Clinical and Practical Psychopharmacology

Major Malformation Risk, Pregnancy Outcomes, and Neurodevelopmental Outcomes Associated With Metformin Use During Pregnancy

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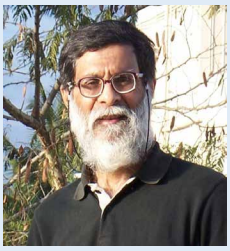

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

There are several reasons why metformin treatment may be considered for women in neuropsychiatric practice. These include prevention or attenuation of antipsychotic-associated weight gain, prevention or treatment of gestational diabetes mellitus (GDM), treatment of type 2 diabetes mellitus, and improvement of conception chances and pregnancy outcomes in the presence of polycystic ovarian disease (PCOD). This article examines the benefits and risks associated with metformin use during pregnancy. The available data suggest that metformin exposure during the first trimester is not associated with major congenital malformations; that metformin reduces the risk of early pregnancy loss, preeclampsia, preterm delivery, and GDM in women with PCOD; that metformin is associated with at least comparable benefits relative to insulin treatment in women with mild GDM; and that neurodevelopmental outcomes at age 1.5–2.5 years are comparable after gestational exposure to metformin and insulin. Whereas study designs were not always ideal and sample sizes were mostly small to modest, the study findings are more encouraging than discouraging and can guide shared decision-making in women who are receiving or may need metformin during pregnancy.

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Metformin in Neuropsychiatry

Metformin, a biguanide, is classified as an oral hypoglycemic agent. There are many reasons why this drug may be prescribed in neuropsychiatric practice:

1. Major mental illness and its treatments are associated with an increased risk of weight gain, type 2 diabetes mellitus (T2DM), and the metabolic syndrome.[1–4] Metformin may be useful in such patients. For example, primary prevention randomized controlled trials (RCTs) suggest that metformin can reduce weight gain and insulin resistance in patients who initiate olanzapine.[5,6] A meta-analysis[7] of 31 RCTs (pooled N = 4,570) found that, in patients at risk of diabetes mellitus, metformin reduced body weight, improved indices of glycemic control, and reduced key lipid levels; additionally, metformin was associated with a significant reduction in the risk of progression to diabetes (odds ratio [OR] = 0.6; 95% CI, 0.5–0.8). Another meta-analysis[8] of 21 RCTs (pooled N = 1,547) found that metformin was associated with medium effect sizes (standardized mean differences, 0.51–0.69) for decrease in weight, improvement in measures of glycemic control, and reduction in lipid levels when it was advised for the prevention or treatment of metabolic conditions associated with antipsychotic drugs.
2. Metformin is a low-cost, low-risk, effective, and approved oral hypoglycemic agent for T2DM.[9] Metformin is therefore an important treatment option for T2DM that arises independently of or in association with major mental illness and its pharmacologic management (as described above).
3. Gestational diabetes mellitus (GDM) may develop in association with the metabolic dysregulation observed in major mental illness. For example, antipsychotic use in pregnancy has been associated with GDM.[10] Metformin is an important treatment option in patients with GDM. A meta-analysis[11] of 8 clinical trials (pooled N = 1,712) comparing metformin with insulin in GDM found that metformin treatment was associated with benefits comparable to those with insulin on measures such as fasting blood sugar, postprandial blood sugar, and hemoglobin A_{1c} (HbA_{1c}) levels at 36–37 weeks of gestation (but 14%–46% of metformin patients required additional insulin). Importantly, metformin was associated with a lower risk of neonatal hypoglycemia (relative risk [RR] = 0.74; 95% confidence interval [CI], 0.58–0.93) and neonatal intensive care admission (RR = 0.76; 95% CI, 0.59–0.97). Another meta-analysis[12] of 8 metformin vs insulin RCTs (pooled N = 1,592) found that metformin was associated with a lower risk of pregnancy-induced hypertension (RR, 0.54; 95% CI, 0.31–0.91).

Clinical Points

- There are many reasons why a prescription of metformin may be considered for women in neuropsychiatric practice. It is therefore important to know the benefits and risks associated with use of metformin during pregnancy.
- The available data suggest that exposure to metformin during the first trimester of pregnancy does not increase the risk of birth defects; that continuation of metformin during pregnancy improves many pregnancy outcomes in women with polycystic ovarian disease and gestational diabetes mellitus; that pregnancy outcomes are comparable after metformin or insulin exposure in women with mild gestational diabetes; and that metformin exposure during pregnancy is not associated with poorer neurodevelopmental outcomes at age 1.5–2.5 years relative to insulin exposure.

In this meta-analysis, the two treatments did not differ on risks of neonatal hypoglycemia, large-for-gestational-age fetuses, respiratory distress syndrome, perinatal death, and other adverse outcomes.

4. Polycystic ovarian disease (PCOD) affects, conservatively, 4%–8% of women in the reproductive age group, and the prevalence may be as high as 15%–20%, depending on the criteria applied.[13] PCOD has been associated with epilepsy[14,15] and particularly with valproate treatment of epilepsy.[16] However, there may not be a link between PCOD and bipolar disorder,[17] another neuropsychiatric indication for valproate. Metformin is used to improve the chances of conception in women with PCOD.[18,19] As shown in a later section, metformin is also used to improve pregnancy outcomes in PCOD.

Clinical Question

Women in neuropsychiatric practice may require or receive metformin in one or more of the contexts described in the previous section. A woman receiving metformin may conceive, and the indication for metformin would almost certainly continue to exist after conception. Metformin, unlike insulin, crosses the placental barrier,[20] so what benefits and risks might be associated with continuation of metformin during the first trimester and all through pregnancy? This article examines evidence from recent meta-analyses and other studies on the subject.

First-Trimester Exposure to Metformin and the Risk of Birth Defects

Cassina et al[21] described a systematic review and meta-analysis of English-language prospective and retrospective controlled studies on the risk of birth defects following first-trimester exposure to metformin. They identified 9 studies of women with PCOD (N = 351) who had been exposed to metformin during the first trimester; there were 178 control women with PCOD who had discontinued metformin upon conception or confirmation of pregnancy. Most studies dosed metformin in the region of 1,500 mg/d (range, 500–2,550 mg/d). There was no significant increase in the risk of major birth defects after first-trimester metformin exposure; however, the confidence interval was very wide and included the possibility of risk reduction to one-fifth as well as the possibility of quadrupling of the risk (9 studies; OR = 0.86; 95% CI, 0.18–4.08). There was no significant heterogeneity in the data.

Cassina et al[21] also examined studies that did not qualify for meta-analysis. Putting all the non-overlapping PCOD studies together, even those without an appropriate control group, they found that the overall rate of major congenital anomalies was 0.5% in women (N = 634) who continued metformin all through the first trimester and 0.6% in women (N = 517) who discontinued metformin after conception or confirmation of pregnancy. The unexpectedly low rate in exposed and unexposed pregnancies was surprising, given the oft-cited 2%–3% risk in the general population. Nevertheless, the absence of increased risk with metformin was reassuring.

Cassina et al[21] also identified 6 studies of birth defects following first-trimester exposure to metformin in women with T2DM. However, the data were insufficient for meta-analysis. A PubMed search conducted on March 2, 2016, using the search term *metformin* with *teratogenicity, malformation, "congenital abnormalities,"* and *"birth defects"* (separately), identified no new data on the subject published after December 2013, the end date of the search described by Cassina et al.[21]

Metformin and Pregnancy Complications in Women With PCOD

PCOD is associated with adverse pregnancy outcomes, including an increased risk of GDM, pregnancy-induced hypertension, preeclampsia, preterm birth, cesarean section, low birth weight, and neonatal intensive care admissions, relative to controls.[22] Zheng et al[23] described a systematic review and meta-analysis of 2 prospective randomized and 6 prospective nonrandomized controlled studies (pooled N = 1,106) that examined complications of pregnancy associated with metformin use all through gestation (regardless of initial time, dose, and use of other medications) in women with PCOD. Control women were normal pregnant women, or women with PCOD who received no treatment or placebo. Metformin was dosed at 1–3 g/d in these studies.

Zheng et al[23] found that metformin was associated with reduced odds of all of the 4 adverse pregnancy outcomes examined in the meta-analysis: early pregnancy loss (4 studies; OR = 0.32; 95% CI, 0.19–0.55), GDM (6 studies; OR = 0.37; 95% CI, 0.25–0.56), preeclampsia (4 studies; OR = 0.53; 95% CI, 0.30–0.95), and preterm delivery (4 studies; OR = 0.30; 95% CI, 0.13–0.68). The GDM and preeclampsia analyses were characterized by significant heterogeneity that was partly explained by study design (greater effect size in the nonrandomized studies).

A later meta-analysis[24] on the same subject omitted 3 of the studies included by Zheng et al[23] without specifying

the reason(s). This meta-analysis[24] found that metformin significantly reduced the risks of miscarriage and preterm birth, but not the risks of GDM and preeclampsia.

The benefits of metformin with regard to pregnancy complications associated with GDM have already been referred to in the introductory section of this article.

Metformin and Neurodevelopmental Outcomes

Tertti et al[25] used the Bayley Scales of Infant and Toddler Development (Bayley-III) and the Hammersmith Infant Neurological Examination to compare neurodevelopmental outcomes at age 2 years in the offspring of women with T2DM who had been randomly assigned to receive metformin or insulin during pregnancy. They found that there were no significant differences between the two groups (comprising 75 and 71 children, respectively) in cognitive development, receptive communication, expressive communication, fine motor development, or gross motor development, as assessed by the Bayley-III Scales. Global Hammersmith scores also did not differ significantly between groups. No child had a significant neurodevelopmental problem.

Wouldes et al[26] examined children of women who had been randomized at weeks 20–33 of gestation to receive either metformin or insulin for GDM; the sample comprised 108 and 133 evaluable children in the metformin and insulin groups, respectively. At age (approximately) 2.5 years, there were no significant differences between groups on the Bayley-II mental and psychomotor development indices. Bayley-II Behavior Rating Scale measures of orientation, emotional regulation, motor quality, and total score also did not differ significantly between the two groups.

Other studies have been similarly reassuring. For example, Glueck et al[27] found that in women with PCOD who conceived on and continued metformin (1.5–2.55 g/d) all through pregnancy, motor-social developmental scores at 3–18 months of age were 94%–98% of the Centers for Disease Control and Prevention infant norms. Ijäs et al[28] compared children of women with GDM who had been randomly assigned to receive either metformin (n = 47) or insulin (n = 50) during pregnancy; they found that clinically assessed motor, social, and linguistic development at age 18 months did not differ between the two groups.

Overall, the data seem to suggest that neurodevelopment outcomes at 1.5–2.5 years are as good after gestational exposure to metformin as after gestational exposure to insulin in women with T2DM or GDM.

Conclusions

The data reviewed in this article suggest that first-trimester exposure to metformin is not associated with an increased risk of birth defects; that continuation of metformin during pregnancy improves pregnancy outcomes in women with PCOD and GDM; that metformin is associated with benefits that are comparable with or better than those with insulin in mild GDM; and that exposure to metformin during pregnancy is not associated with poorer neurodevelopmental outcomes at age 1.5–2.5 years relative to exposure to insulin. These findings should be reassuring to women with neuropsychiatric conditions who may require metformin during pregnancy.

When applying the findings reviewed in this article, readers must be careful not to generalize beyond the contexts from which the findings were obtained. For example, if metformin improves pregnancy outcomes in PCOD, it need not necessarily improve these outcomes in schizophrenia patients who are receiving metformin to protect against weight gain and the risk of antipsychotic-related GDM.

The findings presented in this article are based on sample sizes that were mostly small to modest, and study designs that were not ideal for the formation of firm conclusions. However, the data are encouraging rather than discouraging and could guide shared decision-making in women who are receiving or may need metformin during pregnancy.

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