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Citation

Stanford, Fatima C., Nasreen Alfaris, and Madhusmita Misra. "Metformin versus Placebo in Obese Pregnant Women without Diabetes." *N Engl J Med* 374 (2016): 434-43.

Published Version

doi:10.1056/NEJMc1603067

Permanent link

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Metformin versus Placebo in Obese Pregnant Women without Diabetes

TO THE EDITOR: Syngelaki et al. (Feb. 4 issue)¹ describe the efficacy of metformin in reducing gestational weight gain in women with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of more than 35. Although their study does not show a reduction in the neonatal birth weight, their results underscore the ability of metformin to reduce gestational weight gain in women with moderate-to-severe obesity without diabetes.

One question is whether the exclusion of patients who were started on insulin after the oral glucose-tolerance test would alter the results of the study. Another question is whether a larger sample size would result in significant results for the proportion of women with miscarriages, premature births, or live births across groups. Studies have shown that metformin is safe during pregnancy, with efficacy in treating gestational diabetes mellitus and the polycystic ovary syndrome, and that the drug has no effect on the growth of several cancers.^{2,3} It would be interesting if the authors of this and concurrent studies were to consider whether the use of metformin during pregnancy in women who are obese (BMI, >30) and those who are not obese (BMI, ≤30) would decrease weight retention after birth.^{1,4} Postpartum weight retention contributes to obesity in all weight classes, and the use of metformin would be an attractive option to reduce this risk.⁵

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1603067

TO THE EDITOR: Regarding the use of metformin in obese pregnant women without diabetes mellitus: the fetal period is a time during which exposure to drugs and chemicals that are normally not harmful may initiate processes that ultimately result in adult diseases. We do not have enough long-term data about adults who have had fetal exposure to metformin, which is an endocrine disrupter. It has been reported that exposure to metformin during fetal life is associated with increased rates of high blood pressure and hyperglycemia in children at the age of 8 years.¹ Tartarin et al. reported that metformin may have harmful effects on the human testis in fetal life.² We know that metformin reduces the levels of folate and vitamin B₁₂.³ Deficiencies in folate and vitamin B₁₂ may retard growth and brain development.⁴ Since we have safer options for the treatment of diabetes during pregnancy, we would be reluctant to use metformin in pregnant patients without diabetes. Until substantial benefits are proved, we believe it is better to recommend proper diet, exercise routines, and regular prenatal care without medication.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1603067

THE AUTHORS REPLY: In response to Stanford et al.: after the exclusion of patients receiving insulin, the median gestational weight gain among the women in our study was lower in the metformin group than in the placebo group (4.6 kg [interquartile range, 1.3 to 7.2] vs. 6.3 kg [interquartile range, 2.9 to 9.2], $P<0.001$). In an evaluation of changes in postpartum weight from the initial antenatal visit, the median gestational weight loss was higher in the metformin group than in the placebo group (1.9 kg [interquartile range, -5.1 to 0.2] vs. 0 kg [interquartile range, -3.9 to 1.5], $P=0.02$). We agree that metformin might reduce the risk of long-term obesity in these women.

In response to Sahin and Corapcioglu: the American Diabetes Association classifies metformin as a category B drug (i.e., no evidence of risk in humans) during pregnancy. In the United Kingdom, metformin is recommended by the National Institute for Health and Care Excellence.¹ There is no evidence of an increase in congenital malformations (including testicular abnormalities or defects in growth or motor development) in babies born to mothers treated with metformin.^{2,3} Blood-pressure results in a large cohort of 2-year-old children showed no differences between those whose mothers had received insulin and those whose mothers had

received metformin.⁴ Active B₁₂ (holotranscobalamin) and methylmalonic acid are better measures of vitamin B₁₂ status than are serum levels and do not appear to be pathologically altered in patients with type 2 diabetes after metformin treatment.⁵

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1603067

Transient Smartphone “Blindness”

TO THE EDITOR: Transient monocular vision loss is a common clinical presentation, and the cause is not always thromboembolic.¹ We present two cases in which careful history taking established a benign cause (for the case histories, see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

A 22-year-old woman presented with a several months' history of recurrent impaired vision in the right eye that occurred at night. The results of ophthalmic and cardiovascular examinations were normal. Vitamin A levels and the results of magnetic resonance angiography, echocardiography, and a thrombophilia screening were also normal.

The second case involved a 40-year-old woman

who presented with a 6-month history of recurrent monocular visual impairment on waking, lasting up to 15 minutes. The results of investigations for a vascular cause were again normal. Aspirin therapy had been commenced.

When the patients were seen in our neuro-ophthalmic clinic, detailed history taking revealed that symptoms occurred only after several minutes of viewing a smartphone screen, in the dark, while lying in bed (before going to sleep in the first case and after waking in the second). Both patients were asked to experiment and record their symptoms. They reported that the symptoms were always in the eye contralateral to the side on which the patient was lying.

We hypothesized that the symptoms were due