The effects of metformin on weight loss in women with gestational diabetes: a pilot randomized, placebo-controlled trial

Jerrie S. Refuerzo, MD; Oscar A. Viteri, MD; Maria Hutchinson, MS; Claudia Pedroza, PhD; Sean C. Blackwell, MD; Jon E. Tyson, MD, MPH; Susan M. Ramin, MD

OBJECTIVE: We sought to compare weight loss in the first 6 weeks postpartum among women with gestational diabetes mellitus (GDM) treated with metformin or placebo, a promising therapy to reduce later risk of progression to diabetes mellitus.

STUDY DESIGN: We conducted a pilot, randomized trial of metformin vs placebo in postpartum women with GDM. Women with pre-GDM, unable to tolerate metformin, resumed on insulin or oral hypoglycemic agent, delivered <34 weeks' gestation, or with a body mass index <20 kg/m^2 were excluded. Women were randomized to either metformin 850 mg daily for 7 days, then metformin 850 mg twice a day for the next 5 weeks or placebo prescribed in a similar frequency. The subject, health care provider, and research staff were blinded to the treatment. The primary outcome was weight change from delivery to 6 weeks postpartum. Secondary outcomes included the percentage of women achieving their self-reported prepregnancy weight, reported medication adherence, adverse effects, and satisfaction. Differences in weight change between groups were determined by Wilcoxon rank sum test and in achieving prepregnancy weight by χ^2 test.

RESULTS: Of 114 women randomized, 79 (69.3%) completed the 6 weeks; 36 (45.6%) were randomized to metformin and 43 (54.4%) to placebo. Metformin and placebo groups were similar in median weight loss (6.3 kg [range, −0.3 to 19.8] vs 6.5 kg [range, −0.3 to 12.1], $P = .988$) and percentage of women achieving reported prepregnancy weight (41.7 vs 37.2%, $P = .69$). Self-reported adherence in taking >50% of medication was 75% at 3 weeks and 97% at 6 weeks. Nausea, diarrhea, and hypoglycemia were reported in approximately 11-17% of women and 56-63% reported dissatisfaction with the medication.

CONCLUSION: Women with GDM lost approximately 6 kg by 6 weeks' postpartum. This was similar in both groups and resulted in <50% of women achieving their prepregnancy weight. Although the reported adherence and satisfaction with the medication was high, adverse effects were reported with nearly 1 in 5 women including nausea, diarrhea, and hypoglycemia. Contrary to expectation, we found no evidence of benefit from metformin. However, longer treatment periods and larger studies with minimal attrition may be warranted.

Key words: gestational diabetes, metformin, weight loss

Cite this article as: Refuerzo JS, Viteri OA, Hutchinson M, et al. The effects of metformin on weight loss in women with gestational diabetes: a pilot randomized, placebo-controlled trial. Am J Obstet Gynecol 2015;212:x.ex-x.ex.

Gestational diabetes mellitus (GDM) is carbohydrate intolerance first recognized in pregnancy.[1] After delivery, carbohydrate intolerance is expected to resolve gradually. Once a woman develops GDM, she remains at risk of recurrence in future pregnancies, and has a 7-fold risk of developing type 2 diabetes mellitus (DM) later in life.[2-4] Additionally, GDM develops in 14% of obese women.[5] Excessive gestational weight gain (EGWG) occurs in approximately 45% of obese pregnant women, many of whom have GDM, and has been linked to postpartum weight retention.[6] This

From the Division of Maternal Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences (Drs Refuerzo, Viteri, and Blackwell and Ms Hutchinson), and Center for Clinical Research and Evidence-Based Medicine, Division of Neonatology, Department of Pediatrics (Drs Pedroza and Tyson), University of Texas Health Science Center at Houston, and Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine (Dr Ramin), Houston, TX.

Received Aug. 15, 2014; accepted Dec. 15, 2014.

This research was supported by the Center for Clinical and Translational Sciences, which is funded by National Institutes of Health Clinical and Translational Award number UL1 000371 from the National Center for Advancing Translational Research, and by the Larry C. Gilstrap, MD, Center for Perinatal and Women's Health Research, University of Texas Health Science Center at Houston (both to J.S.R.).

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Research or the National Institutes of Health.

The authors report no conflict of interest.

Presented in oral format at the 81st annual meeting of the Central Association of Obstetricians and Gynecologists, Albuquerque, NM, Oct. 8-11, 2014.

Corresponding author: Jerrie S. Refuerzo, MD. Jerrie.S.Refuerzo@uth.tmc.edu

0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2014.12.019

fuels the progression of obesity even after pregnancy ends and, as a result, places these women at further risk of developing type 2 DM.[7]

Weight loss is a key element associated with preventing the onset of diabetes.[8-10] Every 1 kg lost is associated with a 16% reduction in diabetes risk.[8] Lifestyle modifications focused on nutrition and exercise are first-line therapies for prevention and control of type 2 DM in obese, nonpregnant women.[11,12] Though weight loss is recommended after delivery, behavioral alterations are difficult postpartum when mothers have the onset of responsibilities to a newborn. Though good intentions are present, realistic circumstances may fall short of expectations and many cease these behavioral modifications over time. With the failure to reduce postpartum weight gain in multiple randomized trials, the evaluation of new strategies, including medications, is needed.[11]

Metformin is an insulin-sensitizing medication. It functions to improve insulin sensitivity by reducing fasting plasma glucose and insulin concentrations. Importantly, it has been shown to be beneficial in reducing weight.[13,14] However, the true mechanism by which this insulin sensitizer results in weight loss is not fully known. Weight loss is a natural physiologic occurrence in the postpartum period including water loss and adipose tissue. Enhancement of this natural weight loss represents an opportunity for obstetricians to intervene and halt the progression towards persistent obesity. We considered that metformin could act in conjunction with the physiologic weight loss unique to the postpartum period to accentuate the inherent descending slope of weight. Moreover, postpartum women accustomed to taking oral medications, such as prenatal vitamins, would find the concept of an oral daily medication for the purpose of weight loss appealing and be compliant with this medical treatment. If weight loss were enhanced, this could blunt the progression of obesity and potentially avoid the development of type 2 DM later in life in this high-risk group. Our objective was to conduct a pilot study to assess whether metformin increased postpartum weight loss compared to placebo among women with GDM.

Materials and Methods

Study design

We conducted a pilot randomized, placebo-controlled trial of metformin vs placebo from January 2011 through January 2014, at the Memorial Hermann Hospital-Texas Medical Center and Lyndon B. Johnson Hospital in Houston, TX. On the postpartum ward, women with GDM were invited to participate within 24 hours of delivery and prior to discharge. Women were excluded if they had pre-GDM (either type 1 or 2 DM), reported inability to tolerate metformin, discharged home on insulin or oral hypoglycemic agent, delivered <34 weeks of pregnancy, were <18 or >49 years old, or had a body mass index (BMI) <20 kg/m^2. The diagnosis of GDM (treated with insulin, oral hypoglycemic agent, or diet control) was made >24 weeks based on a documented 1-hour glucola screen >200 mg/dL or by a confirmatory 3-hour glucola test (based on either the Carpenter and Coustan or the Diabetes Task Force criteria).[1]

Informed consent and randomization

This study was approved by the institutional review board at University of Texas Health, Houston, TX (no. HSC-MS-10-0426, approved October 2010). After reviewing the potential benefits, risks, and adverse effects of the medication and placebo, written informed consent was obtained. Subjects were randomized to either metformin or placebo via central randomization conducted by the Investigational Drug Service (IDS) pharmacy at Memorial Hermann Hospital-Texas Medical Center and stratified by site. Permuted block randomization with a random fashion was used to prevent imbalances between groups. The subject, health care provider, research staff, and statistician were blinded to the treatment group. Only the IDS pharmacy knew the treatment group. The randomization scheme was unmasked after completion of the analysis.

Study procedures

Prior to discharge, the subject was started on either metformin or placebo. The metformin dose was 850 mg daily for 7 days, then 850 mg twice a day for the next 5 weeks. The placebo was similar in size, color, and taste, and prescribed in a similar frequency: once daily for 7 days, then twice daily for the next 5 weeks for a total of 6 weeks. The metformin and placebo were compounded by a licensed compounding pharmacy and monitored on a routine schedule for quality assurance and potency of the drugs by the IDS. The subject received the medication or placebo in prefilled push cards designating the regimen for subject convenience. There were no drop-in, drop-out, or crossover of subjects.

Within 24 hours of delivery, maternal weight was measured using a single specified digital weight scale (did not require calibration) on a hard surface at each site. A research nurse counseled all participants regarding their diet and provided a simple exercise plan of walking a minimum of 30 minutes, 3-5 times a week.[15,16] Maternal demographics, clinical characteristics, and neonatal outcomes were collected. At 3 weeks postpartum (range, 2–4 weeks), a research nurse contacted the subject via telephone to inquire about adverse effects and ability to take the prescribed medication (metformin or placebo). At 6 weeks postpartum (range, 5–8 weeks), maternal weight was measured with the same digital weight scale used for the initial maternal postpartum weight. The research nurse again inquired about adverse effects and conducted a satisfaction survey.

Study outcomes

The primary outcome was weight change in kilograms defined as: weight change = $\text{Weight}_{\text{postpartum(PP)}}$-$\text{Weight}_{\text{6wk}}$.[17] Secondary outcomes included the rate of retained gestational weight represented as the percentage of women achieving their self-reported prepregnancy weight and percentage of women achieving their ideal body weight. Demographic, pregnancy characteristics, self-reported medication adherence, and adverse