

sFlt-1:PlGF ratio normal at 24 to 28 weeks: Discontinue aspirin for preterm preeclampsia prevention?

No, discontinuation of aspirin at 24 to 28 weeks' gestation for women who initiated aspirin in the first trimester due to a high risk for preterm preeclampsia should not be universally adopted just yet. Although noninferiority of this practice was demonstrated in a multicenter randomized trial that included data from 936 participants, this extremely limited study population may not represent the full scope of patients who benefit from varying degrees and doses of aspirin exposure in pregnancy.

Mendoza M, Bonacina E, Garcia-Manau P, et al. Aspirin discontinuation at 24 to 28 weeks' gestation in pregnancies at high risk of preterm preeclampsia: a randomized clinical trial. JAMA. 2023;329:542-550. doi:10.1001/jama.2023.0691.

EXPERT COMMENTARY

Jaimey M. Pauli, MD, is Professor, Department of Obstetrics and Gynecology; Chief, Division of Maternal-Fetal Medicine, Pennsylvania State College of Medicine, Milton S. Hershey Medical Center, Hershey, Pennsylvania. She serves on the OBG MANAGEMENT Board of Editors.

Aspirin is, to date, the only proven preventative treatment to reduce the risk of preeclampsia in pregnancy. While aspirin initiation, optimally prior to 16 weeks, generally is accepted, the best timing for discontinuation remains uncertain due to conflicting data on risk of bleeding and different doses used. The American College of Obstetricians and Gynecologists recommends a broad range of patients

eligible for low-dose aspirin with continuation through delivery, citing data that support no increase in either maternal or fetal/neonatal complications, including bleeding complications.¹ Other guidelines recommend reduction in pregnancy exposure to aspirin with strict guidelines for which patients are considered “high risk” as well as discontinuation at 36 weeks prior to labor onset to reduce the risk of potential bleeding complications.

Recently, Mendoza and colleagues tested the hypothesis that, in patients at high risk for preterm preeclampsia (based on high-risk first-trimester screening followed by a low risk of preeclampsia at 24 to 28 weeks based on a normal sFlt-1:PlGF [soluble fms-like tyrosine kinase-1 to placental growth factor] ratio), discontinuing aspirin is noninferior in preventing preterm preeclampsia compared with continuing aspirin until 36 weeks.²

Details of the study

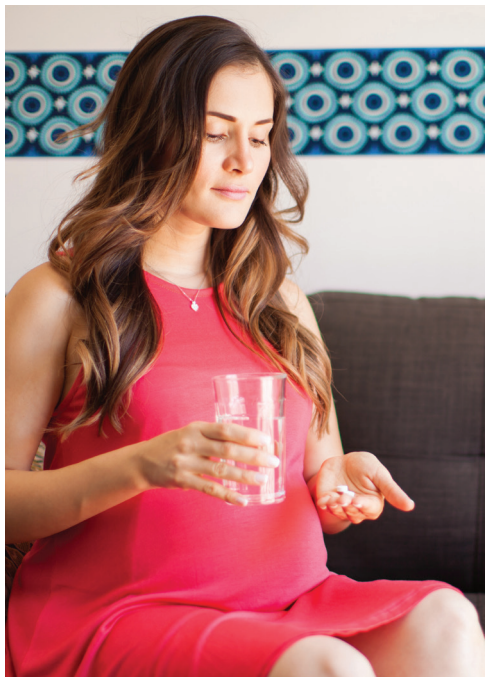
Mendoza and colleagues conducted a multicenter, open label, randomized,

FAST TRACK

Aspirin is, to date, the only proven preventative treatment to reduce the risk of preeclampsia in pregnancy

The author reports no financial relationships relevant to this article.

doi: 10.12788/obgm.0278



FAST TRACK

For the primary outcome, the incidence of preeclampsia at less than 37 weeks was 1.48% in the intervention group and 1.73% in the control group (absolute difference, -0.25%, which meets study criteria for noninferiority)

phase 3, noninferiority trial that randomly assigned 968 participants prior to stopping recruitment based on the findings from a planned interim analysis.²

The patient population included women with singleton pregnancies between 24 and 28 weeks who had initiated aspirin 150 mg daily by 16 6/7 weeks due to high-risk first-trimester screening for preterm preeclampsia. Additionally, these patients also had an sFlt-1:PlGF ratio of 38 or less between 24 and 28 weeks' gestation, which prior studies have demonstrated to exclude the diagnosis of preeclampsia.

Patients were randomly assigned to either discontinue aspirin at 24 to 28 weeks' gestation (intervention group) or continue aspirin until 36 weeks' gestation (control group). The primary outcome was delivery due to preeclampsia at less than 37 weeks, with secondary outcomes of preeclampsia at less than 34 weeks, preeclampsia at 37 or more weeks, or other adverse pregnancy outcomes.

Results. For the primary outcome (936 participants' data analyzed), the incidence of preeclampsia at less than 37 weeks was 1.48% in the intervention group and 1.73% in the control group (absolute

difference, -0.25%, which meets study criteria for noninferiority).

No difference occurred in the secondary outcomes of adverse outcomes at less than 34 weeks or at less than 37 weeks. While there was no difference in the incidence of the individual adverse outcomes at 37 or more weeks, the intervention group had a decrease in the incidence of having "any" adverse outcome (-5.04%) as well as a decrease in minor antepartum hemorrhage (nose and/or gum bleeding) (-4.7%).

The authors therefore concluded that aspirin discontinuation at 24 to 28 weeks' gestation in pregnant patients at high risk for preterm preeclampsia and a normal sFlt-1:PlGF ratio is noninferior to aspirin continuation for prevention of preterm preeclampsia. They also suggested that this discontinuation may reduce the risk of adverse pregnancy outcomes at 37 or more weeks as well as minor bleeding complications.

Study strengths and limitations

The authors cited the novelty of this study at considering using aspirin for the prevention of preterm preeclampsia in a specific patient group for the shortest amount of time needed to achieve this goal. Potential benefits could be decreased bleeding complications, cost, anxiety, and visits.

They also noted the following study limitations: open-label design, a predominantly White patient population, early termination due to the interim analysis, inadequate power for more rare complications, and a query as to the appropriate choice for the threshold for noninferiority. Noninferiority trials have inherent weaknesses as a group that should be considered before major practice changes occur as a result of their findings.

Several other factors in the study limit the generalizability of the authors' recommendations, especially to patient populations in the United States. For example, the study used an aspirin dose of 150 mg daily, which is almost double the dose recommended in the United States (81 mg). The reasoning for this was that doses higher than 100 mg have been shown to be the most

CONTINUED ON PAGE 49

effective for preeclampsia prevention but also may have higher rates of bleeding complications, including placental abruption. The demonstrated increase in complications may not hold at a lower dose.

Additionally, patients in this study were selected for aspirin by a first-trimester algorithm that may not be in general use everywhere (and differs from the US Preventive Services Task Force recommendations for low-dose aspirin use in pregnancy). Finally, although extremely interesting, the use of the sFlt-1:PIFG ratio at 24 to 28 weeks is not in widespread use in the United States and may incur an additional cost not equivalent to the low cost of a daily aspirin.

Essentially, this is an extremely limited study for a very specific population. Before globally discontinuing low-dose aspirin in high-risk patients, the different doses and eligibility criteria should be studied for effect of early discontinuation. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Low-dose aspirin should continue to be used for prevention of preeclampsia in high-risk pregnant patients, optimally starting at 12 to 16 weeks' gestation and continuing either through 36 weeks or delivery. Further study is needed to determine the optimal timing for earlier discontinuation of aspirin based on dose, risk factors, and other measures of preeclampsia risk as the pregnancy progresses.

JAIMEY M. PAULI, MD

References

1. ACOG committee opinion no. 743: low-dose aspirin use during pregnancy. *Obstet Gynecol.* 2018;132:e44-e52. doi:10.1097/AOG.0000000000002708.
2. Mendoza M, Bonacina E, Garcia-Manau P, et al. Aspirin discontinuation at 24 to 28 weeks' gestation in pregnancies at high risk of preterm preeclampsia: a randomized clinical trial. *JAMA.* 2023;329:542-550. doi:10.1001/jama.2023.0691.