials of clomiphene citrate compared with metformin.

Study, drug (dose, mg/day) and schedule	Number of patients	Mean age (years ± SD)	Mean (±SD) BMI (kg/m ²); BMI >25 kg/m ² (%); BMI >30 kg/m ² (%)	Ovulation rate (%)	Cumulative pregnancy rate (%)	Live birth rate (%); twins, triplets (%)	First-trimester abortion rate (%)
Palomba <i>et al.</i> (2005) ⁵⁴							
Clomiphene citrate (150); 6 cycles	45	25.9±2.7	26.7±2.9; 76; 0	62.9	34.0	NR	37.5
IR metformin (1,700); 6 cycles	47	26.4±2.9	27.0±2.9; 78; 0	67.0	68.9 ^a	NR	9.7 ^b
Moll <i>et al.</i> (2006) ⁵⁵							
Clomiphene citrate (50–150); 6 cycles	114	28.4±4.7	27.8±6.7; 55; NR	72.0	46.0	NR	22.6 ^c
Clomiphene citrate (50–150)+IR metformin (2,000); 6 cycles	111	27.9±3.7	28.5±7.1; 57; NR	64.0	40.0	NR	29.5 ^c
Legro <i>et al.</i> (2007) ⁵⁶							
Clomiphene citrate (50–150); 6 months	209	27.9±4.0	36.0±8.9; NR; 72.7	49.0 ^d	29.7 ^d	22.5 ^d ; 4.0, 2.0	22.6
ER metformin (2,000); 6 months	208	28.1±4.0	35.6±8.5; NR; 72.1	29.0	12.0	7.2; 0, 0	40.0
Clomiphene citrate (50–150)+ER metformin (2,000); 6 months	209	28.3±4.0	34.2±8.4; NR; 68.9	60.4 ^{e,f}	38.3 ^e	26.8 ^e ; 3.1, 0	25.0

^a*P*<0.001 for metformin versus clomiphene citrate; ^b*P*<0.05 for metformin versus clomiphene citrate; ^crecalculated from the actual pregnancy rate rather than by intent-to-treat analysis; ^d*P*<0.001 for clomiphene citrate versus metformin; ^e*P*<0.001 for clomiphene citrate plus metformin versus metformin alone; ^f*P*<0.01 for clomiphene citrate plus metformin versus clomiphene citrate alone. Abbreviations: ER, extended release; IR, immediate release; NR, not reported.

have examined conception and/or live-birth rates as end points (Table 2).^{54–56}

A single-center, Italian, placebo-controlled RCT⁵⁴ in nonobese (BMI <30 kg/m²) women with PCOS compared metformin alone with clomiphene alone (~50 patients per arm) as first-line therapy. This RCT found similar ovulation rates in both treatment arms, but a significantly increased conception rate in the metformin arm. An extension study suggested that the live-birth rate was also higher with metformin than with clomiphene, but this outcome was not an end point of the RCT itself. A nonrandomized trial from this same group of investigators,⁵⁷ done in women with PCOS and a range of body weights (~40 individuals per arm), found similar ovulation, conception and spontaneous abortion rates with metformin alone compared with clomiphene alone as first-line therapy for infertility.

A large (~100 patients per arm), multicenter Dutch RCT⁵⁵ examined ovulation as a primary end point and pregnancy as a secondary end point. This trial found no benefit from a combination of metformin plus clomiphene compared with clomiphene alone, for either end point, in previously untreated women with newly diagnosed PCOS; 55–60% of women in each arm had BMI >25 kg/m².

The only RCT⁵⁶ to examine live-birth rates as the primary end point was a very large (~200 women per arm) US multicenter study of metformin alone compared with clomiphene alone compared with combination therapy. This trial found that metformin alone was inferior to clomiphene alone for ovulation, conception (among those who ovulated) and live-birth rates. Combination therapy resulted in significantly higher ovulation rates than either treatment alone, despite no significant differences in pregnancy or live-birth rates compared with clomiphene alone. There were no significant differences in the rates of multiple pregnancies between the groups, although all such pregnancies occurred in women who were treated with clomiphene, alone or in combination.

When the live-birth rate (rather than ovulation or conception rates) is examined as an end point, there is no difference in efficacy between metformin in combination with clomiphene or clomiphene alone;^{55,56} further, use of metformin on its own results in significantly lower rates of ovulation, conception and live births than are observed with combination therapy.⁵⁶ The US RCT⁵⁶ did find that ovulation and conception rates were significantly higher with combination therapy than with clomiphene alone, analogous to the results of the meta-analysis,³⁴ whereas the

Dutch RCT⁵⁵ found these therapies to be equivalent. Of note, the meta-analysis was based on a series of small, primarily single-center trials whereas the recent studies were large, multicenter studies with robust statistical power.⁵⁸

Differences in the patient populations with respect to body weight, duration of infertility (e.g. newly diagnosed or not), previous treatment (e.g. failure to respond to clomiphene treatment alone), or ethnicity could also have contributed to the differing results. The US RCT⁵⁶ used extended-release metformin (1 g twice daily) whereas all other studies used an immediate-release preparation. The extended-release preparation has similar efficacy for glycemic control⁵⁹ to the immediate-release form. There were significant decreases in BMI and total testosterone levels and significant increases in levels of sex-hormone-binding globulin with extended-release metformin in the US trial. There were, however, no significant changes in fasting markers of insulin resistance.

There is evidence for a dose–response effect of immediate-release metformin in obese women with PCOS;⁴⁷ fasting markers of insulin resistance did not change when 500 mg of this formulation was given three times daily, but improved when 850 mg of immediate-release metformin was given three times daily. Different metformin preparations might, therefore, have differences in efficacy in PCOS. It is important to note, however, that most RCTs of ovulation induction in PCOS have used 1.5–1.7 g daily rather than maximal doses of immediate-release metformin.^{34,57}

Pregnancy

Observational studies suggest that women with PCOS are at increased risk for spontaneous abortion.^{60,61} Much of this increased risk is apparently accounted for by obesity rather than PCOS *per se*.^{56,62,63} The continued use of metformin during pregnancy has, nevertheless, been advocated to reduce spontaneous abortions in women with PCOS.^{60,61,64} A few RCTs have assessed pregnancy outcomes in PCOS,^{54–56,65} in all of these studies, metformin was stopped when the pregnancy was confirmed. Two studies by Palomba and colleagues found that metformin, when used alone, resulted in significantly reduced spontaneous abortion rates compared with laparoscopic ovarian diathermy followed by placebo⁶⁵ in overweight women with clomiphene-resistant PCOS. Similar results were seen for metformin compared with clomiphene alone in nonobese women with PCOS.⁵⁴

By contrast, both the Dutch⁵⁵ and the US⁵⁶ multicenter RCTs did not show a decrease in spontaneous abortions with metformin, alone or in combination with clomiphene, compared to clomiphene alone. The first-trimester spontaneous abortion rates in these studies were lower than those reported in the trials of Palomba and colleagues (Table 2)^{54,65} as well as in many observational studies of metformin and pregnancy outcomes,^{60,61} which have reported spontaneous abortion rates as high as 50%. The rate of intrauterine pregnancy loss after confirmed fetal heart motion in the US RCT was, furthermore, in the same range as that seen in women of similar age who used their own eggs for *in vitro* fertilization ($\leq 12\%$ versus $\sim 13\%$).⁵⁶ None of these RCTs was designed to examine spontaneous abortions as an end point, however, and the number of these events, even in the large trials, was small.

Metformin use during pregnancy has also been advocated⁶⁶ to reduce the risk of GDM in women with PCOS.¹¹ A small, randomized, placebo-controlled trial of metformin in pregnancy⁶⁷ found that 20% of 40 women with PCOS fulfilled criteria for GDM at randomization at around the eighth week of pregnancy, consistent with the prevalence of impaired glucose tolerance in women with PCOS.⁶⁸ By the end of pregnancy, about 40% of the cohort had GDM, whether or not they received metformin.

Metformin is a pregnancy category B drug, which means that there is no evidence that it has risks to the fetus in animal studies but there are no adequate human safety studies. Several small studies^{69–71} as well as a meta-analysis reported in abstract form in 2006⁷² have not found evidence for adverse pregnancy outcomes in women receiving metformin. One study did find an increase in perinatal mortality in diabetic women receiving metformin compared with those receiving insulin or sulfonylureas;⁷³ this study was, however, confounded by the presence of poorly controlled pregestational diabetes and other maternal comorbidities such as preeclampsia. There is an RCT of metformin use during pregnancy, the Metformin in Gestational Diabetes (MiG) trial,⁷⁴ which completed enrollment in 2006. This trial will evaluate the safety and efficacy of metformin compared with insulin therapy for GDM. There will also be long-term follow-up of the offspring to examine whether maternal metformin treatment influences their subsequent health.

In summary, the limited data from RCTs do not support the use of metformin during pregnancy to reduce spontaneous abortions or GDM in PCOS. The safety of metformin use in pregnancy remains unknown and is currently under study. The available thiazolidinediones are both pregnancy category C drugs because they have been shown in animal studies to increase fetal loss and retard fetal growth; their use during pregnancy should be avoided.

METABOLIC ABNORMALITIES

Body weight and composition

Although observational studies (e.g. Velazquez *et al.*³²) have reported weight loss during metformin therapy in women with PCOS, there was no consistent effect of metformin on body weight in the meta-analysis of RCTs.³⁴ In a subsequent RCT⁴⁷ specifically designed to evaluate the effects of metformin therapy on body weight, BMI decreased significantly (by ~4%) in both obese and morbidly obese women with PCOS after metformin therapy (500 mg or 850 mg three times daily) without lifestyle intervention; further, although it was not an end point of the trial, there were significant reductions in BMI in groups that received metformin alone or in combination with clomiphene in the US RCT.⁵⁶

By contrast, an RCT⁷⁵ of metformin (850 mg twice daily) plus lifestyle modification did not find a significant reduction of body weight compared with lifestyle modification alone in obese women with PCOS; however, the study was not powered to examine weight loss as an end point. Nevertheless, the metformin group lost twice as much weight as the placebo group and; furthermore, metformin therapy resulted in significant reductions in waist circumference compared with lifestyle changes alone.

Consistent with this observation, metformin (850 mg twice daily) in combination with a hypocaloric diet has resulted in significant reductions in visceral fat mass compared with the hypocaloric diet alone in several studies from Pasquali and colleagues.^{76–78} Metformin (500 mg three times daily) without lifestyle modification did not, however, result in a significant reduction in visceral fat mass compared to placebo in another RCT.⁷⁹ These studies suggest that metformin therapy might facilitate modest weight loss and visceral fat reduction, particularly when combined with a hypocaloric diet, but some of these effects may be dose-related.

Cardiovascular risk factors

Metformin therapy resulted in significant decreases in systolic blood pressure and LDL-cholesterol levels in the meta-analysis of RCTs³⁴ and in subsequent RCTs,^{47,79} whereas troglitazone had no significant effects on lipid levels in the single, large RCT in PCOS.⁸⁰ An RCT⁷⁵ published in 2006 reported that the addition of metformin to lifestyle modification resulted in weight reduction but did not further reduce total cholesterol or triglyceride levels. Small studies have shown that both metformin and thiazolidinediones improve endothelial dysfunction in PCOS.^{38,81} Thiazolidinediones also improve fibrinolysis in PCOS.³⁹

COMPARATIVE STUDIES

Metformin and thiazolidinediones

There are several small RCTs (6–26 women per arm) that compare thiazolidinediones and metformin in PCOS.^{48,49,82} In a trial that compared 6 months of treatment with either 30 mg of pioglitazone daily or 850 mg of metformin three times daily in overweight or obese, insulin-resistant women with PCOS (~25 individuals per arm),⁴⁸ fasting insulin levels decreased to a similar extent with both drugs whereas the AUC of insulin levels decreased more significantly with pioglitazone than with metformin. By contrast, BMI and waist:hip ratio increased significantly with pioglitazone but remained unchanged with metformin. Androgen levels and hirsutism, however, decreased to a similar extent with both drugs.

Neither fasting parameters of insulin sensitivity nor weight changed in an RCT of rosiglitazone 4 mg daily compared to metformin 850 mg twice daily.⁸² One 6-month RCT compared rosiglitazone (4 mg twice daily), metformin (850 mg twice daily), a combination of these drugs, and placebo. This study, in nonobese women with PCOS but without evidence for insulin resistance, showed that metformin and a combination of metformin and rosiglitazone reduced fasting insulin levels and the AUC of insulin levels compared with placebo, whereas rosiglitazone alone did not. There was significant weight gain in the rosiglitazone group; however, waist:hip ratios decreased in all active-treatment groups.⁴⁹ Free testosterone levels decreased to a similar extent in all active-treatment groups.

In the first of two very small RCTs, rosiglitazone (4 mg twice daily) resulted in significantly greater decreases in bioavailable testosterone and the

AUC of insulin levels than metformin (1 g twice daily) did in obese women with PCOS.⁸³ In the other small RCT, which involved women with clomiphene-resistant PCOS, rosiglitazone (4 mg twice daily) in combination with clomiphene also resulted in significantly higher ovulation rates than metformin (500 mg three times daily) in combination with clomiphene;⁸⁴ however, pregnancy rates did not differ significantly between groups in the latter trial.

There is a suggestion from these studies that thiazolidinediones are more effective than metformin at lowering free or bioavailable testosterone levels and AUCs for insulin levels. There is, however, minimal evidence for a difference in clinical outcomes such as hirsutism with the two therapies, and thiazolidinediones may result in weight gain in women with PCOS.

Metformin and oral contraceptive agents

There are data to suggest that oral contraceptives containing ethinyl estradiol—combined with a progestin⁸⁵ or with cyproterone acetate⁸⁶—reduce insulin sensitivity in women with PCOS. These observations, combined with the known actions of oral contraceptives to reduce insulin sensitivity and increase triglyceride levels, have resulted in concerns that these drugs could have adverse metabolic effects in women with PCOS.⁸⁷ There are no prospective, long-term studies of oral contraceptive use in women with PCOS but a small observational study⁸⁸ did not find adverse metabolic outcomes in women with PCOS who used oral contraceptives and were followed up for 6–18 years. A meta-analysis published in 2007 that compared metformin with oral contraceptives⁸⁹ found evidence that metformin is more effective at lowering insulin and triglyceride levels than oral contraceptives are. There was insufficient evidence to assess clinical end points such as hirsutism, diabetes prevention and weight loss. The studies included in the meta-analysis were small and short-term; in most studies, the oral contraceptive was ethinyl estradiol plus cyproterone acetate.

Two RCTs that were also published in 2007^{90,91} compared metabolic end points in patients receiving either metformin or oral contraceptives. Metformin improved fasting parameters of insulin sensitivity but ethinyl estradiol plus cyproterone acetate did not worsen these end points.⁹¹ An oral contraceptive containing 35 µg ethinyl estradiol plus cyproterone acetate increased the AUC for insulin levels and arterial

stiffness compared with metformin and compared with 20 µg ethinyl estradiol plus levonorgestrel with spironolactone (100 mg daily).⁹⁰ These observations suggest that, as in women not affected by PCOS,⁹² the type of progestin, the dose of ethinyl estradiol or both might influence metabolic outcomes in women with PCOS.

In summary, metformin improves insulin sensitivity and, unlike oral contraceptives, can also lower triglyceride levels. Oral contraceptives might worsen insulin sensitivity; however, prospective, long-term trials are needed to determine whether any of these changes translate into differences in clinical outcomes between women treated with metformin and those treated with oral contraceptives.

ADVERSE EFFECTS

In most RCTs, metformin caused a significantly increased incidence of nausea, vomiting and gastrointestinal distress in women with PCOS.^{34,56} There are no published reports of lactic acidosis with metformin therapy in women with PCOS and a meta-analysis of metformin RCTs in patients with T2DM indicated that this adverse event did not occur if the prescribing precautions were followed, and the drug was not administered to individuals with compromised renal or hepatic function.⁹³

The manufacturer withdrew the first thiazolidinedione approved for clinical use—troglitazone—from the market in 2000 because of hepatotoxicity.²³ In the RCT of troglitazone therapy in women with PCOS, there were no significant differences compared with placebo in the development of elevated hepatic enzymes.³⁶ Hepatotoxicity does not seem to be a thiazolidinedione class effect and has not been noted with pioglitazone or rosiglitazone.^{23,37} Thiazolidinediones are, however, associated with weight gain, in part related to their mechanism of action as PPAR γ ligands, and fluid retention that could result in edema and dilutional anemia.²³ Dose-dependent weight gain has been reported in some studies of thiazolidinediones in women with PCOS,^{36,37,48,49} but not in others.^{33,50,82} In the one RCT that reported additional adverse events of treatment with a currently available thiazolidinedione,³⁷ an increase in peripheral edema, sleep disorders, headache and stomach pain (sic) was seen with pioglitazone therapy compared with placebo in women with PCOS.

Two large, placebo-controlled RCTs of the currently available thiazolidinediones found

Table 3 Author's recommended therapies for polycystic ovary syndrome.

Stage of therapy	Reproductive aspect targeted			Metabolic aspect targeted ^a			
	Hirsutism ^b	Infertility ^c	Endometrial protection ^d	T2DM	Impaired glucose tolerance	Metabolic syndrome	Obesity
First-line therapy	Spironolactone plus ethinyl estradiol and progestin, or cyproterone acetate plus ethinyl estradiol	Clomiphene citrate	Ethinyl estradiol and progestin	Metformin	Lifestyle changes	Lifestyle changes	Lifestyle changes
Additional or alternative therapy	Metformin for coexisting metabolic abnormalities	Gonadotropins	Intermittent progestin or metformin if regular menses restored	Thiazolidinediones	Metformin	Metformin	Metformin

^aLifestyle changes or insulin-sensitizing drugs could restore ovulatory function; women not interested in conception must be cautioned about the need for additional contraception. ^bConsider metformin and spironolactone if hypertriglyceridemia precludes use of ethinyl estradiol; adequate nonsteroidal contraception is required. ^cMetformin can be continued in women already receiving it. ^dEnsure menses are ovulatory with metformin. Abbreviation: T2DM, type 2 diabetes mellitus.

significantly increased rates of heart failure—in patients with T2DM and macrovascular disease who were receiving pioglitazone in addition to other antidiabetic therapy,⁹⁴ and in generally healthy individuals with impaired glucose tolerance or impaired fasting glucose who were receiving rosiglitazone for diabetes prevention,⁹⁵ respectively. A meta-analysis published in 2007⁹⁶ suggested that there was a significant increase in the risk for cardiovascular events in patients with T2DM receiving rosiglitazone. An interim analysis of data from an open-label, randomized trial,⁹⁷ however, found no significant increase in myocardial infarction in patients with T2DM who were receiving rosiglitazone in addition to metformin and sulfonylurea, compared with patients receiving metformin and sulfonylurea alone. Rosiglitazone was associated with an increased risk for heart failure; however, both the study by Nissen and Wolski⁹⁶ and the interim analysis⁹⁷ have limitations.⁹⁸

Accordingly, there are substantial new cardiovascular safety concerns about thiazolidinediones, in addition to the well-substantiated reports of an increased risk for heart failure. As a consequence of these issues, as well as concerns about the safety of thiazolidinediones during pregnancy, these drugs should be used only with extreme caution in otherwise healthy women with PCOS until further safety data are available.

CONCLUSIONS

Most data suggest that the NIH diagnostic criteria for PCOS identify those women who are at risk for the metabolic sequelae of the disorder. Recent RCTs suggest that clomiphene is equivalent or

superior to metformin alone for the treatment of anovulatory infertility in women with PCOS. There are no data to support metformin use during pregnancy to reduce either spontaneous abortion rates or the risk for GDM.

Lifestyle modification is the first-line therapy in overweight and obese women with PCOS who have features of metabolic syndrome and/or impaired glucose tolerance (Table 3).^{99,100} Metformin remains a useful additional therapy in such patients. In women with PCOS and T2DM, metformin is an appropriate first-line medical therapy.

It is important to caution women who are receiving metformin monotherapy and are not interested in conception about the need for added contraception. Menstrual bleeding could, furthermore, become more regular in women who receive insulin-sensitizer monotherapy in the absence of ovulation^{33,101} and it is unknown whether such anovulatory bleeding is sufficient for endometrial protection.^{89,102} In clinical practice it is, therefore, prudent to ensure that menses are ovulatory in patients on insulin-sensitizer monotherapy.

Unless there is a metabolic benefit (e.g. weight loss, reversal of glucose intolerance or of the metabolic syndrome) to support continued insulin-sensitizer therapy, there are minimal data to guide therapy since there are no RCTs that support the use of these drugs in any population of individuals with insulin resistance *per se*. The potential cardiovascular risk of thiazolidinediones precludes their use in healthy women with PCOS, although these agents could still have a role in women with PCOS and T2DM.

KEY POINTS

- Metformin is the only insulin-sensitizing drug recommended for use in women with polycystic ovary syndrome (PCOS) who do not have type 2 diabetes because of concerns about the cardiovascular safety of thiazolidinediones
- Metformin is effective at ameliorating glucose intolerance and other features of the metabolic syndrome in women with PCOS
- For the treatment of infertility in women with PCOS, recent data indicate that the live-birth rate with clomiphene citrate monotherapy is superior to that with metformin monotherapy; there is no evidence that combination therapy is superior to clomiphene citrate alone
- There is no evidence to support the use of metformin during pregnancy to prevent spontaneous abortions or gestational diabetes mellitus

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