The use of metformin in reproductive medicine has exploded since clinical trials showed that a metabolic medication improved reproductive abnormalities in women with polycystic ovary syndrome (PCOS) (1). Metformin soon became an essential element for restoring ovulation (2), curing infertility (3), preventing pregnancy loss (4), and reducing pregnancy complications such as gestational diabetes mellitus (GDM), preeclampsia, and preterm labor, all of which were linked to insulin resistance and systemic inflammation in PCOS (5). Metformin lost the mantel of a medication, to be used judiciously for specific indications, and became instead a new vitamin, vitamin M, to be used ubiquitously to enhance every reproductive process in women with PCOS.

The study by Vanky et al. (6) should bring this practice, or at least the routine use of metformin during pregnancy in women with PCOS, to a halt. This landmark study showed that metformin initiated during the first trimester (at an average of 10 wk gestational age) and continued until delivery did not improve a composite outcome based on the integrated rates of preeclampsia, preterm delivery, and GDM. The overall rate of these complications was 25.9% in the metformin group and 24.4% in the placebo group (rate difference, 1.4%; 95% confidence interval, −8.9 to 11.3%) (6). The study did not note a statistically significant prevention of any of these outcomes individually with metformin use, although there are intriguing and contradictory trends toward metformin preventing preterm delivery but exacerbating preeclampsia. The authors merit special commendation for conducting this large study and reporting the results, which obliterates those from their previous pilot study demonstrating a remarkable benefit of metformin in preventing pregnancy complications in PCOS (5).

Rather than rest on their laurels and smugly reject the null hypothesis, the authors nested up to it and crafted a multicenter, double-blind, randomized, controlled trial to replicate and validate the results of their original trial.

They failed. Let’s first look at the original trial, which found that the women in the metformin group (n = 22) had no major complications (i.e. 0% rate), whereas the placebo group (n = 18) had seven major complications (i.e. an astounding 32% rate), including preterm delivery and a pulmonary embolus, but also rare pregnancy complications such as streptococcal sepsis and acute respiratory distress syndrome. Those results were both too good and too bad to be true in the larger population of the subsequent trial (n = 256 subjects) (6). Indeed, it is interesting to note that in this substantially larger trial almost all of the major maternal complications were now in the metformin group, including a pulmonary embolism, postpartum circulatory shock, and a peripartum cardiomyopathy. This suggests that these events in pregnant women with PCOS are not as frequent as expected and are most likely unrelated to metformin.

The strengths of this trial include the multicenter trial design by a consortium of academic health centers, the use of an identical active medication and placebo supplied by the manufacturer, the double-blinding, appropriate allocation concealment, the intention to treat analysis, the central data monitoring core, the limitation to singleton pregnancies to avoid the confounding effects of multiple pregnancy on the outcomes, the overall excellent retention in the study (dropout rates under 10% in both treatment arms), and the focus on outcomes of clear public health interest (preeclampsia, preterm labor, and GDM) (6). There is no study of metformin during pregnancy in women with PCOS that even comes close to this one in...
to prevent miscarriage or IV alcohol to treat preterm labor.

Nonetheless, there are still some limitations and minor flaws to the trial. One limitation, as the authors note, is that this was not a trial to prevent pregnancy loss, most of which occurs early in the first trimester. The subjects were randomized after evidence of a viable intrauterine pregnancy on ultrasound, mostly later in the first trimester. Therefore, this study was not designed to answer the question of the utility of metformin in preventing miscarriage, although a recent systematic review found preconceptional metformin had no benefits for preventing spontaneous abortion (7). Pundits can argue that metformin, like folic acid to prevent neural tube defects, needs to be given early in pregnancy (or preconception, although 30% of the subjects conceived on metformin), and not after the developmental period has passed, although this remains a hypothesis without clear mechanisms. One flaw of the current study is the use of the same subjects more than once (n = 17) because subjects were allowed to reenroll in subsequent pregnancies. Although this did not alter the results when repeat participations were excluded in a separate analysis, this form of double jeopardy clouds the analysis and interpretation of results and is likely related to slowing enrollment as the trial progressed.

Although the sample size is large, it is still relatively small for a trial powered to detect differences in major pregnancy complications. In other such trials, the total sample size can number in the thousands (8), with much greater power to avoid a type II error of failing to detect a difference in treatment outcomes. Even with the relatively smaller sample size in this trial, recruitment occurred more slowly than expected, and the investigators did not meet the goal of 300 subjects as listed in the clinical trials registration site (www.clinicaltrials.gov NCT00151411). The fact that medication was beginning to expire accelerated the decision to close enrollment. This declining enrollment, according to the authors, appears to have occurred because eligible subjects were already on metformin, and recruitment slowed accordingly during the last 18 months of the trial.

This is particularly disturbing, and it is not unique to this trial. An experimental intervention becomes the standard of care without evidence of its safety and efficacy. Can you say thalidomide or electronic fetal monitoring? One flaw of the current study is the use of the same subjects more than once (n = 17) because subjects were allowed to reenroll in subsequent pregnancies. Although this did not alter the results when repeat participations were excluded in a separate analysis, this form of double jeopardy clouds the analysis and interpretation of results and is likely related to slowing enrollment as the trial progressed.

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This is particularly disturbing, and it is not unique to this trial. An experimental intervention becomes the standard of care without evidence of its safety and efficacy. Can you say thalidomide or electronic fetal monitoring? Why do practitioners of reproductive medicine jump on the bandwagon before the horses are set or the band is ready to play? We certainly have enough devastating examples of harm or uselessness to mothers and fetuses from our interventions during pregnancy, be it diethylstilbestrol to prevent miscarriage or IV alcohol to treat preterm labor. Certainly these experiences have contributed to substantial ethical, legal, and institutional hurdles to avoid or prevent harmful interventions during pregnancy. Perhaps this milieu has fueled the fervor of a magic bullet to prevent major complications of pregnancy, according to some broad but unifying hypothesis of origin, such as oxidative stress or insulin resistance.

What conclusions, or more importantly, what future use can be made of the secondary analyses and post hoc analyses from this study? It is intriguing that metformin use was associated with a near significant reduction in absolute risk of preterm labor by 4.4% (95% confidence interval, −10.1 to 1.2), that reached significance (P = 0.03) in the prespecified subgroup analysis of patients with “good and acceptable compliance” with the drug therapy (6). In this admittedly select subgroup, this would represent a greater than 3-fold reduction in risk of preterm labor (to 2.8%, although the control rate was only 10%) (6). If this indeed would hold up in a larger trial, this could have significant public health benefit. Preterm delivery is the major cause of neonatal morbidity and mortality in developed countries, including the United States where it affects 8–10% of pregnancies (9). Its etiology and treatment remain problematic.

However, these findings must be balanced against that of a near significant trend toward increased preeclampsia with metformin, which lessened in the compliant subgroup analysis (6). Still, this result is perplexing because metformin tends to improve blood pressure in nonpregnant women with PCOS (10) and also because preeclampsia remains a major iatrogenic indication for preterm delivery, so the two events should go hand in hand, i.e. less preeclampsia and less preterm delivery. The antioxidant vitamins C and E unexpectedly required more treatment of hypertension, including hospitalization, in trials to prevent preeclampsia (11). Metformin has also been theorized to reduce oxidative stress (12). Alternatively, these findings may just involve events that hover around the cutoffs, with no major maternal or fetal morbidity because severe preeclampsia and early preterm delivery (i.e. less than 32 wk) were rare events in the study cohort. This is suggested by the mean normal birth weights, which didn’t differ between groups (3550 g with metformin vs. 3527 g with placebo).

Furthermore, it is a blow to the use of metformin during pregnancy to discover that there is no prevention of GDM and, based on the previous study, no effect on glucose levels during pregnancy (13). Can the same drug that prevents diabetes in men and women with impaired glucose tolerance (14), that has equivalent benefits in controlling glucose levels in women with GDM as insulin (15), have

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no benefit in preventing or reducing the existing prevalence (7.4% in the metformin group at baseline) of GDM (6)?

Perhaps this study cohort was overall a relatively healthy group of women with PCOS who had no real need for metformin. They had a low prevalence and conversion to GDM by the liberal World Health Organization GDM criteria (baseline rates would likely have been well under 5% based on the more stringent American College of Obstetrician and Gynecologist GDM criteria). There was a relative lack of obesity in the women at baseline (mean body mass index was less than 30 kg/m²), and by using the Rotterdam criteria for the diagnosis of PCOS (16), the study likely included less metabolically challenged patients (17). Therefore, the results may not be generalizable to other more obese, glucose-intolerant populations with PCOS such as are found in the United States (18).

Would it be worthwhile to consider a larger trial of metformin to specifically prevent preterm delivery in women with PCOS, or in obese women with or without stigmata of the metabolic syndrome? Obese women showed no particular benefit on metformin in subgroup analysis, although the more severely affected PCOS group (by “National Institutes of Health criteria”) did. The results of this study underscore previous studies showing that the risk/benefit ratio for metformin during pregnancy remains favorable and metformin is well tolerated (15). Women have side effects that are largely gastrointestinal-related without any clear predisposition to major adverse effects during pregnancy. Metformin has no known fetal teratogenicity and no known fetal harm, although it crosses the placenta readily, and it is unbound in serum (19). It remains Food and Drug Administration Category B during pregnancy. There is still plenty of room between alpha and omega for further trials of metformin during pregnancy in women with PCOS, and evidence-based medicine demands it.

However, if metformin is to be given during pregnancy, let it be given as a drug and not as a vitamin. The previous experiences with vitamin supplementation to prevent pre-eclampsia in at-risk populations could serve as an admonition (8, 11); these trials all failed to show a benefit, and some showed harm. Further narrowing of the criteria identifying pregnant women with PCOS likely to respond to the drug may benefit future trials. In the meantime while such experiments are conducted, take metformin off the vitamin rack of pregnancy and put it back in the research pharmacy.

Acknowledgments

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References


