Use of metformin in polycystic ovary syndrome

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Women with polycystic ovary syndrome (PCOS) have a myriad of phenotypic and clinical features that may guide therapeutic options for metabolic protection and ovulation induction. The use of metformin may prove beneficial in a subset of the population of women with PCOS. Hyperinsulinemia, as demonstrated by elevated insulin levels on a 2-hour 75-g load glucose tolerance test, is an important parameter in deciding whether or not to initiate metformin therapy to women with PCOS with the hope of preventing or delaying the onset of type 2 diabetes mellitus (DM). Cardiovascular risk factors including markers of subclinical inflammation, and dyslipidemia may also be improved by metformin therapy. For ovulation induction, metformin is not as effective as clomiphene citrate as first-line therapy for women with PCOS. There are no clear data to suggest that metformin reduces pregnancy loss or improves pregnancy outcome in PCOS, and it is currently recommended that metformin be discontinued with the first positive pregnancy test result, unless there are other medical indications (eg, type 2 DM). This review addresses practical management guidelines for the uses of metformin in women with PCOS.

Key words: infertility, insulin resistance, metformin, polycystic ovary syndrome, pregnancy

A lthough it was in 1935 when Stein and Leventhal[1] first published their report describing what is now called the polycystic ovary syndrome (PCOS), it is the last 2 decades that has seen a flurry of interest in the disorder. PCOS affects 7-10% of reproductive-aged women,[2,3] is the most common cause of oligoovulatory

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infertility, and accounts for a significant fraction of health care costs.[4] The disorder is generally considered to exhibit androgen excess, ovulatory dysfunction, and polycystic ovaries, and is diagnosable after the exclusion of related ovulatory or other androgen excess disorders (eg, thyroid dysfunction, hyperprolactinemia, androgen-secreting neoplasms, or nonclassic adrenal hyperplasia). Hyperinsulinemia is a cornerstone of both the metabolic syndrome and of PCOS, and is associated with a high risk of developing type 2 diabetes mellitus (DM). In comparison with women who do not have PCOS, the prevalence of type 2 DM is 5-10 times higher in women with PCOS. In addition to lifestyle modification, metformin has been proposed to reduce the risk of DM in women with PCOS.

Infertility is also a common issue faced by women with PCOS, most often attributed to anovulation. In addition, other factors may be operant in PCOS to lower these women's fertility, including reduced oocyte quality, defects in endometrial development, and implantation abnormalities.[5] However, the primary goal of treatment for PCOS-associated infertility continues to be the restoration of ovulation. Several approaches have been proposed for the restoration of ovulation in women with PCOS, including lifestyle modifications, clomiphene citrate (CC), metformin, ovarian drilling, and gonadotropins. In this review, we will provide clinically relevant management guidelines for the role of metformin in the prevention of metabolic morbidities and the treatment of infertility in women with PCOS.

Insulin resistance in PCOS

Insulin resistance (IR) and secondary hyperinsulinemia affect approximately 65-70% of women with PCOS.[6,7] Many of these women are also obese, which further exacerbates their IR. Insulin stimulates ovarian theca cell androgen production and secretion, and suppresses the hepatic production of sex hormone-binding globulin. The increased intraovarian androgens then disrupt folliculogenesis.[8] Hyperinsulinemia may also directly cause premature follicular atresia and antral follicle arrest.[9] The resulting anovulation also leads to unopposed estrogen production and endometrial proliferation in women with PCOS, leading to an increased risk of endometrial hyperplasia.

Consistent with the high prevalence of IR and obesity, patients with PCOS demonstrate a greater prevalence of impaired glucose tolerance (IGT),[10] type 2 DM,[11] dyslipidemia, and chronic subclinical inflammation.[12,13] Recognition of a dysmetabolic pattern of elevated triglycerides, modestly altered low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL)[14,15] is clinically important when counseling patients regarding lifestyle modifications and in following up patients longitudinally as a baseline for comparison. In addition, many patients with PCOS demonstrate features consistent with the metabolic (or dysmetabolic) syndrome.[16]

Clinical considerations

1. The practical management of metabolic syndrome in women with PCOS must include tight blood pressure control, weight loss, diet modification, and possibly the use of agents for lipid modification.

2. As with other cases of oligomenorrhea, women with IR and subsequent oligomenorrhea should be considered for endometrial biopsy, particularly if a thickened endometrial stripe (> 10 mm) is seen on ultrasound.

Treatment of IR in PCOS

Dietary restriction

Weight reduction is a critical component in the treatment of PCOS, particularly in the 60-70% of women with PCOS who are overweight or obese, at least in the United States. Weight reduction has been shown to normalize ovulation, improve hyperandrogenism, and increase rates of conception in women with PCOS.[17] Although IR is a major contributing factor in the resultant abnormalities seen in PCOS, restriction of carbohydrates in particular has not been shown to have a distinctive benefit over fat restriction.[11] Women who lose even 5-10% of their total body weight can reduce central fat up to 30%, improve insulin sensitivity, and restore ovulation.[18] Increased physical activity and exercise is also an important component of healthy lifestyle, and evidence exists to support benefit for the metabolic disturbances typically seen in PCOS.[19]

Thiazolidinediones

Thiazolidinediones (TZDs) (including pioglitazone, rosiglitazone, and the previously used troglitazone) have been used in PCOS to reduce IR. Obese women with PCOS who were administered troglitazone demonstrated benefit in insulin sensitivity, glucose tolerance, and hyperandrogenemia.[20,21] A double-blind placebo-controlled trial, in which ovulation increased, testosterone levels decreased, and glycemic parameters normalized in a dose-dependent manner in women with PCOS treated with troglitazone, confirmed previous findings.[22] Although TZDs have been considered to paradoxically induce weight gain, more recent data suggest that TZDs in women with PCOS may not cause as much weight gain as first anticipated.[23] In clinical practice, the use of TZDs in reproductive-aged women with PCOS is not routinely advocated.

Metformin

Metformin is currently the most widely used drug worldwide for the treatment for type 2 DM. Its primary action appears to be an inhibition of hepatic glucose production and an increase in peripheral insulin sensitivity. The benefits of metformin on insulin sensitivity have been demonstrated in non-DM women with PCOS. The use of metformin is associated with increased menstrual cyclicity, improved ovulation, and a reduction in circulating androgen levels.[24] Metabolic benefits are enhanced in the presence of weight loss, and weight loss itself may be enhanced in the presence of metformin.[25] Below, we discuss further the mechanisms of action of metformin and its clinically relevant role in the treatment of PCOS.

Clinical considerations

1. Women who lose even 5-10% of their total body weight can reduce central fat up to 30%, improve insulin sensitivity, and restore ovulation. Lifestyle intervention should be the cornerstone of therapy.

2. In clinical practice, the use of TZDs in reproductive-aged women with PCOS is not recommended routinely.

3. The initiation of metformin may be considered in women with PCOS who exhibit abnormal results on the 75-g load oral glucose tolerance test (OGTT), but do not meet the criteria for DM.

4. In a subset of patients with oligomenorrheic PCOS, the initiation of metformin will instigate regular menstrual cycles.

Metformin: mechanisms of action

Metformin (1,1-dimethylbuguanide hydrochloride) is a biguanide currently used as an oral antihyperglycemic agent, and is approved by the US Food and Drug Administration to manage type 2 DM. Its primary clinical action is to inhibit hepatic glucose production, although it also decreases intestinal glucose uptake and increases insulin sensitivity in peripheral tissues. Metformin has antilipolytic effects, lowering circulating free fatty acid concentrations, which ultimately aids in reducing gluconeogenesis.[26,27]

Metformin activates the adenosine monophosphate (AMP)-activated protein kinase pathway (AMPK), both in vitro and in vivo,[28,29] resulting in decreased glucose production and increased fatty acid oxidation in hepatocytes, skeletal muscle cells,[30] and mouse ovarian tissue.[31] The mechanism by which metformin activates the AMPK is not clear; however, phosphorylation of threonine in AMPK is necessary for metformin's action.[30] A recent study suggests that metformin inhibits hepatic gluconeogenesis through an AMP-activated protein kinase-dependent regulation of the orphan nuclear receptor small heterodimer partner (SHP),[32] although not all investigators agree.[33]

Metformin is available as 500-, 850-, and 1000-mg tablets with a target dose of 1500-2550 mg per day. Many studies in PCOS have used a dose of 850 mg twice a day for 6 months. A sustained release preparation is also available (Glucophage-XR; Bristol-Myers Squibb, New York, NY). Side effects of metformin are mainly gastrointestinal (GI) and are listed in Table 1, although the sustained release preparation may have an overall lower rate of side effects. Metformin is best taken on an empty stomach. The sustained release is usually taken with the evening meal. To reduce the incidence of GI side effects, it is recommended that the dose of metformin is started low (eg, 250-500 mg/day) and then gradually increased during a period of 4-6 weeks. It is our experience that patients who do not tolerate metformin because of its GI side effects may benefit from the extended release formulation, albeit given in divided doses.

Because metformin may cause malabsorption of vitamin B12, patients taking metformin should be monitored for signs and symptoms of vitamin B12 de-

TABLE 1

Side effects of metformin

Gastrointestinal side effects	Diarrhea
	Nausea
	Vomiting
	Bloating
	Abdominal discomfort
	Flatulence
	Indigestion
	Constipation
	Heartburn
	Unpleasant metallic taste in mouth
Other side effects	Sneezing
	Cough
	Runny nose
	Flushing of skin
	Nail changes
Rare side effects	Lactic acidosis
	Chest pain
	Rash

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ficiency including numbness, paresthesia, macroglossia, memory loss, behavioral changes, and pernicious anemia.[24] Although lactic acidosis is cited as a major concern, it is a rare complication. Metformin should not be prescribed to women with renal insufficiency, congestive heart failure, or sepsis,[34] or be administered to patients with hepatic dysfunction or a history of alcohol abuse.[24] Metformin is indicated in patients older than 10 years, and the sustained preparation is indicated in those older than 17 years.

Metformin as treatment for PCOS-associated subfertility
Metformin, body weight, and fertility
During preconception counseling of obese patients with PCOS, weight loss is an important recommendation with the goal of decreasing gestational DM (GDM) and perinatal complications. Anecdotally, Glueck et al[35] reported that women with PCOS who conceived while taking metformin had a lower likelihood of developing GDM. An informative study designed to evaluate the effects of a hypocaloric diet combined with 6 months of metformin (1700 mg/day) vs hypocaloric diet and placebo in 20 obese women with PCOS and the abdominal phenotype and 20 obese women who were comparable for age and pattern of body fat distribution but without PCOS was conducted.[36] The combination of metformin and hypocaloric diet induced a greater reduction in body weight and abdominal fat, particularly visceral deposits, and a more consistent decrease in serum insulin, testosterone, and leptin concentrations in the obese women with PCOS and abdominal obesity compared with control subjects.

Clinical considerations

1. In clinical practice, close follow-up of patients with monitoring of their weight at each visit and food diaries has motivated patients to maintain weight loss and the addition of metformin has improved their hyperinsulinemia and appears to decrease their appetite.

Metformin alone for the treatment of subfertility
Metformin likely plays its role in improving ovulation induction in women with PCOS through a variety of actions, including reducing insulin levels and altering the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation, and endometrial growth. Also, potentially through a direct effect, it inhibits ovarian gluconeogenesis and thus reduces ovarian androgen production.[37-39] In determining which clinical parameters may predict which patients will benefit most from metformin for ovulation induction, fasting insulin levels and glucose to insulin ratios do not predict the ovulatory response to metformin.[40]

In a meta-analysis, metformin alone has been shown to have a significant benefit on inducing ovulation in women with PCOS, but there is limited evidence that it improves pregnancy rates.[41] Another meta-analysis of 17 randomized control trials (n = 1639 patients with PCOS) compared metformin vs placebo, and CC alone vs metformin plus CC.[42] In a pooled statistical estimate comparing metformin with placebo, metformin alone statistically improved the odds of ovulation (odds ratio [OR], 2.94), but did not statistically improve the rate of clinical pregnancy (OR, 1.56) or live birth rate (OR, 0.44). With regard to ovulation metformin alone appeared to be more effective in non-CC-resistant women.[42]

Alternatively, metformin alone is not as effective as CC alone for the treatment of infertility in women with PCOS. In the largest study to date of more than 600 therapeutically naïve women with PCOS seeking fertility randomized to treatment with metformin alone, CC alone, and metformin and CC combined (the Pregnancy in PCOS [PPCOS] trial), Legro et al[41] reported that CC alone resulted in significantly greater live birth rates than metformin alone, 22.5% vs 7.2%. Of note, multiple births were only seen with CC therapy (6.0% in the CC group, 0% in the metformin group, and 3.1% in the combination therapy group). Assuming that the goal of infertility treatment is to achieve a singleton gestation, it may be argued that CC is not quite as successful as suggested by the data of the PPCOS trial.[37]

Metformin in combination with CC for the treatment of subfertility
Metformin has been suggested for the treatment of PCOS oligoovulatory infertility, either alone (see above), or in combination with dietary restriction (see above), CC, or gonadotropins. In the PPCOS trial, Legro et al[41] reported that metformin alone was significantly less successful than the combination of CC and metformin (live birth rates 7.2% vs 26.8%) (Figure 1). However, the combination of metformin and CC was not significantly different from the rate of CC alone (see above). Other investigators have confirmed these data in somewhat smaller, albeit randomized studies.[43,44] In a meta-analysis, the combination of metformin and CC significantly improved ovulation and pregnancy rates (OR, 4.39 and 2.67, respectively) when compared with CC alone. However, combined therapy did not improve the odds of live birth (OR, 2.01). The results suggested combination therapy (metformin plus CC) as the treatment of choice in CC-resistant women.[42]

In contrast to its use in therapeutically naive patients, it is possible that women who have failed to ovulate with CC (ie,

CC-resistant) may benefit from the addition of metformin. Even though the reason for the ovulatory resistance to CC has not been clearly identified, it can be hypothesized that metformin therapy would augment the induction of ovulation in CC-resistant women because of its favorable change in androgens, gonadotropins, and insulin, through mechanisms distinct from those of CC.[45] It is plausible to assume that women with CC resistance receiving metformin have an increased response to CC secondary to an intrinsic alteration of the microenvironment of the follicle caused by the effect of metformin pretreatment on insulin and the insulin growth factor (IGF)-I pathway in granulosa cells.[46,47] More specifically, Tosca et al[48] reported that in bovine granulose cells, metformin decreases steroidogenesis and mitogen-activated protein kinase (MAPK)3/MAPK1 phosphorylation through AMPK activation.

In a study by Vandermolen et al,[45] a significant improvement on both ovulation and pregnancy rates were observed in women with CC-resistant PCOS who were treated with metformin alone. Other investigators have also observed an improvement in ovulatory or pregnancy rates in CC-resistant patients treated with a combination of metformin and CC vs placebo and CC,[49-51] however, all of these studies were small and underpowered. Despite the lack of convincing data that metformin improves live birth rates, there may be value in attempting this treatment prior to proceeding to more expensive and invasive therapies, such as laparoscopic ovarian drilling (LOD) or low-dose gonadotropins.[45] The ability of metformin to restore responsiveness to CC in obese women with PCOS, and the low rates of multiparity and ovarian hyperstimulation syndrome (OHSS), are additional potential benefits of metformin therapy in the CC-resistant patient.[49]

Clinical considerations

1. Patients with IR desiring fertility within the next few years may be considered for metformin therapy. More expedient desires for concep-

tion should consider CC or other alternatives.
2. The likelihood of a singleton gestation is higher when metformin is added to CC than with CC alone.
3. Metformin may be used as an adjunct in women who are CC resistant, and may be stopped at the time of positive pregnancy test result.

Metformin and TZDs
As metformin and TZDs modulate insulin sensitivity and insulin levels via different mechanisms, it is possible that the combination of these medications may have a greater effect on ovulation. Unfortunately, few randomized controlled trials have been performed. In a randomized trial, 25 women with CC-resistant PCOS and mild obesity (mean body mass index [BMI] $\sim$31 kg/m^2) were treated with rosiglitazone plus CC or metformin plus CC for 3 months. Rouzi and Ardawai[52] observed that the ovulation rate in the rosiglitazone and CC group was significantly higher than the metformin and CC group (64.3% vs 36.4%, respectively, $P = .035$). Likewise, the pregnancy rate was higher in the rosiglitazone and CC group than the metformin and CC group, but the difference did not reach statistical significance (50% vs 38.5%, respectively, $P = .58$). In contrast, Baillargeon et al[53] randomized 128 women with PCOS to metformin, rosiglitazone, and metformin and rosiglitazone combination for 6 months. These investigators observed a higher ovulation rate among women treated with metformin alone, or metformin plus rosiglitazone, compared with rosiglitazone alone (Figure 2). There was no significant difference between metformin alone and metformin and rosiglitazone. Of note, all patients with PCOS included in this study were nonobese and had normal glucose tolerance (NGT) and normal fasting and glucose-stimulated insulin levels.

Clinical considerations

1. The value of combining metformin with TZDs in PCOS for the purpose of conception is not supported by current data. Further studies are needed.
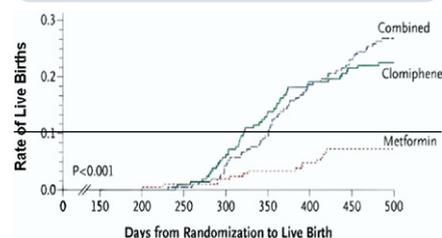
Metformin, gonadotropins, and intrauterine insemination cycles
Many clinicians must decide whether or not to continue metformin during a gonadotropin cycle. There is a paucity of data regarding this commonly faced issue. Van Santbrink et al[54] reported that metformin cotreatment in IR normogonadotropic anovulatory women resulted in the normalization of the endocrine profile and led to monofollicular development during gonadotropin stimulation for ovulation induction. Yarali et al[55] randomized 32 patients to metformin (1700 mg/d) or placebo for 6 weeks. Recombinant follicle stimulating hormone (rFSH) therapy was then given to those women who did not ovulate on metformin (n = 10) or placebo (n = 15), and metformin or placebo was continued. Overall, although pregnancy rates were higher in the metformin + rFSH combination therapy in comparison with the placebo + rFSH therapy (31.3% vs 6.3%, respectively), the differences did not reach significance.

Clinical considerations

1. In clinical practice, tailoring the management of rFSH with or without the continuation of metformin depends on the degree of IR.
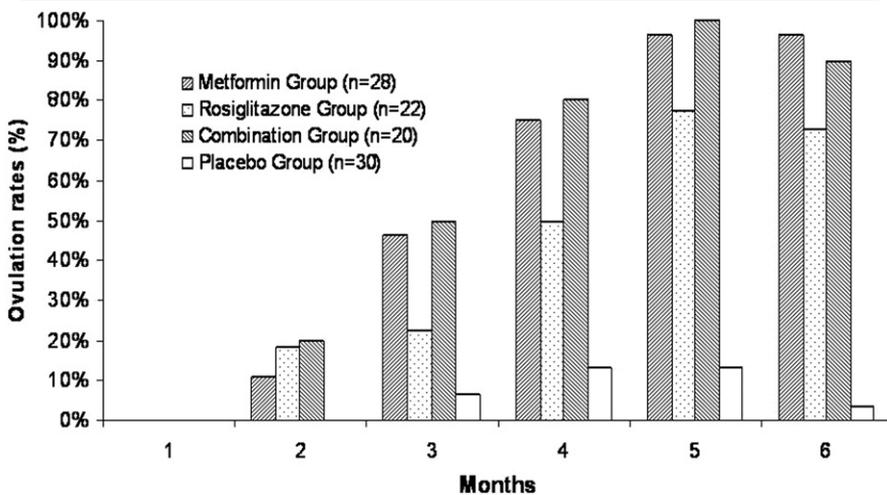
Ovulation rates for women with polycystic ovary syndrome (PCOS) taking metformin, rosiglitazone, combination, or placebo. Monthly ovulation rates in nonobese women with PCOS and normal indices of insulin sensitivity after administration of insulin-sensitizing drugs (metformin [1700 mg/day], rosiglitazone [4 mg/day], or combination of metformin and rosiglitazone) or placebo for 6 months. Values are number of women who ovulated during each month in group, divided by total number of subjects in that group. $P < .001$ for differences among months using mixed-model repeated-measures logistic regression. Adapted from Baillargeon et al.[53]

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Strictly looking at the insulin levels during the 2-hour glucose tolerance test (> 100) may help in this decision-making process.

2. Ultimately, if metformin (1700 mg/d) is given in conjunction with rFSH, it is stopped if the pregnancy test result is positive.

Another randomized controlled trial evaluated the pretreatment of metformin with a low-dose step-up gonadotropin stimulation protocol in 70 nonobese women with IR PCOS and either timed intercourse or intrauterine insemination (IUI) for up to 3 cycles.[56] The number of vials of gonadotropins ($P < .001$) and number of days of stimulation ($P < .001$) used were higher in the metformin arm, and the final number of dominant follicles ($P = .019$) and the peak estradiol levels ($P = .001$) were significantly lower in the metformin arm in comparison with the placebo arm. The monoovulatory cycle rates were significantly more frequent in patients cotreated with metformin vs placebo ($P = 85.9\%$ vs 64.4%, $P = .002$, respectively). How-

ever, no difference between groups was detected in ovulation, cycle cancellation, pregnancy, abortion, live birth, multiple pregnancies, or OHSS.

Clinical considerations

1. The goal of achieving monoovulatory cycles to avoid multiple pregnancy and OHSS may be taken into consideration when tailoring the patient's gonadotropin protocol with or without metformin.

Metformin and in vitro fertilization

A randomized, placebo-controlled, double-blind study was performed on 111 women with PCOS undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment using a long gonadotropin-releasing hormone agonist protocol.[57] Subjects received either metformin (850 mg) or placebo twice daily from the start of the down-regulation process until the day of oocyte collection. These investigators reported a significant decrease in the incidence of severe OHSS in the metformin group compared with placebo group (3.8% vs 20.4%, respec-

tively, $P = .023$), but no difference was noted in the rate of fertilization. However, not all data support even this beneficial effect of metformin during IVF in patients with PCOS. A meta-analysis of randomized controlled trials evaluating the coadministration of metformin during gonadotropin ovulation induction or IVF in women with PCOS was performed.[58] Eight studies were included, and the results were inconclusive. Overall, the beneficial effect of metformin coadministration during gonadotropin ovulation induction and/or IVF cycles remains unclear. Similar to patients undergoing rFSH and IUI cycles, the degree of IR may be a factor in deciding whether or not to add metformin to the cycle regimen until the pregnancy test.

Chang et al[59] showed that the insulin levels and the degree of beta-cell function (as measured by homeostasis assessment model [HOMA] beta-cell percent) are highest in oligoovulatory women with PCOS who are both hirsute and hyperandrogenemic, as compared with patients with PCOS who are either hyperandrogenemic or hirsute only. In this regard, a greater improvement in effectiveness (defined as decreases in luteinizing hormone [LH], estradiol, insulin, and C-peptide) was observed among women with PCOS who were both hyperandrogenic and hyperinsulinemic.[60] In addition, Moghetti et al[61] performed a logistic regression analysis of baseline characteristics in patients with PCOS who responded (ie, had an improvement in menstrual bleeding frequency; n = 17) or who did not respond (n = 14) to metformin treatment after receiving 1500 mg/day for 11.0 ± 1.3 months (open trial; range 4-26 months). The researchers observed that higher plasma insulin, lower serum androstenedione, and less severe menstrual abnormalities were independent predictors of clinical efficacy of metformin.

Clinical considerations

1. Phenotypic features of the patient with PCOS may play an important role in determining which patients will benefit most from the addition of metformin to the gonadotropin regimen.

TABLE 2
Histology of serial endometrial biopsy and corresponding ovulation rate on insulin sensitizer treatment

Subject	Randomized medication	Ovulation rate, %[a]	Baseline biopsy	Second biopsy[b]	Third biopsy[b]
1	Rosiglitazone	0	—[c]	Proliferative	Weakly proliferative
2	Metformin	50	Simple hyperplasia	Secretory	Mid proliferative
3	Rosiglitazone	0	Proliferative	Weakly proliferative	Weakly proliferative
4	Metformin	66	Mid proliferative	Early proliferative	Weakly proliferative
5	Rosiglitazone	17	Early proliferative	Late proliferative	Proliferative
6	Rosiglitazone	66	Proliferative	Proliferative	Secretory
7	Metformin	—[c]	Simple hyperplasia	Proliferative	—[c]
8	Rosiglitazone	83	Early proliferative	Mid proliferative	—[c]
9	Rosiglitazone	83	Proliferative	Secretory	Mid proliferative
10	Metformin	0	Proliferative	Proliferative	Proliferative
11	Rosiglitazone	0	Mid proliferative	Mid proliferative	Weakly proliferative
12	Rosiglitazone	83	Early proliferative	Proliferative	Secretory
13	Metformin	0	Weakly proliferative	Simple hyperplasia	Weakly proliferative
14	Metformin	33	Mid proliferative	Proliferative	Proliferative
15	Rosiglitazone	17	Secretory	Proliferative	Secretory
16	Metformin	—[c]	Adenocarcinoma	—[c]	—[c]

Adapted from Legro et al.[68]

[a] Six treatment cycles of either metformin (2000 mg/day) or rosiglitazone (8 mg/day). [b] After 3 months of combined therapy. [c] No evaluable data for these outcomes.

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Metformin in the treatment of PCOS-associated oligoovulatory infertility: summary

In summary, metformin alone does not appear to be a highly effective initial therapy for the treatment of oligoovulatory infertility in PCOS, at least compared with CC ovulation induction; nonetheless, it is more effective than placebo alone and is associated with a significantly lower multiple pregnancy and OHSS rate. In general, metformin should not be used as first-line monotherapy. However, metformin alone may play a role in the rare patient who desires improvement in both metabolic and reproductive function, but who is not on a fast track toward obtaining a pregnancy, or in those who absolutely wish to avoid multiple gestations, or in patients who do not tolerate CC (eg, secondary to mood changes, visual disturbances). Of interest, genetic factors may modulate the effectiveness of metformin in inducing ovulation. Data from the PP-COS trial indicated that a polymorphism of a serine-threonine kinase gene expressed in the liver, *STK11* (formerly known as *LKB1*), was associated with a significantly decreased chance of ovulation in women with PCOS treated with metformin.[62]

Metformin may be effective in inducing ovulation in some women with PCOS and CC resistance. Whether metformin is of value in patients with PCOS undergoing gonadotropin ovulation induction or IVF remains to be determined; perhaps the severity of IR noted on a 2-hour 75-g load glucose tolerance test may help in this decision. In agreement, Moll et al[63] performed a meta-analysis including 27 trials evaluating the effectiveness of metformin in subfertile women with PCOS with the primary outcome being live birth rate. Prior to initiating gonadotropins, the combination of CC and metformin in CC-resistant women is the preferred treatment. This combination usually requires a dose of at least 1500 mg/day of metformin. Alternatively, this analysis concluded that there was no evidence for an improvement in live birth rate when adding metformin to LOD or gonadotropins.

Clinical considerations

1. Overall, it should be remembered that metformin is a modestly acting agent, operating indirectly to improve ovulation, and the expectation that it is a powerful ovulatory drug for PCOS is unfounded.

Metformin, the endometrium, and menstrual bleeding

Researchers have found that excess insulin levels stimulate endometrial growth, and may serve to stimulate endometrial proliferation.[64] Metformin may have an impact on the endometrium, hypothetically both improving the potential for a successful pregnancy implantation and reducing the long-term risks of unopposed endometrial proliferation. Jakubowicz et al[65,66] observed that metformin treatment enhanced uterine vascularity and

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TABLE 3
Metformin alone for treatment of hirsutism

Study	N (hirsute/control)	Duration (mos)	Placebo controlled	Improved	Change in FG score
Kolodziejczyk et al,[83]	34/0	3	No	Yes	-2.3%
Moghetti et al,[61]	32/0	11.3	No	No	—
Pasquali et al,[36]	9/4	6	Yes	Yes	-15%
Kelly and Gordon,[84]	5/5	14	Yes	Yes	N/D[a]

FG, Ferriman-Gallwey hirsutism.

[a] Not documented.

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blood flow in women with PCOS. Palomba et al[67] studied uterine vascularization, endometrial thickness, and endometrial pattern in 37 patients with anovulatory PCOS treated with metformin for 6 months, and in 30 age-matched control subjects. In the patients with PCOS, metformin was observed to improve a majority of parameters of endometrial receptivity, although it did not improve endometrial thickness.

A randomized open-label study of metformin and rosiglitazone in 16 women with PCOS consisted of a 6-week baseline observation period, a 3-month treatment period of single-agent therapy (rosiglitazone or metformin), and then a 3-month period of combined therapy. Investigators observed that endometrial histology tended to normalize during the course of the study as shown in Table 2.[68] Three subjects displayed abnormal endometrial histology at the baseline biopsy (simple hyperplasia or adenocarcinoma), 1 subject had abnormal histology after 3 months of single-agent therapy (simple hyperplasia), and no subjects had abnormal histology at 6 months. When examining the prevalence of secretory endometrial hyperplasia indicative of ovulation based on the random biopsies, a steady increase in the frequency of this histology during the course of the study was observed, although no significant differences or trends in the 32 graded histologic items by treatment arm were noted (Table 3).

Overall, metformin appears to improve ultrasound-detected markers of endometrial receptivity and endometrial histology through: (1) improved ovulatory function; (2) possibly reduced circulating levels of insulin; and (3) other undetermined factors. Consequently, metformin administration has the potential to reduce the risk of unopposed endometrial proliferation, hyperplasia, or carcinoma by improving the regularity of ovulatory function and by reducing the effect of hyperinsulinemia on the endometrium. However, definitive studies are lacking.

We should note that it is not infrequent for there to be a disconnect between ovulatory response and the frequency or regulation of withdrawal bleeding. Periodic vaginal bleeding may arise as a result of the decline in estrogen and progesterone at the end of an ovulatory cycle in a nonpregnant patient (ie, a menstrual bleed). Alternatively, periodic (although not necessarily regular) vaginal bleeding may also occur when the growth properties of the endometrium are altered, through alterations in circulating hormones and uterine vascularity, as described above. Many studies examining the effect of metformin on ovulatory function have reported primarily on the frequency of vaginal bleeding (assumed to be a menstrual flow) and not on the degree of ovulatory function. However, in many oligoamenorrheic patients with PCOS treated with metformin there is discordance between the improvement in periodic vaginal bleeding and the development of regular ovulatory function. For example, Moghetti et al[61] assessed ovulatory function by a serum progesterone measured in the luteal phase of 39 cycles in 10 women experiencing regular menses after treatment with metformin. In only 32 of these assessments (79%), did the serum progesterone levels confirm ovulation.

Thus, the periodicity and frequency of vaginal bleeding in a patient receiving metformin should not be used as evidence of ovulatory function or endometrial protection.

Clinical considerations

1. The presence of ovulation in patients treated with metformin alone should be confirmed through the measurement of luteal phase (cycle day 20-24) progesterone levels (with levels generally above 3-4 ng/mL indicating prior ovulation).

Metformin and pregnancy loss
A number of observational studies have suggested that metformin reduces the risk of pregnancy loss.[35,69,70] However, in the prospective randomized PPCOS trial, spontaneous abortion rates were similar in all 3 treatments and there was a trend toward a greater rate of miscarriages in the metformin only group (40.0% in the metformin only group vs 25.8% in the CC only group vs 30.0% in the CC plus metformin group).[41] Alternatively, Moll et al[43] randomized 228 therapeutically naïve women with PCOS to metformin plus CC or placebo plus CC, and did not observe a difference in the pregnancy loss rate (11% vs 12%). Zain et al[44] did not observe any difference in pregnancy losses among 115 patients with PCOS randomized to receive metformin (1500 mg/day) (38 patients), CC at incremental doses (39 patients), or both medications in combination (38 patients).

Clinical considerations

1. At the present time there are no conclusive data to support a beneficial effect of metformin on pregnancy loss, although the trend toward a higher miscarriage rate in the PPCOS trial, which used extended release metformin, is concerning.

Metformin use during pregnancy

For women who become pregnant it is important to note that the TZDs pioglitazone and rosiglitazone are both classified as pregnancy category C, associated with fetal growth retardation in mid to late gestation in animal studies. In contrast, metformin is classified as pregnancy category B.[71] Despite the absence of contradictory data, the safety of metformin in pregnancy has not yet been established. A meta-analysis of 8 studies focusing on pregnancy outcome after metformin use in women with PCOS concluded that there was no evidence of an increased risk for major malformations (95% confidence interval, 0.15-1.60).[72]

It is possible that the use of metformin during pregnancy might reduce the risk of developing GDM and other pregnancy complications potentially associated with IR (eg, pregnancy-induced hypertension). In a prospective observational study of 42 pregnancies in 39 women with PCOS, Glueck et al[73] suggested that metformin in combination with dietary control reduced the likelihood of developing GDM and prevented androgen excess in the fetus. Kovo et al[74] evaluated the neonatal outcomes of 33 women with PCOS and 66 healthy women. These investigators observed a significantly lower mean birth weight percentile of neonates exposed to metformin in utero during the first trimester compared with the mean birth weight percentile of neonates not exposed to metformin. A recent study evaluated 126 infants born to 109 mothers with PCOS who conceived on and continued metformin through pregnancy.[75] These investigators concluded that: (1) metformin reduced the risk of developing GDM; (2) metformin was not ter-

atogenic; and (3) metformin did not adversely affect birth length, birth weight, growth, or motor-social development in the first 18 months of life.[75]

In summary, there are few data to suggest that metformin might be harmful during pregnancy. Although observational and anecdotal data suggest that metformin may be beneficial in pregnancy by potentially reducing the risk of GDM or other IR-associated pregnancy complications, at present, the routine use of metformin during pregnancy in patients with PCOS to prevent these morbidities is not recommended. In fact, definitive data regarding the continuation of metformin during pregnancy for women with documented IR are also lacking.

Clinical considerations

1. Although observational and anecdotal data suggest that metformin may be beneficial in pregnancy by potentially reducing the risk of GDM or other IR-associated pregnancy complications, at present, the routine use of metformin during pregnancy for patients with PCOS to prevent these morbidities is not recommended.

2. At present, cessation of metformin on a positive pregnancy test result is a reasonable course of action.

Effects of metformin on androgens and hirsutism

Ample evidence supports the beneficial effect of metformin on the hyperandrogenism of patients with PCOS.[25,41,76-78]

In a study comparing metformin (2250 mg/day) with flutamide (250 mg/day) as a treatment for nonobese young women with PCOS, free testosterone decreased significantly with both treatments.[79] In addition, a comparison of metformin alone (2250 mg/day), rosiglitazone alone (4 mg/day), and the combination of both drugs, to placebo in nonobese, non-IR women with PCOS observed that the mean serum-free testosterone levels in subjects on therapy were significantly lower than the levels found in subjects on placebo (metformin: 2.34 pg/mL, rosiglitazone: 3.06 pg/mL, and combination: 2.39 pg/mL vs

7.26 pg/mL for placebo, $P < .05$).[53] These findings suggest that 6 months of treatment with either metformin or rosiglitazone in the doses studied ameliorated hyperandrogenemia in nonobese women with PCOS.

Conversely, when Yilmaz et al[80] compared metformin (1700 mg/day) with rosiglitazone (4 mg/day) administered for 12 weeks to groups of lean and obese patients with PCOS, they observed decreases in testosterone, androstenedione, or dehydroepiandrosterone status (DHEAS) levels in all 4 groups, although only the decreases in the rosiglitazone groups were statistically significant. Lastly, when comparing the effects of metformin (2250 mg/day) and pioglitazone (30 mg/day) randomly administered for 6 months in 52 women with PCOS, a ~30% decrease in the hirsutism score was observed in both groups. In addition, both treatments demonstrated significant decreases in free testosterone, androstenedione, and LH.[81]

Metformin may reduce hirsutism through amelioration of their hyperandrogenemia (see above) and possibly by reducing circulating insulin levels. Androgens stimulate the terminalization of vellus hairs and the growth of terminal hairs in skin areas that are sensitive to the effects of these steroids (ie, those exhibiting sufficient androgen receptor, 17-β-hydroxysteroid dehydrogenase, and 5α-reductase, and areas with reduced aromatase activities). In addition to the pubic and axillary regions, an exaggerated androgen effect in these areas can lead to excess terminal hair growth in a male-like pattern (ie, hirsutism). Finally, as insulin also acts as an anabolic growth factor in hair,[82] it is possible that the suppression of circulating insulin levels alone may be sufficient to ameliorate the rate of terminal hair growth.

A number of small studies, some controlled, others not (Table 2), have generally indicated modest improvements in hair growth.[36,61,83,84] Two small, randomized trials have compared the effect of metformin alone with an oral contraceptive pill (OCP) alone. Morin-Papunen et al[85] randomized 18 patients to receive either metformin (1000 mg/day for 3 months, then 2000 mg/day for 3

FIGURE 3
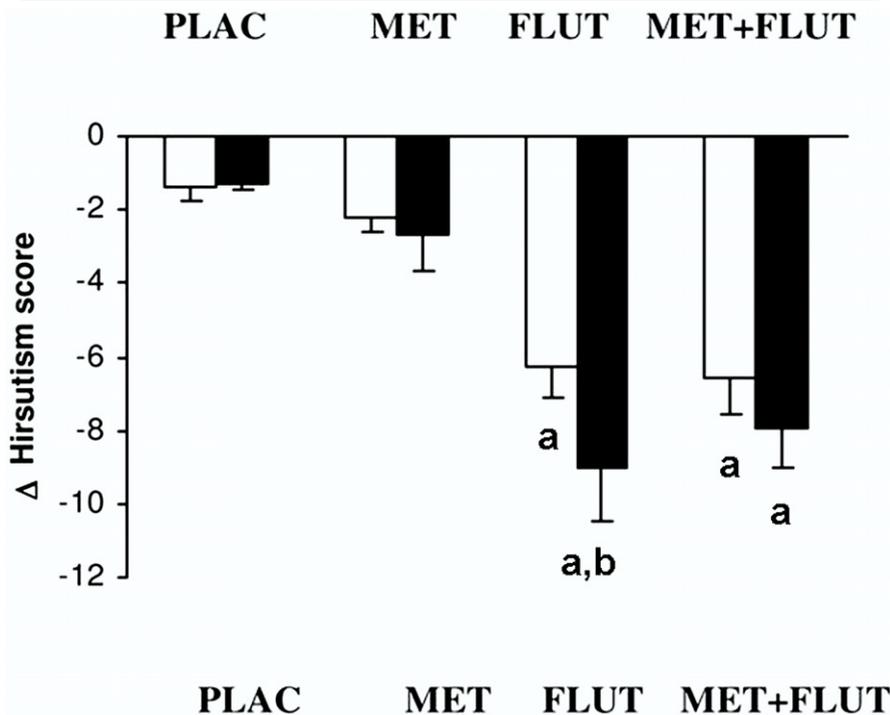
Changes in Ferriman-Gallwey hirsutism score in women with polycystic ovary syndrome (PCOS) taking placebo (PLAC), metformin (MET), flutamide (FLUT), or combination. Changes (Δ) in score at 6 (*white bars*) and 12 (*black bars*) months in patients with PCOS treated with PLAC, MET (1700 mg/day), FLUT (500 mg/day), and MET+FLUT. Data are shown as mean ± SEM. *a, P* < .001 refers to differences in changes of hirsutism score from baseline to 6 months, and from baseline to 12 months, between groups treated with MET, FLUT, or MET+FLUT and PLAC. *b, P* < .05 refers to differences in changes of hirsutism score from 6 to 12 months between groups treated with MET, FLUT, or MET+FLUT and PLAC. Adapted from Gambineri et al.[88]

Mathur. Use of metformin in polycystic ovary syndrome. Am J Obstet Gynecol 2008.

additional months) or an OCP (35 μg of ethinyl estradiol and 2 mg of cyproterone acetate), and observed a greater decrease in the hirsutism score with the OCP. Luque-Ramirez et al[86] randomized 34 consecutive patients with PCOS to oral treatment with metformin (1700 mg/day) or with an OCP (35 μg of ethinyl estradiol plus 2 mg of cyproterone acetate) for 24 weeks. They observed that although the hirsutism score, serum-free testosterone levels, and androstenedione levels decreased with treatment in the group as a whole, the improvements resulted mostly from the decrease observed in the patients treated with the OCP, which was marked down much more than those observed with metformin. Alternatively, in a similar design, Harborne et al[87] randomized 37 patients to receive either the same OCP or met-

formin (1500 mg/day) for 12 months. They reported a greater decrease in the hirsutism score with metformin than the OCP arm (-25% vs -5%, *P* < .01).

Metformin alone is much less effective for the treatment of hirsutism compared with antiandrogen therapy. Gambineri et al[88] carried out a prospective, randomized, placebo-controlled trial of 76 obese women with PCOS.[88] After a 1-month diet, the patients were allocated to treatment with placebo, metformin (1700 mg/day), flutamide (500 mg/day), or metformin plus flutamide for the following 6 months, while continuing hypocaloric dieting. Flutamide treatment alone was significantly more effective than metformin alone for treating hirsutism; combination therapy with metformin did not add any further benefit (Figure 3).

Clinical considerations

1. Although metformin, like OCPs, may have a beneficial effect on excess hair growth, both agents have a relatively modest effect during an extended period. Antiandrogen therapy, alone or preferably in combination with androgen suppression, is the preferred first-line treatment for PCOS-associated hirsutism.

Metformin and the prevention of metabolic morbidity in women with PCOS

Metformin, hyperinsulinemia, and IR

By the age of 30 years, 30-50% of obese women with PCOS develop IGT or overt type 2 DM. This is a 3- to 7-fold greater risk than an age-comparable population.[89-91] In addition, many patients with PCOS demonstrate features consistent with the metabolic syndrome.[16] The use of metformin in women with PCOS generally increases insulin sensitivity,[25,53,78-81,92] and decreases weight and BMI.[25,77,79,93] In a meta-analysis of 13 studies, metformin improved fasting insulin levels, blood pressure, and levels of LDL cholesterol,[69] perhaps as a result of changes in body weight. Salpeter et al[94] performed a meta-analysis of the pooled results of 31 trials with 4570 participants followed up for 8267 patient-years to assess the effect of metformin on metabolic risk. These investigators did not observe a significant difference in results between PCOS and non-PCOS individuals, although unfortunately no trial examined the effect of metformin on the incidence of type 2 DM. In this meta-analysis, women with PCOS experienced a 5.3% decrease in BMI, a 2.6% mean decrease in fasting glucose, and a 19.7% improvement in IR as assessed by the HOMA (HOMA-IR). Fasting insulin decreased by 5.7%, although the difference did not reach significance. In addition, HDL cholesterol increased by a mean of 9.4% whereas triglycerides decreased by 11.9%. These results were of similar magnitude to those of non-PCOS, except the measurement of fasting insulin, which in non-PCOS was improved by a mean of 16.1%.

Metformin appears to benefit people with PCOS irrespective of their weight or degree of IR.[25,80] A study including lean, overweight, and obese patients with PCOS observed that all 3 groups of patients demonstrated a significant decrease in fasting insulin and HOMA-IR after 6 months of metformin treatment, irrespective of their pretreatment degree of IR.[25] In addition, the overweight and obese groups demonstrated a significant decrease in area under the curve of insulin ($AUC_{insulin}$) response to an oral glucose challenge. Investigators studying normal-weight women with PCOS observed that metformin significantly improved insulin sensitivity and the $AUC_{glucose}$ to $AUC_{insulin}$ ratio in comparison with both the baseline assessment and against a placebo group.[92] Even in studies performed to examine the effects of metformin in women with PCOS with normal weight and with normal insulin sensitivity, significant decreases in fasting insulin, $AUC_{insulin}$, and HOMA-IR were observed.[78]

Clinical considerations

1. In women with PCOS and hyperinsulinemia, metformin improves fasting insulin levels, blood pressure, and levels of LDL cholesterol. Studies are needed to determine whether this translates into improved morbidity and mortality.

Metformin vs TZDs or OCPs

Comparisons have been made between metformin and other medications to evaluate degrees of efficacy on insulin sensitivity. Metformin (2550 mg/day) was compared with pioglitazone (30 mg/day).[81] Both medications improved fasting insulin levels and insulin sensitivity comparably. Pioglitazone was associated with an increase in the waist-to-hip ratio (WHR), body weight, and BMI. When comparing rosiglitazone with metformin in both lean and obese patients with PCOS, both treatments significantly decreased fasting insulin levels, C-peptide levels, and HOMA-IR.[80] However, in this study rosiglitazone more effectively decreased androgen levels and increased menstrual regularity than metformin. Other investigators compared

metformin alone with rosiglitazone alone with a metformin plus rosiglitazone combination, and observed that insulin sensitivity was significantly increased in the metformin alone and the metformin plus rosiglitazone groups, but not in the rosiglitazone alone group.[53]

Although OCPs help hyperandrogenic symptoms and regulate menstrual cycles in women with PCOS, they may worsen insulin sensitivity.[95] This remains controversial. In a meta-analysis comparing 3 trials of metformin vs OCPs,[85,87,96] fasting insulin levels were significantly lower in patients who were treated with metformin whereas the insulin levels in those treated with OCP did not change; there were no differences in fasting glucose levels between the 2 interventions.[97] When a comparison of 2 trials[32,98] was performed analyzing a metformin-OCP combination vs OCPs alone, fasting insulin levels demonstrated a nonsignificant trend in favor of the metformin-OCP combination.[97]

Clinical considerations

1. Overall, current data suggest that metformin appears to be equally as effective, if not more, than TZDs for the treatment of hyperinsulinism in PCOS, and may be of additional value in patients taking OCPs.

Metformin and the risk of Type 2 DM

Metformin may slow the progression to type 2 DM.[24] Most of the data to support this assertion arise from study populations that may include women with PCOS, but these studies do not specifically identify this subset. The Diabetes Prevention Trial enrolled 3234 subjects with IGT who were at risk for type 2 DM, and randomized them to metformin (1700 mg/day), intensive lifestyle intervention, or standard of care/control (the original design had a fourth arm, troglitazone therapy, which was discontinued after 18 months secondary to the emerging risk of hepatic dysfunction).[99] The average follow-up for this study was 2.8 years. Compared with the control group, subjects treated with metformin demonstrated a 31% decrease in the relative risk

for progression to overt type 2 DM, although the decrease was greatest in the group of patients treated with intensive lifestyle intervention (-58%).

One retrospective study of women with PCOS treated with metformin for an average of 43 months found that metformin appeared to delay or prevent the development of IGT and type 2 DM.[100] These investigators found an 11-fold decrease in the annual conversion rate from NGT to IGT, with 55% of patients with IGT reverting to NGT.

Clinical consideration

1. Although it is likely that metformin will reduce the risk of type 2 DM specifically in PCOS, prospective and controlled studies have not been conducted in this particular population to evaluate the long-term metabolic benefits of metformin and the effects of subsequent drug discontinuation.

Metformin and weight loss

Metformin has been suggested to assist in weight loss in patients with PCOS. Tan et al[25] analyzed data from 3 groups of patients with PCOS: (1) lean, (2) overweight, and (3) obese, and found that metformin use was significantly associated with decreased body weight and BMI in the overweight and obese groups. In one study, the use of metformin was observed to decrease body weight even in nonobese women with PCOS.[79] Other investigators observed a significant reduction in waist circumference but no significant change in weight in obese subjects treated with metformin.[101] In another study, researchers observed that metformin reduced BMI in patients both with and without IR, but it had no influence on the WHR.[77] Conversely, other investigators have concluded that metformin has no effect on BMI or waist circumference.[69] These differences in resultant weight loss among studies have yet to be explained.

It is possible that the differences in weight loss after treatment with metformin are dose dependent. A prospective cohort study of 4 groups of obese PCOS subjects on 2 different doses of metformin were analyzed: (1) obese

PCOS on 1500 mg/day; (2) morbidly obese PCOS on 1500 mg/day; (3) obese PCOS on 2550 mg/day; and (4) morbidly obese PCOS on 2550 mg/day.[93] Although all of the patients who received 8 months of metformin treatment demonstrated significant reductions in weight and BMI, only obese women with PCOS responded to metformin in a dose-dependant manner, with the greater weight loss evident at the higher dose. Morbidly obese women demonstrated a similar degree of weight loss at both doses of metformin, and a similar amount of weight loss was observed in the obese group at the higher metformin dose.

The use of metformin in combination with dietary restriction for weight loss has also been studied. A meta-analysis of 3 such trials[85,87,96] reviewing the effect of metformin vs OCPs (ethinyl estradiol 35 μg combined with cyproterone acetate 2 mg) did not observe a difference in BMI or WHR between the 2 treatments.[97] A trial comparing 6 months of OCPs (ethinyl estradiol 35 μg combined with 250 μg norgestimate in a cyclic regimen of 21 days of active pills followed by 7-day pill-free interval) alone vs the OCP combined with metformin (1500 mg/day) also reported no significant differences in body weight.[32] Finally, meta-analysis of 2 studies investigating OCP alone vs OCP combined with metformin[32,98] revealed no difference in BMI between the groups.[97]

Clinical consideration

1. These data suggest that the effect of metformin on weight is minimal, and patients should be advised that this agent should not be used solely for the purpose of weight reduction.

Metformin and cardiovascular risk

Because the metabolic syndrome and IR increase the risk of cardiovascular disease (CVD), it is important to consider IR and long-term health when selecting a medical treatment in overweight women with PCOS.[102] At baseline, many patients with PCOS have some degree of dyslipidemia. Typically, this can include reduced levels of HDL cholesterols and modestly increased levels of LDL cholesterol, triglycerides, and total choles-

terol.[103] In a meta-analyses of 2 studies[87,104] comparing metformin with OCP therapy, no difference in total, HDL, or LDL cholesterols was observed. However, in comparison with the OCP therapy, metformin did result in significantly lower triglyceride levels.[97] Other investigators studying normal-weight women with PCOS found that metformin significantly improved their LDL cholesterol levels when compared with their baseline levels and with the placebo group.[92]

Metformin has been shown to improve endothelial function, as measured by brachial arterial flow-mediated vasodilation.[105] Metformin is also reported to improve coronary microvascular function and coronary flow rate.[106] One group of investigators evaluated the serum levels of cellular adhesion molecule (CAM), which reflect the degree of low-grade chronic inflammation and have been associated with several IR states.[107] They found that women with PCOS (n = 62) in comparison with control subjects (n = 45) had significantly higher levels of high-sensitivity C-reactive protein (CRP), soluble intracellular CAM-1, and soluble endothelial leukocyte adhesion molecule-1 (sE-selectin). Soluble vascular CAM (sVCAM)-1 did not differ between the 2 groups. In women with PCOS, baseline levels of high-sensitivity CRP and sVCAM-1 levels were significantly reduced by taking a dose of metformin (1700 mg/day) for 6 months. In obese women with PCOS, metformin alone reduces circulating levels of CRP.[108] However, in combination with an OCP containing ethinylestradiol and cyproterone acetate, the reductions seen in CRP was attenuated.

In summary, some, but not all studies have indicated that metformin decreases parameters implicated as cardiovascular risk factors in women with PCOS. In particular, benefit may be seen in atherogenic profiles, including markers of subclinical inflammation, dyslipidemia, and IR. Enhanced endothelial function, coronary microvascular function, and coronary flow rate may also be seen in addition to the overall benefit of a decrease in total body weight. Notwithstanding the improvements observed in secondary

CVD markers with metformin therapy in women with PCOS, conclusive and prospective long-term studies have yet to be carried out. A recent position statement from the Androgen Excess and PCOS Society recommended that women with PCOS, regardless of weight, be screened for IGT or type 2 DM by an oral glucose tolerance test at their initial presentation and every 2 years thereafter.[109] However, this statement noted that the use of metformin to treat or prevent the progression of IGT could be considered but should not be mandated at this point in time, as well-designed randomized controlled trials demonstrating efficacy have yet to be conducted.

Clinical considerations

1. Subclinical chronic inflammation in women with PCOS may be improved by metformin therapy, yet controversy exists as to whether these effects are long lasting.

Conclusions: clinical considerations for metformin therapy

Metformin is an agent that acts indirectly and modestly to improve ovulation and reduce long-term metabolic complications. The management of metabolic syndrome in women with PCOS must include tight blood pressure control, weight loss, diet modification, and possibly the use of agents for lipid modification. Metformin reduces the circulating levels of many markers of atherosclerosis and subclinical chronic inflammation, suggesting that it may be beneficial in reducing the long-term risk of type 2 DM and CVD in women with PCOS, although long-term studies are lacking. At the present time, the use of TZDs in reproductive-aged women with PCOS is not routinely recommended.

Pregnancies achieved on metformin are more likely to be singleton and to carry less risk of OHSS. There may be a role for metformin in women with PCOS who are CC resistant. Periodic vaginal bleeding improves in many patients with PCOS, but this does not ensure that all episodes of bleeding result from an ovulatory cycle. In addition, there are no clear data to suggest that metformin re-

duces pregnancy loss or improves pregnancy outcome in PCOS, and it is currently recommended that metformin be discontinued with the first positive pregnancy test result, unless there are other medical indications (eg, type 2 DM) for continued therapy. Phenotypic features of the patient with PCOS may play an important role in determining which patients will benefit most from the addition of metformin (Table 3). ■

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