Impact of aspirin on fetal growth in diabetic pregnancies according to White classification

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BACKGROUND: Current US Preventive Services Task Force and other guidelines recommend low-dose aspirin for all pregnant women with pregestational diabetes mellitus to prevent preeclampsia and small-for-gestational-age birth. The Maternal-Fetal Medicine Units High-Risk Aspirin trial did not show a reduction in either preeclampsia or small-for-gestational-age birth in diabetic women.

OBJECTIVE: Our objective was to reassess the impact of aspirin on fetal growth in diabetic pregnancies overall and according to White classification. We hypothesized that aspirin improves fetal growth in pregnancies with vascular complications of diabetes at highest risk for poor fetal growth.

STUDY DESIGN: We conducted secondary analysis of the cohort of diabetic women enrolled in the Maternal-Fetal Medicine Units High-Risk Aspirin trial. The impact of aspirin prophylaxis on birthweight was assessed in the overall cohort and in 2 groups categorized according to White classification as nonvascular (White class B, C, D) or vascular (White class R, F, RF). Birthweight was converted to Z-score normalized for gestational age at delivery and neonatal sex. Difference in birthweight Z-score between aspirin and placebo was tested with a 2-sample *t* test. The effect of vascular group, aspirin vs placebo randomization, and the interaction of the 2 on normalized birthweight percentile was estimated with linear regression with a multivariable model including covariates body mass index, tobacco use, race, and parity. The percentage of small and large-for-gestational-age newborns born to aspirin- vs placebo-treated women was compared between groups using Pearson exact χ^2 analysis, and an adjusted model was estimated by logistic regression.

RESULTS: All 444 women with pregestational diabetes and complete outcome data were included (53 vascular, 391 nonvascular). Aspirin was significantly associated with a higher birthweight Z-score (0.283; 95% confidence interval, 0.023—0.544) in the overall cohort ($P = .03$). In the adjusted model, the association of aspirin with higher birthweight Z-score was confined to neonates of women with nonvascular diabetes (0.341; 95% confidence interval, 0.677—0.006; $P = .044$). An opposite but nonsignificant effect was observed among neonates from women with vascular diabetes (—0.416; 95% confidence interval, —1.335 to 0.503; $P = .6$). This difference in the relationship of aspirin and birthweight Z-score by vascular group was significant at $P = .046$. Aspirin-randomized women with nonvascular diabetes had more large-for-gestational-age births than those treated with placebo (40.2 vs 26.6%; $P = .005$). Small-for-gestational-age births occurred at the same frequency with aspirin vs placebo randomization in the overall cohort (8% in each group) and in each vascular group.

CONCLUSION: Inconsistent with our hypothesis, aspirin did not reduce small-for-gestational-age births in the overall cohort or either group. The increased incidence of large-for-gestational-age infants in aspirin-treated diabetic gestations is of potential concern given the known increased maternal and neonatal morbidity associated with macrosomia.

Key words: aspirin, diabetes, fetal growth, large for gestational age, macrosomia

Introduction

In late 2014, the US Preventive Services Task Force (USPSTF) recommended that low-dose aspirin (60-150 mg/d) be administered to all pregnant women with pregestational type 1 or type 2 diabetes in an effort to reduce the incidence of preeclampsia.[1] Additional proposed benefits of aspirin administration are reductions in preterm birth and small-for-gestational-age (SGA) birth. These USPSTF recommendations are in agreement with previously published guidelines from the World Health Organization (WHO)[2] and the National Institute for Health and Care Excellence,[3] both of which also specifically recommend aspirin for pregnant women with pregestational diabetes (PGDM). The American Congress of Obstetricians and Gynecologists endorsed these guidelines in 2016.[4]

PGDM is a known risk factor for preeclampsia.[5] The impact of PGDM on fetal growth is more complex and relates to White classification. For example, in a recent report, patients with vascular complications (White classifications R, F, RF, and H) were at increased risk for SGA births (17%), while those with White classification B, C, and D had increased rates of large-for-gestational-age (LGA) newborns (34%, 28%, and 21%, respectively).[6]

While aspirin may reduce the risk of SGA in pregnancies at risk for preeclampsia in general, the impact of aspirin on fetal growth in diabetic pregnancies is not well understood. Of the 13 studies that formed the basis of the USPSTF conclusion that aspirin reduces SGA, only the Maternal-Fetal Medicine Units (MFMU) High-Risk Aspirin (HRA) trial enrolled women with PGDM.[7] In this trial, aspirin was of no benefit in reducing either preeclampsia or SGA. Most other trials explicitly excluded women with PGDM.

To better understand the possible impact of aspirin on fetal growth in patients with PGDM, we performed a secondary analysis of the MFMU HRA trial. Our hypothesis was that aspirin

Cite this article as: Adkins K, Allshouse AA, Metz TD, et al. Impact of aspirin on fetal growth in diabetic pregnancies according to White classification. Am J Obstet Gynecol 2017;volume:x.ex-x.ex.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2017.05.062

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would reduce the risk of SGA in women with vascular complications of diabetes.

Materials and Methods

We performed a secondary analysis of the MFMU Network randomized controlled trial of aspirin (60 mg) for the prevention of preeclampsia in high-risk women.[7] The original inclusion criteria were pregnancies with at least 1 risk factor for preeclampsia: preexisting insulin-dependent diabetes, chronic hypertension, multiple gestation, or preeclampsia in a previous pregnancy. Women were enrolled into 1 of 4 mutually exclusive high-risk groups defined as: (1) diabetes (with or without prior preeclampsia or chronic hypertension), (2) chronic hypertension (with or without prior preeclampsia), (3) multifetal gestation (with or without prior preeclampsia), and (4) previous preeclampsia (and no other risk factor). The protocol received institutional review board approval at each center, and all participating women provided written informed consent. This secondary analysis was considered exempt by the Colorado Multiple Institutional Review Board.

Full details of the study design are available in the original article. Briefly, enrollment of eligible women occurred in the calendar years 1991 through 1995 during the 13th through 26th week of pregnancy. Women were randomized 1:1 to receive aspirin (60 mg) or placebo in a double-blind, randomized, placebo-controlled trial design to assess the impact of aspirin on the incidence of preeclampsia. Adherence to study drug regimen was measured by questioning of women, counting pills, and measuring thromboxane in serum.

For this analysis, we included all women in the MFMU HRA study with PGDM for whom complete outcome data were available. Women with PGDM and chronic hypertension were class D in accordance with the revised White classification.[8]

Women were assigned to 1 of 2 mutually exclusive vascular groups: nonvascular (White class B, C, D) or vascular (White class R, F, RF). We used a previously published algorithm for transforming birthweight into a normalized Z-score for gestational age at delivery and neonatal sex.[9] From Z-scores, neonates were categorized as SGA, average for gestational age, or LGA.

Body mass index (BMI) calculated from prepregnancy weight was categorized according to WHO classifications with <18.5 kg/m^2 underweight, 18.5-24.9 kg/m^2 normal, 25.0-29.9 kg/m^2 overweight, and ≥ 30 kg/m^2 obese. For some analyses, underweight and normal BMI categories were combined because of the low frequency of women categorized as underweight.

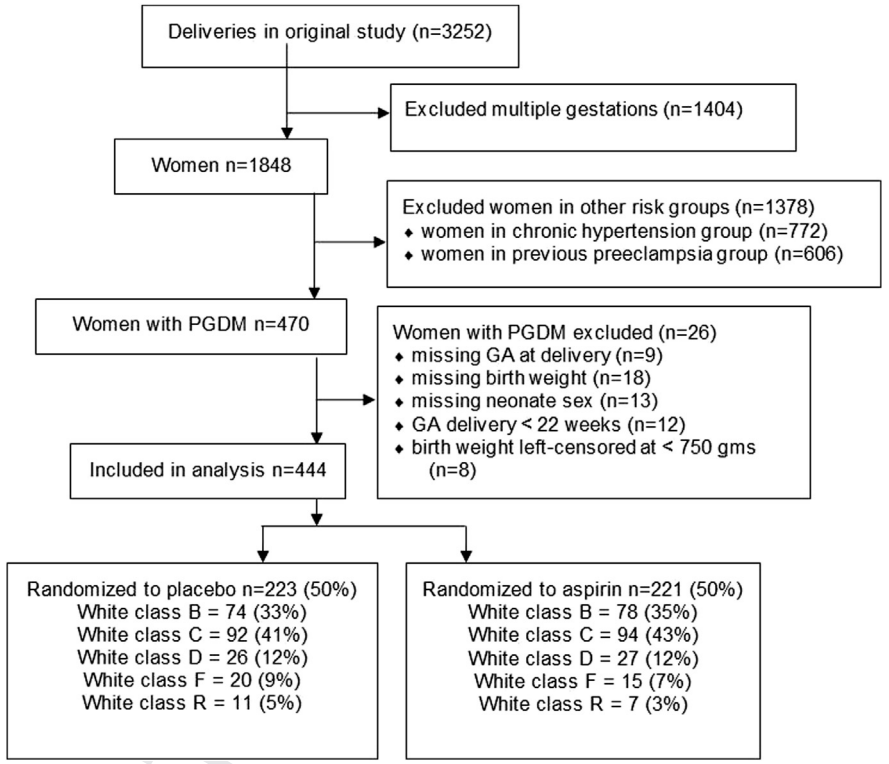
Statistical Methods

The success of randomization within this study population was assessed by comparing demographics between placebo- and aspirin-randomized women, with differences tested using χ^2 for categorical and 2-sample t tests for continuous measures.

The effect of vascular group, aspirin vs placebo randomization, and the interaction of the 2 on normalized birthweight percentile was estimated using linear regression with a multivariable model including covariates expected to impact birthweight based on clinical judgement: BMI category, tobacco use, race, and parity. The interaction of vascular group and randomization was parameterized as part of our primary hypothesis.

The percentage of SGA and LGA newborns born to aspirin- vs placebo-treated women was compared between groups using Pearson exact χ^2 analysis, and a logistic regression model was estimated to adjust for covariates expected to impact birthweight based on clinical judgement: maternal BMI category, smoking, race, and parity. The adjusted estimates for the overall cohort include vascular group as a

FIGURE 1



Patient selection from Maternal-Fetal Medicine Units High-Risk Aspirin trial. Q3

GA, gestational age; *PGDM*, pregestational diabetes.

Adkins et al. Aspirin and fetal growth in diabetic pregnancies. Am J Obstet Gynecol 2017.

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