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The Use of Metformin in Pregnancy

BY MARIA KRAW, MD

Metformin is an oral medication currently approved for the treatment of type 2 diabetes. Its off-label use in the treatment of anovulation associated with polycystic ovary syndrome (PCOS) has been supported by several studies and systematic reviews. When these women conceive on metformin, the issue of whether to continue the drug throughout the pregnancy has become an increasingly relevant clinical dilemma. This issue of *Endocrinology Rounds* examines the current evidence regarding the safety and efficacy of metformin in the management of pregnancies complicated by PCOS.

Use of metformin in polycystic ovary syndrome

PCOS is a disorder characterized by oligoanovulation, hyperandrogenism, and polycystic ovaries on imaging.¹ Insulin resistance is a common feature in women with PCOS. The resultant hyperinsulinemia contributes not only to androgen excess and anovulation, but also to a variety of metabolic derangements such as dysglycemia, dyslipidemia, and hypertension.

Metformin is the most commonly prescribed oral medication used in the treatment of type 2 diabetes. It acts through the inhibition of hepatic glucose production and by increasing the sensitivity of peripheral tissues to insulin. The off-label use of metformin in women with PCOS has been shown to improve ovulation rates and menstrual cyclicity, reduce androgen levels, hirsutism, and acne scores. For more information, readers are directed to a recent review on the role of metformin in the treatment of PCOS.²

Over the past few years, several trials have been published comparing the efficacy of metformin, clomiphene citrate (CC), or a combination, in the short-term management of subfertile women with PCOS.³⁻⁶ A meta-analysis of 27 such trials with live-birth rate as the primary outcome revealed no difference between metformin and CC (relative risk [RR] 0.73; 95% confidence interval [CI], 0.51-1.1) or comparing metformin plus CC with CC (RR 1.0; 95% CI, 0.82-1.3) among treatment-naïve women.⁷ In CC-resistant women, metformin plus CC led to higher live-birth rates than CC alone (RR 6.4; 95% CI, 1.2-35). Palomba et al⁸ recently published a nonrandomized, prospective controlled study confirming similar ovulation, pregnancy, or miscarriage rates in women treated with metformin compared to those treated with CC.

Whether alone, or in combination with CC, it is likely that some women will become pregnant while using metformin and will seek guidance on whether and when to stop the drug. Physicians must be prepared to discuss the potential risks and benefits in light of the currently available published information.

Early pregnancy loss in PCOS

The association between PCOS and early pregnancy loss (EPL) remains controversial, since the prevalence of EPL in women with PCOS who conceive spontaneously is unknown. Observational studies of spontaneously conceiving healthy couples report EPL rates of 25% (defined as clinically unrecognized pregnancy loss detected only by daily urinary human chorionic gonadotropin [hCG] assay) and clinical miscarriage rates of 8% (defined as loss between 6-28 weeks gestation).⁹ Because definitions of EPL and miscarriage rates vary, comparison between studies is often difficult.



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Table 1: The effect of metformin on early pregnancy loss (EPL) in polycystic ovary syndrome (PCOS)¹⁶			
Study type (n, patients)	Metformin dose	Control EPL (n, pregnancies)	Metformin (n, pregnancies)
Retrospective case-control (96) ¹⁷	1-2 g/day throughout pregnancy	41.9% (12/31)	8.8% (6/68)
Prospective pilot (19) ¹⁸	1.5-2.55 g/day throughout pregnancy	39% (103/265) – 73% (16/22)	10.5% (2/19)
Prospective cohort (72) ¹⁹	2.55 g/day throughout pregnancy	62% (62/100)	17% (14/84)
Case series (48) ²⁰	1-1.5 g/day for 12 weeks	Estimated to 35%	35% (7/20)
Prospective cohort (200) ²¹	1-2 g/day throughout pregnancy	36.3% (29/80)	11.6% (14/120)

Currently published studies of EPL in women with PCOS all include women undergoing some form of ovulation induction or stimulation. CC has a miscarriage rate (pregnancy loss before 9 week gestation) of 24%.¹⁰ Factors implicated in EPL in women on CC include the presence of PCOS, higher luteinizing hormone (LH) levels, obesity, the antiestrogenic action of CC on endometrial estrogen receptors, and suppression of pinopode formation.¹⁰⁻¹² High rates of EPL have also been demonstrated with both conventional¹³ and low-dose¹⁴ gonadotropin ovulation induction protocols. Another confounding variable is that women undergoing ovulation induction at fertility clinics tend to receive closer scrutiny during early pregnancy, resulting in a higher detection of EPL. Nonetheless, a meta-analysis comparing women with PCOS undergoing *in vitro* fertilization (IVF) with matched controls indicated no difference in number of miscarriages per biochemical pregnancy.¹⁵ Finally, women with PCOS are a very heterogeneous group with regard to clinical symptoms and laboratory manifestations. Studies involving such women are rarely powered to allow subgroup analysis of these differences.

Role of metformin in reducing EPL in PCOS

Given the challenges in assessing the risk of EPL in women with PCOS, it is difficult to interpret whether any intervention can mitigate this risk. The available data suggest a protective effect of metformin on EPL, but they are limited by a lack of prospective randomized trials (Table 1). If metformin actually reduces the risk of EPL, it is tempting to speculate on the relationship between metformin and the etiological factors associated with EPL in women with PCOS.

Obesity

PCOS is often associated with obesity, which alone is strongly associated with an increased prevalence of EPL.²² Although a study by Wang et al²² demonstrated an increased rate of EPL in women with PCOS undergoing IVF compared with a non-PCOS group (28% vs 18%, $P < 0.01$), this significance was lost when the data were adjusted for obesity and treatment type. The authors concluded that the higher rate of EPL in the PCOS group was due to the higher prevalence of obesity in this group of women.

Hyperinsulinemia and hypercoagulability

Insulin resistance and subsequent hyperinsulinemia are common features of PCOS, particularly when associated with obesity. Although high insulin levels have not been directly linked to EPL, they are strongly associated with obesity and elevated levels of plasminogen activator inhibitor (PAI-1), a glycoprotein, and a potent inhibitor of fibrinolysis.²³ Women with PCOS are more likely to have a hypofibrinolytic genotype for the PAI-1 gene and elevated concentrations of PAI-1.²⁴ Elevated production of PAI-1 by endothelial and decidualized endometrial cells might promote clot formation in the uterine vascular bed.²⁵ Metformin has been demonstrated to reduce PAI-1 levels in women with PCOS both before and during pregnancy.¹⁸ Thus, the potential benefit of metformin on pregnancy outcomes may be mediated by its effect on insulin and PAI-1 concentrations.

High serum LH concentrations

Approximately 40% of women with PCOS have elevated follicular phase LH concentrations.²⁶ Elevated serum LH concentrations (>10 IU/L) in the early to mid-follicular phase have been associated with EPL in women with^{27,28} and without²⁹ PCOS. This association was maintained even when corrected for other hormonal parameters such as androgens, follicle-stimulating hormone (FSH), and prolactin.²⁶ Although metformin has been associated with decreased LH concentrations,³⁰ the most significant reductions in LH levels are observed following laparoscopic ovarian drilling.³¹ There is also some evidence that the use of gonadotropin-releasing hormone (GnRH) agonists to reduce elevated LH concentrations can reduce the prevalence of EPL.¹²

Endometrial dysfunction

The hormonal and metabolic abnormalities found in women with PCOS may have complex effects on the endometrium, contributing to impaired implantation and EPL. Biomarkers of endometrial receptivity to embryonic implantation (eg, $\alpha v \beta 3$ -integrin³² and

Table 2: Pregnancy outcomes in women with PCOS compared with controls⁴¹

Outcome	Odds ratio	95% confidence interval
Gestational diabetes	2.94	1.70–5.08
Pregnancy-induced hypertension	3.67	1.98–6.81
Pre-eclampsia	3.47	1.95–6.17
Preterm birth (<37 weeks)	1.75	1.16–2.62
Admission to NICU*	2.31	1.25–4.26
Perinatal mortality†	3.07	1.03–9.21

* Neonatal intensive care unit
 † Unrelated to multiple births

glycodelin) are decreased in both the luteal phase and first trimester of pregnancy.³³ Hyperinsulinism down-regulates hepatic insulin-like growth factor binding protein-1 (IGFBP-1) that plays a role in sustaining early pregnancy by mediating intracellular adhesion at the maternal-fetal interface.³⁴ Elevated insulin levels can also adversely affect endometrial blood flow, endometrial receptivity, and endometrial stromal differentiation (decidualization).³⁵

Metformin therapy has been revealed to increase both glycodelin and IGFBP-1 levels, either directly or as a result of lowered insulin levels.³⁶ Other uterine effects of metformin therapy that could affect implantation include increased endometrial thickness, reduced vascular resistance of the spiral arteries, and improved uterine blood flow.³⁷

Hyperandrogenism

Elevated androgen levels are more common in pregnant women with PCOS compared with controls. Hyperandrogenism has been implicated in EPL through effects of ovarian dysfunction³⁸ and detrimental effects on endometrial function.³⁹ Using a mouse model of androgen-induced EPL, Solano et al⁴⁰ found that metformin prevents embryonic resorption induced by hyperandrogenization with dehydroepiandrosterone.

Late-pregnancy outcomes in women with PCOS

Late-pregnancy outcomes were examined in a meta-analysis of 720 women with PCOS compared with 4,000 controls.⁴¹ The results revealed significantly higher rates of complications in women with PCOS (Table 2).

Pregnancy-related hypertensive disorders

Hyperinsulinemia and obesity are associated with pregnancy-induced hypertension.⁴² Elevated androgen levels have also been associated with pre-eclampsia^{43,44} and may play a role in preterm labour. Intravenous (IV) androstenedione has been shown to induce early third-

trimester labour in monkeys.⁴⁵ Pre-eclampsia and fetal growth restriction are thought to be related to impaired trophoblastic invasion of the maternal spiral arteries, resulting in increased impedance to uterine artery flow.⁴⁶ In a randomized trial of 40 pregnant women, metformin treatment reduced uterine artery impedance and was associated with a reduction in pregnancy complications (preterm delivery, severe pre-eclampsia, or postpartum events).⁴⁷ Taken together, it could be speculated that the modulating effects of metformin on hyperinsulinemia and hyperandrogenemia may affect the risk of hypertension, pre-eclampsia, and preterm labour. However, such speculations must be tested and confirmed in randomized clinical trials before any conclusions on metformin therapy in the prevention of pregnancy-related hypertensive disorders could be drawn.

Gestational diabetes mellitus

Since the diagnosis of gestational diabetes mellitus (GDM) is based on high plasma glucose levels, and metformin reduces plasma glucose, it is likely that fewer women on metformin will fulfill the criteria for GDM. Three prospective cohort studies by Glueck have demonstrated a reduction in the occurrence of GDM in relation to metformin therapy.^{18,48,49} Among women with PCOS receiving metformin, only 3%-7% developed GDM compared with 26%-30% in previous pregnancies without metformin. In 15 women who previously had GDM with no use of metformin, GDM developed in 5 (31%) of 16 subsequent pregnancies on metformin. In 32 women who were previously free of GDM without metformin, GDM developed in 1 (3%) of 34 subsequent pregnancies on metformin.⁴⁹ However, a randomized prospective study by Vanky et al⁵⁰ in 40 women with PCOS revealed no difference in the prevalence of GDM among women treated with metformin (8/18; 44%) compared with those not on metformin (9/22; 41%). As a result, even though it is assumed that metformin therapy decreases the risk of GDM, these assumptions currently lack the backing of adequate clinical trials.

Safety of metformin in pregnancy

If metformin is to be used throughout pregnancy, further data are needed about its safety and its fetal effects. It must be possible to weigh the potential benefits listed above with a certainty of no possible harm to the mother or fetus. Metformin is currently listed as a category B drug in pregnancy. (Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.)

Pharmacokinetics of metformin in pregnancy

Metformin – a dimethylbiguanide – is a small basic compound of 129 Da that remains ionized at physio-

logical pH.⁵¹ The absorption of metformin in the gastrointestinal (GI) tract is decreased in the presence of food and with increased GI transit time. It has negligible plasma protein binding and a moderately large volume of distribution. Metformin is eliminated unchanged in urine, with renal clearance exceeding glomerular filtration rate (GFR), suggesting active tubular secretion.

The physiological changes of pregnancy, such as increased plasma volume, decreased GI motility, and a 40%-50% increase in GFR by the second trimester, can significantly affect metformin pharmacokinetics. Hughes et al⁵² studied serum metformin concentrations (area under the curves [AUC] for concentration time from 0 to 4 hours post dose) in 7 women with type 2 diabetes on 2 occasions, once at 28-36 weeks gestation and once at least 8 weeks postpartum. The mean serum concentration of metformin in pregnancy was 80% (95% CI, 51.3-107.8; $P = 0.053$) of the postpartum value. This decrease in AUC seen in pregnancy is likely the result of both an increase in renal clearance resulting from the pregnancy-associated rise in GFR and an increase in total body water volume during pregnancy that would dilute the concentration of this hydrophilic drug. The authors suggest that, clinically, their results may necessitate an increase of approximately 20% in metformin dosing to maintain a therapeutic effect in the second and third trimester.

Placental passage of metformin

A high transplacental transfer of metformin would be expected due to its low molecular weight, hydrophilic nature, and lack of plasma protein binding. An *ex vivo* technique of dual perfusion of placental lobule (DPPL) has been used to study the extent of placental transfer of drugs *in vivo*.⁵³ Using DPPL, Nanovskaya et al⁵⁴ found that metformin crosses the placenta freely and that the levels in the fetal circulation can reach 50% of those in the maternal circuit. Given that the metformin transferred to the fetus remains unbound and, therefore, active in the fetal circulation, it may have a direct effect on fetal physiology.

The same study revealed that placental tissue retained low amounts of metformin (<20% of that in maternal circuit). Since most of the drug was in the extracellular space water, the authors concluded that metformin is unlikely to affect placental function. This is supported by data indicating that placental glucose uptake and transport are not altered by metformin.⁵⁵

A study examining the umbilical cord blood of women with PCOS demonstrated that the concen-

tration ratio of metformin in the umbilical artery to the vein was approximately 1.⁵⁶ This suggests that fetal distribution and metabolism of metformin is likely negligible and that the elimination by the placenta to the maternal circulation is more likely.

Adverse effects of metformin in pregnancy

Maternal and neonatal complications were observed in a historic cohort study of 118 women with type 2 diabetes.⁵⁷ There was an increased risk of pre-eclampsia and perinatal mortality in women treated with metformin compared with those receiving sulphonylureas or insulin. Although these results are a concern, they should be interpreted with caution, since the trial was retrospective, lacked blinding and randomization, and contained several confounders. Women exposed to metformin were significantly more obese, the degree of glycemic control was unavailable for most patients, and the women were only exposed to the drug after 35 weeks gestation, making the etiological role of the drug in pre-eclampsia unlikely.

Several observational studies in women with PCOS taking metformin in pregnancy have not shown any increase in maternal complications.⁵⁸ There were no cases of lactic acidosis or maternal hypoglycemia.^{18,47} One small, prospective randomized trial revealed a decreased risk of pregnancy or postpartum complications in the 18 women assigned to metformin therapy in pregnancy (3 minor pregnancy complications) compared with the 22 taking placebo (3 minor pregnancy complications, 6 major pregnancy complications, including 5 preterm deliveries, 1 severe pre-eclampsia, and 3 major postpartum complications: sepsis, acute respiratory distress syndrome [ARDS], deep vein thrombosis [DVT] with massive pulmonary embolism [PE]).⁵⁰

Neonatal outcomes were assessed in several prospective studies. The newborns had favourable outcomes: median gestational age was 39–39.7 weeks;¹⁸ they were appropriate for gestational age,^{16-18,47} and they had no neonatal hypoglycemia.^{16,47} A meta-analysis of pregnancy outcomes after first-trimester exposure to metformin revealed no evidence of an increased risk of major malformations.⁵⁹ In studies with later trimester exposure to metformin, one infant was born with a patent foramen ovale¹⁷ and another had achondrodysplasia.¹⁶ The latter inherited disorder is unlikely to be related to metformin exposure.

Limited long-term follow-up of infants exposed to metformin *in utero* indicated no difference in weight, height, or motor-social development compared with the norm at 6 months of age.¹⁸ A follow-up study, including 126 infants born to 109

metformin-treated mothers, showed similar results at 18 months of age.⁶⁰ The conclusions of two recent review articles on the safety of metformin in pregnancy and lactation are encouraging, but support the need for further investigations to better define the risks and benefits of metformin in pregnancy.^{61,62}

Conclusion

Although metformin is currently only approved for the treatment of type 2 diabetes, it is frequently used off-label in the treatment of anovulation associated with PCOS. Given that women with PCOS may have an increased risk of early pregnancy loss, pregnancy-induced hypertension, pre-eclampsia, and preterm labour, it is tempting to consider the continuation of metformin in pregnancy to reduce these complications. However, the data behind this are limited to small nonrandomized trials and speculations based on intermediate outcomes and animal studies. While metformin appears to be safe in pregnancy and lactation, these data are also limited and mostly retrospective. Therefore, even though the data on using metformin in pregnancies complicated by PCOS are extremely provocative, confirmation in multicenter randomized trials with adequate blinding of treatment arms is required before metformin can be considered a standard of care in the management of these women and their children.

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3 – 7 May 2008

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CONTACT: http://professional.diabetes.org/Congress_Display.aspx?TYP=9&SID=39&CID=58000

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6 – 9 July 2008

European Society of Human Reproduction and Embryology

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