

In Brief

This article reviews the literature regarding the effects of metformin therapy in pregnant women with polycystic ovary syndrome on weight loss, fertility, early pregnancy loss, malformations, gestational diabetes mellitus, perinatal mortality, placental clearance, lactation, and early childhood development. The pharmacology of metformin is also presented. Preliminary data suggest that metformin for this population may be both safe and effective. Large blinded, randomized clinical trials are underway to confirm the preliminary safety data.

Polycystic Ovary Syndrome and Pregnancy: Is Metformin the Magic Bullet?

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History of Polycystic Ovary Syndrome

Although the first description of polycystic ovary syndrome (PCOS) is generally credited to Stein and Leventhal in 1935, it may have been observed as early as 1721, when the Italian scientist Antonio Vallisneri observed “young married peasant women, moderately obese and infertile, with two larger than normal ovaries, bumpy and shiny, whitish, just like pigeon eggs.”¹ This depiction sounds strikingly similar to the subfertility and obesity commonly found in PCOS. It was not until 1921 that Achard and Theirs² noticed a relationship between hyperandrogenism and insulin resistance in their study of the “bearded diabetic woman.” And in 1935, Stein and Leventhal³ made the connection between amenorrhea and polycystic ovaries. In addition, they also noticed the occurrence of masculinizing changes, such as hirsutism and acne, in many patients with polycystic ovaries.

Several, but not all, of Stein and Leventhal’s original case studies involved women who were overweight. In all seven of their case reports, attempts to treat ovulatory dysfunction with estrogenic hormone failed, and wedge resection was employed. All of their patients gained normal menstruation, and two became pregnant. Surgery for PCOS is uncom-

mon now, although some centers still employ laser drilling of the ovary as a means of inducing ovulation.⁴

Definition of PCOS

Much has changed over the past 80 years in the way we understand, diagnose, and treat PCOS. PCOS is the most common endocrine disorder among women of reproductive age, affecting 5–10% of premenopausal females in the United States.⁵ PCOS encompasses a broad spectrum of signs and symptoms of ovary dysfunction. The 2003 Rotterdam consensus workshop⁶ concluded that PCOS is a syndrome of ovarian dysfunction, with the cardinal features of hyperandrogenism and polycystic ovary morphology.

PCOS remains a clinical syndrome. Fortunately or unfortunately, no single diagnostic criterion (such as hyperandrogenism or polycystic ovaries) is sufficient for clinical diagnosis. The diagnostic code of 620.2 merely requires a clinical judgment and is not dependent on laboratory confirmation. Assigning a code allows for reimbursement for tests and treatment. The clinical manifestations of PCOS include menstrual irregularities, signs of androgen excess (alopecia, acne, hirsutism), and obesity. Insulin resistance and elevated serum luteinizing hormone levels are also common features in PCOS. A fasting insulin level > 20 mU/l correlated in

one study with an abnormal glucose-to-insulin ratio, an indication of insulin resistance.⁷ PCOS is associated with an increased risk of the metabolic syndrome (11 times greater), gestational diabetes mellitus (GDM) (2.4 times greater), type 2 diabetes, hypertension, dyslipidemia, subfertility, spontaneous abortions, cardiovascular events, and the premature development of hormone-sensitive carcinomas.⁸⁻¹⁰

Metformin Therapy

A magic bullet therapy for PCOS would result in weight loss, improve insulin resistance, restore normal ovulatory cycles, increase fertility, decrease hyperandrogenism, decrease the rate of spontaneous abortions, and decrease the risk of GDM. The current front-runner for this magic bullet is the biguanide metformin. It appears to do all of the above—but is it safe to continue throughout pregnancy?

Metformin Pharmacology

While studying effects of parathyroidectomy, it was discovered that guanide derivatives had hypoglycemic actions.¹¹ The initial guanides were toxic. Metformin, a biguanide, is an antihyperglycemic agent that improves glucose intolerance. In patients with type 2 diabetes, it lowers both basal and postprandial plasma glucose concentrations. Its pharmacological mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

The liver does not metabolize metformin. Renal excretion is the primary mode of clearance from the body. It is contraindicated in patients with significant renal dysfunction. The most significant risk associated with metformin is that of lactic acidosis. Although lactic acidosis is associated with 50% mortality, it is exceedingly rare in subjects with normal renal function. In > 20,000 patient-years of exposure to metformin in clinical trials, there were no reports of lactic acidosis. Renal function should be monitored frequently, however. In addition, metformin therapy should be suspended after radiological procedures requiring contrast or surgical procedures until renal function has been reevaluated.

The most common side effects associated with metformin are gastroin-

testinal in nature: abdominal pain, constipation, distended abdomen, diarrhea, dyspepsia/heartburn, taste disturbance, and flatulence. Serum levels of metformin during pregnancy may be altered because pregnant women often have gastrointestinal motility disturbances and increased renal blood flow.

In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels without clinical manifestations was observed in ~ 7% of patients. Such a decrease, possibly resulting from interference with vitamin B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride tablets or vitamin B₁₂ supplementation. Therefore, B₁₂ levels and red blood cell indexes should be monitored frequently in all pregnant patients taking metformin. Replacement therapy should be initiated if patients are found to be B₁₂ deficient.

Animal Toxicity and Teragenicity

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses ≤ 900 mg/kg/day and 1,500 mg/kg/day, respectively.¹² These doses are both approximately four times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Metformin was not teratogenic in

rats and rabbits at doses up to 600 mg/kg/day.¹² This represents an exposure of about two and six times the maximum recommended human daily dose based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin, although the rat placenta has different characteristics than the human placenta.

Weight Loss and Insulin Sensitivity

In a recent 4-year study,¹³ metformin in combination with diet was shown to safely reduce weight by 8% in women with PCOS while also improving their lipid profiles (11% decrease in LDL cholesterol and 11% increase in HDL cholesterol). A modest weight loss often translates to improved insulin sensitivity. Insulin resistance is a major trigger of metabolic and reproductive abnormalities in women with PCOS. Elevated insulin levels, associated with insulin resistance, leads to thecal thickening in the ovary, which in turn leads to anovulation and infertility.¹⁴ PCOS may account for > 75% of the anovulatory infertility.¹⁵ Metformin has shown to be an effective means of achieving ovulation in women with PCOS (odds ratio = 3.88).¹⁶

Early Pregnancy Loss

PCOS is also associated with an elevated rate of early pregnancy loss. The etiology of this association is not known. It may be related to plasminogen activator inhibitor activity,¹⁷ unrecognized hyperglycemia, or a yet-to-be-determined factor associated with PCOS itself. Metformin has beneficial metabolic, endocrine, vascular, and anti-inflammatory effects on the risk factors contributing to first-trimester abortion in PCOS patients.

A prospective cohort study¹⁸ was set up to determine the beneficial effects of metformin on PCOS patients during pregnancy. Two hundred nondiabetic PCOS patients were evaluated while undergoing assisted reproduction. One hundred and twenty patients became pregnant while taking metformin and continued taking metformin at a dose of 1,000–2,000 mg daily throughout pregnancy. Eighty women who discontinued metformin use at the time of conception or during pregnancy comprised the control group. Both groups were similar with respect to all background characteristics (age, BMI,

waist/hip ratio, and levels of follicle-stimulating hormone, luteinizing hormone, estradiol, and dehydroepiandrosterone sulfate). The rate of early pregnancy loss in the metformin group was 11.6% compared with 36.3% in the control group ($P < 0.0001$; odds ratio = 0.23, 95% confidence interval 0.11–0.42). Administration of metformin throughout pregnancy to women with PCOS was associated with a marked and significant reduction in the rate of early pregnancy loss. A smaller prospective pilot study¹⁹ in 19 women with PCOS demonstrated a 63% decrease in spontaneous abortions in women treated with metformin.

GDM

A prospective observational study of 42 pregnancies in 39 women with PCOS that was published in 2004 demonstrated the effectiveness of metformin in reducing the incidence of GDM in this high-risk population. Metformin was used in conjunction with preconception calorie restriction (1,500–2,000 calories/day, including 26% protein and 44% carbohydrate). Calorie restriction was stopped after conception. GDM developed in 7.1% of these pregnancies. The median insulin levels fell 40% from baseline at their last preconception visit. Testosterone levels fell 30% from baseline at their last preconception visit.²⁰

The main limitation in this study is that there was an average weight loss of 11.8 kg before conception. The decrease in GDM may not have been the result of continuation of metformin, but rather may have resulted from one of the cornerstones of therapy for women with PCOS who are planning to become pregnant: preconception weight loss. Another prospective study in 33 women with PCOS demonstrated a tenfold decrease (from 31 to 3%) in the incidence of GDM when metformin was continued during gestation compared with a retrospective control group.²¹

Metformin therapy (2.55 g/day) during conception and continued during pregnancy in 72 oligo/amenorrheic women with PCOS was safely associated with reduction in spontaneous abortion (17% with metformin vs. 62% without) and in GDM (4% with metformin vs. 26% without), was not teratogenic, and did not adversely affect birth weight or height, weight, and motor and social development at 3 and 6 months of life.²² There was no

maternal lactic acidosis, no maternal or neonatal hypoglycemia, and no congenital malformation in live births. The question of whether to use metformin in the treatment of GDM remains a hotly debated subject.²³

Perinatal Mortality

One of the first reports of using biguanides in pregnancy was presented at a symposium in Rimini, Italy, in 1968.²⁴ Forty subjects were studied, including 32 taking metformin and 8 taking phenformin. Most subjects were treated with insulin as well. The perinatal mortality rate was 150 per 1,000 births, which was comparable to insulin-treated patients at the time.

One of the first reported organized studies using metformin in GDM was the Cape Town Experience.²⁵ In Cape Town in the mid-1970s, the perinatal mortality rate of the offspring of patients with untreated GDM was 264 per 1,000 births. The study was designed to achieve the best possible control of the blood glucose levels by means of diet with or without oral hypoglycemic medications. If diet alone was unable to achieve euglycemia, metformin or glibenclamide was administered. Metformin was chosen if the patient was obese. If euglycemia was not achieved on monotherapy and diet, both oral medications were combined. If the combination of both oral agents failed, insulin was added. Fifty-nine of the 476 patients in the study were given only metformin. None of the women was given metformin before the first trimester. The perinatal mortality rates of the metformin-treated group and the diet-alone group were 15 and 16 per 1,000 births, respectively, but the macrosomia rate was ~20% compared to 10% in a control population without GDM.

Malformations

Based on the limited data available today, a recent meta-analysis²⁶ did not demonstrate evidence of an increased risk for major malformations when metformin is taken during the first trimester of pregnancy. Large studies are needed to corroborate these preliminary results. Eight studies (conducted between 1966 and 2004) were included in the meta-analysis. After pooling the studies, the malformation rate in the disease-matched control group was ~7.2%, statistically significantly higher than the rate found in the metformin group (1.7%). Met-

formin passes the placenta, and fetal serum levels are comparable to maternal values.²⁷

Despite the traditional response that all oral hypoglycemic agents are absolutely contraindicated during pregnancy, evidence that metformin is probably safe during the first trimester of pregnancy and beyond is accumulating. Results of another recent meta-analysis²⁸ by the Motherisk Program showed no increase in incidence of major malformations and a potential protective effect in this patient population.

Lactation

Metformin is excreted into breast milk, but the amounts seem to be clinically insignificant. No adverse effects on blood glucose were measured in a small study of three nursing infants.²⁹ Metformin during lactation appears to be safe in the first 6 months postpartum. There was not any difference in the weight, height, or motor-social development between breast- and formula-fed infants.³⁰

Type 2 Diabetes, Pregnancy, and Metformin

The prevalence of type 2 diabetes in women of childbearing age continues to grow as the incidence of type 2 diabetes increases. Recent evidence shows that treatment of GDM and normalization of postprandial glucose concentrations ensure the best possible outcome for pregnancy complicated by GDM. Metformin is a logical treatment in these circumstances, but there has always been concern about its safety for fetuses, particularly because it crosses the placenta and may increase the risk of teratogenesis. Although evidence is accumulating that metformin is useful and has a role in PCOS, a condition of insulin resistance, it is not yet accepted as treatment for type 2 diabetes in pregnancy and GDM. Observational data support the use of metformin in type 2 diabetes in pregnancy, and its role in GDM is currently under investigation.³¹ Because metformin does not effectively target the postprandial glucose concentration, the macrosomia rate may not be normalized with metformin treatment alone.

Metformin may become an important treatment for women with either GDM or type 2 diabetes in pregnancy and indeed may have additional important benefits for women, including reducing insulin resistance, body weight, and the long-term risk of dia-

betes. There is a need for a randomized, controlled trial in women with type 2 diabetes in pregnancy with long-term follow-up of both mothers and children. Until then, the best advice remains that optimized glycemic control and weight loss before conception and during pregnancy is the most important intervention for the best possible pregnancy outcome.

Because of its positive effects on PCOS-induced infertility, metformin has become one of the most common drugs used in this group of patients. The efficacy of metformin and the promising results of the initial studies on its use in pregnancy have encouraged its continued use after conception.³²

Is Metformin the Magic-Bullet Therapy for Women With PCOS?

The available evidence supports consideration of the use of metformin from the earliest stages of treatment in women with PCOS. Metformin restores ovulation, improves fertility, sustains weight loss, and decreases the frequency of both early pregnancy loss and GDM. Preliminary data suggest that it is safe. Large, blinded, randomized clinical trials are necessary to confirm these safety data. In the information age, these studies may be difficult to carry out. Women with PCOS are increasingly being treated with metformin as an insulin-sensitizing agent to reduce symptoms of hyperandrogenism and promote fertility. One recent study³³ was unable to proceed because the recruited patients did not want to stop their metformin therapy during pregnancy. Still, researchers in a multicenter trial³⁴ involving 626 infertile women with PCOS recently published data on the baseline characteristics of their study population.

With luck, these trials will confirm preliminary safety and efficacy data pertaining to the use of metformin in women with PCOS during pregnancy. However, the data from these studies cannot be extrapolated to GDM or type 2 diabetes during pregnancy. A prospective, randomized, controlled trial³⁵ is currently underway comparing metformin to insulin in women with GDM. Any woman with diabetes should be as close to euglycemia as possible before conception and during pregnancy. Thus, women with PCOS must add self-monitoring of blood glucose to their treatment program and aim for achieving both fasting and postprandial normoglycemia.

When metformin treatment is being considered, the individual risks and benefits must be discussed with patients so that an appropriate decision can be reached. When used, metformin should be an adjuvant to general lifestyle improvements and not a replacement for increased exercise and improved diet.³⁶

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