

Aspirin Discontinuation at 24 to 28 Weeks' Gestation in Pregnancies at High Risk of Preterm Preeclampsia

A Randomized Clinical Trial

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IMPORTANCE Aspirin reduces the incidence of preterm preeclampsia by 62% in pregnant individuals at high risk of preeclampsia. However, aspirin might be associated with an increased risk of peripartum bleeding, which could be mitigated by discontinuing aspirin before term (37 weeks of gestation) and by an accurate selection of individuals at higher risk of preeclampsia in the first trimester of pregnancy.

OBJECTIVE To determine whether aspirin discontinuation in pregnant individuals with normal soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1:PlGF) ratio between 24 and 28 weeks of gestation was noninferior to aspirin continuation to prevent preterm preeclampsia.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, open-label, randomized, phase 3, noninferiority trial conducted in 9 maternity hospitals across Spain. Pregnant individuals (n = 968) at high risk of preeclampsia during the first-trimester screening and an sFlt-1:PlGF ratio of 38 or less at 24 to 28 weeks of gestation were recruited between August 20, 2019, and September 15, 2021; of those, 936 were analyzed (intervention: n = 473; control: n = 463). Follow-up was until delivery for all participants.

INTERVENTIONS Enrolled patients were randomly assigned in a 1:1 ratio to aspirin discontinuation (intervention group) or aspirin continuation until 36 weeks of gestation (control group).

MAIN OUTCOMES AND MEASURES Noninferiority was met if the higher 95% CI for the difference in preterm preeclampsia incidences between groups was less than 1.9%.

RESULTS Among the 936 participants, the mean (SD) age was 32.4 (5.8) years; 3.4% were Black and 93% were White. The incidence of preterm preeclampsia was 1.48% (7/473) in the intervention group and 1.73% (8/463) in the control group (absolute difference, -0.25% [95% CI, -1.86% to 1.36%]), indicating noninferiority.

CONCLUSIONS AND RELEVANCE Aspirin discontinuation at 24 to 28 weeks of gestation was noninferior to aspirin continuation for preventing preterm preeclampsia in pregnant individuals at high risk of preeclampsia and a normal sFlt-1:PlGF ratio.

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[+ Visual Abstract](#)

[← Editorial page 539](#)

[+ Supplemental content](#)

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Preeclampsia is a serious multisystem disorder that complicates 2% to 4% of pregnancies and is responsible for more than 70 000 maternal deaths and 500 000 fetal deaths worldwide every year.^{1,2} It is typically characterized by the development of hypertension and proteinuria after 20 weeks of gestation^{3,4} and can be classified according to gestational age at delivery as early-onset preeclampsia (with delivery at <34 weeks of gestation), preterm preeclampsia (with delivery at <37 weeks of gestation), and term preeclampsia (with delivery at ≥37 weeks of gestation).^{4,5} Complications associated with preeclampsia include preterm birth, fetal growth restriction, placental abruption, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, seizures (eclampsia), and other end organ damage (acute kidney injury, stroke, myocardial infarction, pulmonary edema, retinal detachment, and hepatic dysfunction), especially with onset at earlier gestational ages.⁴

Aspirin has been proven to reduce the incidence of preterm preeclampsia by 62%.⁶ Although the exact etiology of preeclampsia is unknown, aspirin inactivates the cyclooxygenase-1 enzyme, suppressing the production of prostaglandins and thromboxane. This results in an inhibition of the oxidative stress and inflammation and platelet aggregation, as well as promotes trophoblast invasion, spiral arteries remodeling, and development of chorionic villi, a phenomenon that mainly occurs during the first trimester of pregnancy and is completed by 20 weeks of gestation.⁷⁻¹⁰ This may explain why prevention of preeclampsia with aspirin is most effective when aspirin is initiated between 11 weeks 0 days and 16 weeks 6 days of gestation.¹¹

Identification of high-risk cases at 11 to 13 weeks of gestation may be based on multivariable models that combine data on maternal characteristics and medical history with various biophysical and biochemical measurements, and can identify 60% of pregnant individuals who will develop preterm preeclampsia.¹²⁻¹⁵ First-trimester preeclampsia screening (11 to 13 weeks of gestation) allows initiation of aspirin (150 mg per day) before 16 weeks of gestation until 36 weeks of gestation. Aspirin may be associated with an increased risk of peripartum bleeding,^{16,17} which could be mitigated by discontinuing aspirin earlier.

Increased soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1:PlGF) ratio due to uteroplacental ischemia is associated with the occurrence of preeclampsia several weeks before its clinical onset.¹⁸ An sFlt-1:PlGF cutoff value of 38 or less has been proven to accurately exclude preeclampsia in pregnant individuals with suspected disease between 24 weeks 0 days to 36 weeks 6 days of gestation.¹⁹ A small nested case-control study conducted with pregnant individuals at high risk of preeclampsia showed that a normal sFlt-1:PlGF ratio between 26 and 28 weeks of gestation had a 100% negative predictive value for excluding early-onset preeclampsia.²⁰

The Detection of False Positives From First-trimester Preeclampsia Screening at the Second-trimester of Pregnancy (StopPRE) Trial was designed to test the hypothesis that discontinuing aspirin in pregnancies at high risk of preterm preeclampsia in the first trimester and with an sFlt-1:PlGF ratio of 38 or less between 24 weeks 0 days and 27 weeks 6 days of

Key Points

Question Among individuals taking aspirin to prevent preterm preeclampsia, can aspirin be discontinued at 24 to 28 weeks of gestation when the soluble fms-like tyrosine kinase-1 to placental growth factor (sFlt-1:PlGF) ratio is normal?

Findings In this randomized trial, incidence of preterm preeclampsia was 1.48% in the intervention group and 1.73% in the control group (absolute difference, -0.25%), indicating noninferiority.

Meaning Aspirin discontinuation at 24 to 28 weeks of gestation is noninferior to aspirin continuation for preventing preterm preeclampsia in individuals at high risk of preeclampsia and a normal sFlt-1:PlGF ratio.

gestation is noninferior to prevent preterm preeclampsia as compared with a control group treated with aspirin until 36 weeks of gestation.

Methods

Study Design and Participants

This multicenter, open-label, randomized, phase 3, noninferiority trial was conducted at 9 maternity hospitals across Spain. Inclusion criteria at randomization were as follows: maternal age of 18 years or older, singleton pregnancy, alive fetus, gestational age between 24 and 28 weeks (24 weeks 0 days to 27 weeks 6 days) of gestation, high risk of preterm preeclampsia (≥1/170) in the first-trimester screening (11 to 13 weeks of gestation) according to the screening algorithm,²¹ aspirin treatment with a dose of 150 mg per day initiated at 16 weeks 6 days of gestation or less until randomization with an adherence of at least 50%,²² and an sFlt-1:PlGF ratio of 38 or less between 24 and 28 weeks of gestation. Race and ethnicity were self-reported by participants from predefined categories; these data were collected because Black and South Asian pregnant individuals have a higher risk of preeclampsia. Exclusion criteria are listed in [Supplement 1](#).

The trial protocol ([Supplement 1](#)) was approved by the institutional review board at each trial center (EudraCT: 2018-000811-26) and by the Spanish Agency for Medicines and Medical Devices (AEMPS). Participants provided written consent.

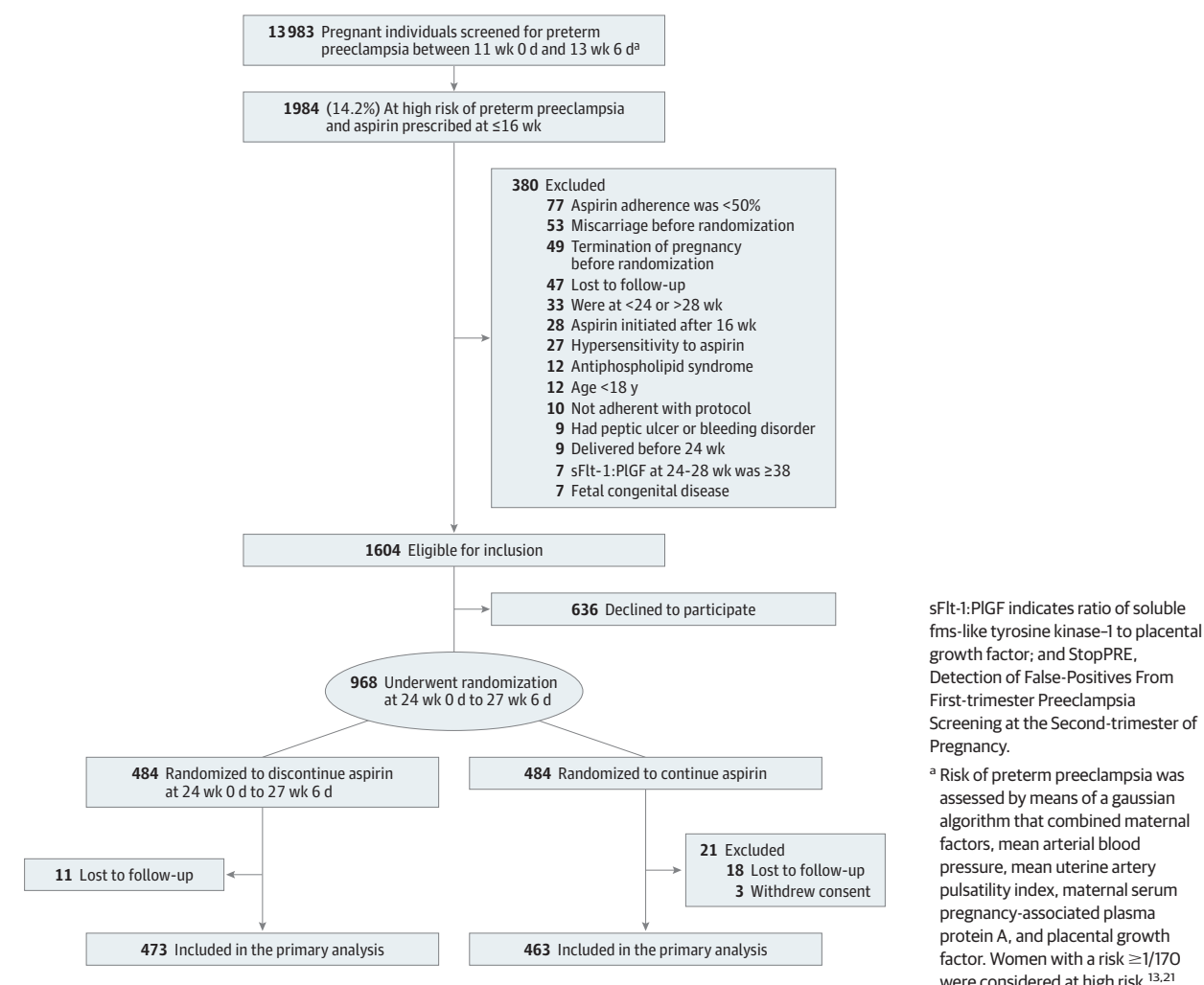
Randomization and Masking

Between 24 and 28 weeks of gestation, participants were randomly assigned, in a 1:1 ratio, to either continue aspirin treatment (control group) or discontinue aspirin treatment (intervention group) ([Figure 1](#)), with the use of REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vall d'Hebron Institut de Recerca.²³ REDCap is a secured, web-based software platform for building and managing online databases.

Procedures

Gestational age was confirmed by fetal crown-rump length measurements.²⁴ All pregnant individuals who had a prenatal visit between 11 weeks 0 days of gestation and 13 weeks

Figure 1. Screening, Randomization, and Follow-up in the StopPRE Trial



6 days of gestation were routinely screened for preterm preeclampsia.¹³ The risk of preterm preeclampsia was assessed by means of a gaussian algorithm that combined maternal factors (age, body mass index, race and ethnicity, parity, and history of chronic hypertension, diabetes, and preeclampsia in a previous pregnancy), mean arterial blood pressure, mean uterine artery pulsatility index,^{25,26} maternal serum pregnancy-associated plasma protein A, and placental growth factor.^{11,24} All participants with singleton pregnancies who were at high risk of preterm preeclampsia ($\geq 1/170$) were treated with aspirin, 150 mg per day, from the time of risk assessment until randomization.

Eligibility for aspirin discontinuation was restricted to those participants at high risk of preterm preeclampsia in the first trimester and an sFlt-1:PlGF ratio of 38 or less between 24 and 28 weeks of gestation. In pregnant individuals assigned to the intervention group, aspirin was discontinued following randomization. In both groups, participants had visits every 4 weeks between randomization and 36 weeks of gestation and weekly after 37 weeks of gestation until delivery. In the 3 visits before 37 weeks of gestation, treatment adherence was veri-

fied by patient self-report and tablet count, and fetal growth and Doppler were assessed by ultrasound. Cardiocotography for fetal assessment was performed in all visits at 37 weeks of gestation or more (eFigure 1 in Supplement 2).

Outcomes

The primary outcome measure was delivery due to preeclampsia before 37 weeks of gestation (preterm preeclampsia). Preeclampsia was defined as new onset of high blood pressure (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) or worsening of previous high blood pressure, in addition to new-onset proteinuria (protein to creatinine ratio >300) or worsening of previous proteinuria, or at least 1 of the following signs and symptoms: cerebral or visual disturbances, elevation of liver enzymes to twice normal concentration, platelet count less than 100 000/ μ L, serum creatinine concentrations greater than 1.1 mg/dL (to convert to μ mol/L, multiply by 88.4), or pulmonary edema.⁴

Secondary outcomes included preeclampsia before 34 weeks of gestation, preeclampsia at or after 37 weeks of gestation, and the presence of any other adverse pregnancy

outcome such as gestational hypertension, small for gestational age (birth weight below the 10th percentile),²⁷ very low birth weight (below the third percentile),²⁷ stillbirth, placental abruption, spontaneous delivery without preeclampsia, neonatal intraventricular hemorrhage of grade II or more, maternal intracranial hemorrhage, postpartum hemorrhage, minor antepartum bleeding complications (nose and/or gum bleeding), major antepartum bleeding complications (hemoptysis, digestive and/or vaginal bleeding), neonatal sepsis, neonatal anemia, necrotizing enterocolitis, ventilation or intubation, and neonatal death. Additional secondary outcomes are shown in eTable 1 in [Supplement 2](#).

Statistical Analysis

The primary objective was to determine whether the incidence of preterm preeclampsia in patients with an sFlt-1:PlGF ratio of 38 or less was not higher after discontinuing aspirin treatment as compared with a control group treated until 36 weeks of gestation. The sample size was calculated assuming an expected incidence of preterm preeclampsia of 1.6% in both groups ([Supplement 1](#)). The required sample size was 540 women in each group (a total of 1080 patients) assuming a 2-tailed type I error of 5% and 80% power for a noninferiority margin of 1.9% between both groups (maximum achievable incidence of preterm preeclampsia was set to 3.5%).

The randomization sequence and statistical analysis were done using Stata Statistical Software (Stata Statistical Software: Release 15, StataCorp LLC.). PASS 2008 software (NCSS LLC, <http://www.ncss.com>) was used for sample size estimation.

We performed 1 planned interim analysis when 50% of participants had been randomized. This analysis was performed by an independent statistician blinded for treatment allocation. The need to continue the study was assessed following interim analysis according to the prespecified stopping rules ([Supplement 1](#)).

Results

In June 2021, 560 pregnant individuals met the inclusion criteria for the interim analysis. According to this analysis, the incidence of preterm preeclampsia in the intervention group would not reach the noninferiority threshold of 1.9% with a conditional power of 96.3%, even if the total sample size of 1080 participants was recruited. The conditional power calculated at an interim analysis by simulations is an appropriate tool for defining stopping rules in noninferiority trials.²⁸ In our trial, a conditional power of more than 95% was required to stop the study for futility. Additionally, the incidence of preeclampsia with delivery at any gestational age tended to be greater in the control group (8.2% [23/282] and 13.3% [37/278], respectively; $P = .05$; 3 cases (1.1%) of placental abruption were diagnosed in the control group, while none were diagnosed in the intervention group ($P = .12$). Although this difference was not statistically significant, it was considered clinically significant because placental abruption is a severe complication that occurs in less than 0.5% of pregnan-

cies at high risk of preeclampsia⁶; some studies have shown that aspirin may increase its incidence when taken after 16 weeks of gestation.^{16,29} For these reasons, patient recruitment was stopped in September 2021, at which point 968 pregnant individuals had already been randomized (additional details in [Supplement 1](#)).

From March 5, 2019, to May 15, 2021, a total of 13 983 pregnant individuals were screened for preeclampsia. Of these, 1984 (14.2%) were identified as being at high risk of preterm preeclampsia and were prescribed aspirin, 150 mg daily, at bedtime (Figure 1). A total of 380 pregnant individuals (19.2%) did not meet the inclusion criteria. Of the 1604 eligible pregnant individuals, 968 (60.3%) agreed to participate in the trial from August 20, 2019, to September 15, 2021. After randomization, 3 pregnant participants withdrew consent and 29 were lost to follow-up. The percentage of pregnant participants with available data for the primary and secondary outcomes was 96.7% ($n = 936$). Baseline characteristics did not differ significantly between groups ([Table](#)).

Preterm preeclampsia occurred in 7 of 473 pregnant participants (1.48%) in the intervention group and 8 of 463 pregnant participants (1.73%) in the control group (absolute difference, -0.25% [95% CI, -1.86% to 1.36%] ([Figure 2](#)). A sensitivity analysis was performed to consider the effect of withdrawal of consent, loss to follow-up, and adherence to the assigned regimen. The sensitivity analysis in which multiple imputation was used for missing data did not change the findings (absolute difference, -0.21% [95% CI, -1.76% to 1.35%] ([Supplement 1](#)). Median gestational age at delivery for cases with preterm preeclampsia was 35.1 weeks (IQR, 34.6 to 36.4) in the intervention group and 35.1 weeks (IQR, 34.0 to 35.7) in the control group ($P = .42$). There were no significant differences between groups related to other adverse outcomes with delivery before 37 weeks of gestation or delivery before 34 weeks of gestation. The reasons for elective delivery before 37 weeks of gestation in cases without preeclampsia are detailed in eTable 2 in [Supplement 2](#). The incidence of adverse outcomes at or after 37 weeks of gestation did not differ significantly between groups when analyzed individually; nevertheless, at least 1 adverse outcome at or after 37 weeks of gestation occurred in 63 of 473 pregnant participants (13.3%) in the intervention group and 85 of 463 pregnant participants (18.4%) in the control group (absolute difference, -5.04% [95% CI, -9.73% to -0.36%]). Median gestational age at delivery of pregnant participants with preeclampsia at or after 37 weeks of gestation was 37.9 weeks (IQR, 37.2 to 39.5) in the intervention group and 38.7 weeks (IQR, 37.9 to 39.4) in the control group ($P = .27$). The cumulative percentages of participants who had delivery with preeclampsia are shown in eFigure 2 in [Supplement 2](#).

Four participants (0.85%) in the intervention group and 2 participants (0.43%) in the control group (absolute difference, 0.42% [95% CI, -0.61% to 1.43%]) had stillbirth or neonatal death. However, none of them occurred in participants with preeclampsia and only 1 case of neonatal death due to intraventricular hemorrhage and sepsis occurred in a pregnancy with fetal growth restriction in the control group. More details of the clinical context of these cases can be seen in

Table. Characteristics of Participants in the StopPRE Trial

Characteristic	No. of events (%)	
	Aspirin discontinuation group (n = 473)	Control group (n = 463)
Gestational age at randomization, median (IQR), wk	26.1 (25.7-26.7)	26.1 (25.7-26.6)
Age, median (IQR), y	32.8 (28-3-36.8)	32.8 (28.1-36.4)
Body mass index, median (IQR) ^a	28.1 (24.7-32.5)	28.3 (24.7-32.4)
Race and ethnicity ^b		
Black	16 (3.4)	16 (3.5)
East Asian	2 (0.4)	2 (0.4)
South Asian	4 (0.8)	10 (2.2)
White	444 (93.9)	426 (92.0)
Multiracial/multiethnic	7 (1.5)	9 (1.9)
Method of conception		
Natural	459 (97.0)	454 (98.0)
In vitro fertilization	13 (2.7)	8 (1.7)
Assisted by use of ovulation drugs	1 (0.2)	1 (0.2)
Current cigarette smoking	41 (8.7)	46 (9.9)
Medical history		
Diabetes type 1 or 2	18 (3.8)	16 (3.5)
Chronic hypertension	17 (3.6)	15 (3.2)
Kidney disease	1 (0.2)	1 (0.2)
Systemic lupus erythematosus	0	1 (0.2)
Obstetrical history		
Multiparous without preeclampsia	222 (46.9)	217 (46.9)
Nulliparous	205 (43.3)	199 (42.9)
Multiparous with preeclampsia	37 (7.8)	28 (6.0)
Risk of preterm preeclampsia as assessed at screening at 11-13 wk, median (IQR), % ^c	2.0 (1.0-5.9)	2.0 (1.0-5.9)
Gestational age for sFlt-1:PLGF measurement at randomization, median (IQR), wk	25.1 (24.7-25.7)	25.3 (24.9-25.9)
sFlt-1:PLGF ratio at randomization, median (IQR)	3.92 (2.59-6.25)	3.86 (2.44-6.01)
Estimated fetal weight at randomization, median (IQR), g	927.0 (852.0-1016.0)	917.0 (841.0-1000.0)
Estimated fetal weight <10th percentile at randomization	3 (0.6)	4 (0.8)
Mean uterine artery pulsatility index at randomization, median (IQR) ^d	0.86 (0.70-1.01)	0.87 (0.72-1.04)
Mean uterine artery pulsatility index >95th percentile at randomization	39 (8.3)	42 (9.1)

Abbreviations: sFlt-1:PLGF, soluble fms-like tyrosine kinase1 to placental growth factor; StopPRE, Detection of False Positives From First-trimester Preeclampsia Screening at the Second-trimester of Pregnancy.

^a Calculated as weight in kilograms divided by height in meters squared.

^b Race and ethnicity were reported by participants from fixed categories.

^c Risk of preterm preeclampsia was assessed by means of a gaussian algorithm that combined maternal factors, mean arterial blood pressure, mean uterine artery pulsatility index, maternal serum pregnancy-associated plasma protein A, and placental growth factor. Pregnant participants with a risk of 1/170 or greater were considered at high risk.^{13,21}

^d Mean uterine artery pulsatility index was obtained by averaging the value of the right and left uterine artery pulsatility index as measured by transabdominal or transvaginal color Doppler ultrasound.^{25,26}

eTable 3 in Supplement 2. The incidence of minor antepartum hemorrhage events was 7.6% in the intervention group and 12.3% in the control group (absolute difference, −4.70% [95% CI, −8.53% to −0.87%]). At least 1 bleeding complication occurred in 38 of 473 participants (8.0%) in the intervention group and 59 of 463 participants (12.7%) in the control group (absolute difference, −4.71% [95% CI, −8.61% to 0.81%]). The incidence of other bleeding complications or adverse neonatal events did not differ significantly between groups (Figure 2 and Figure 3).

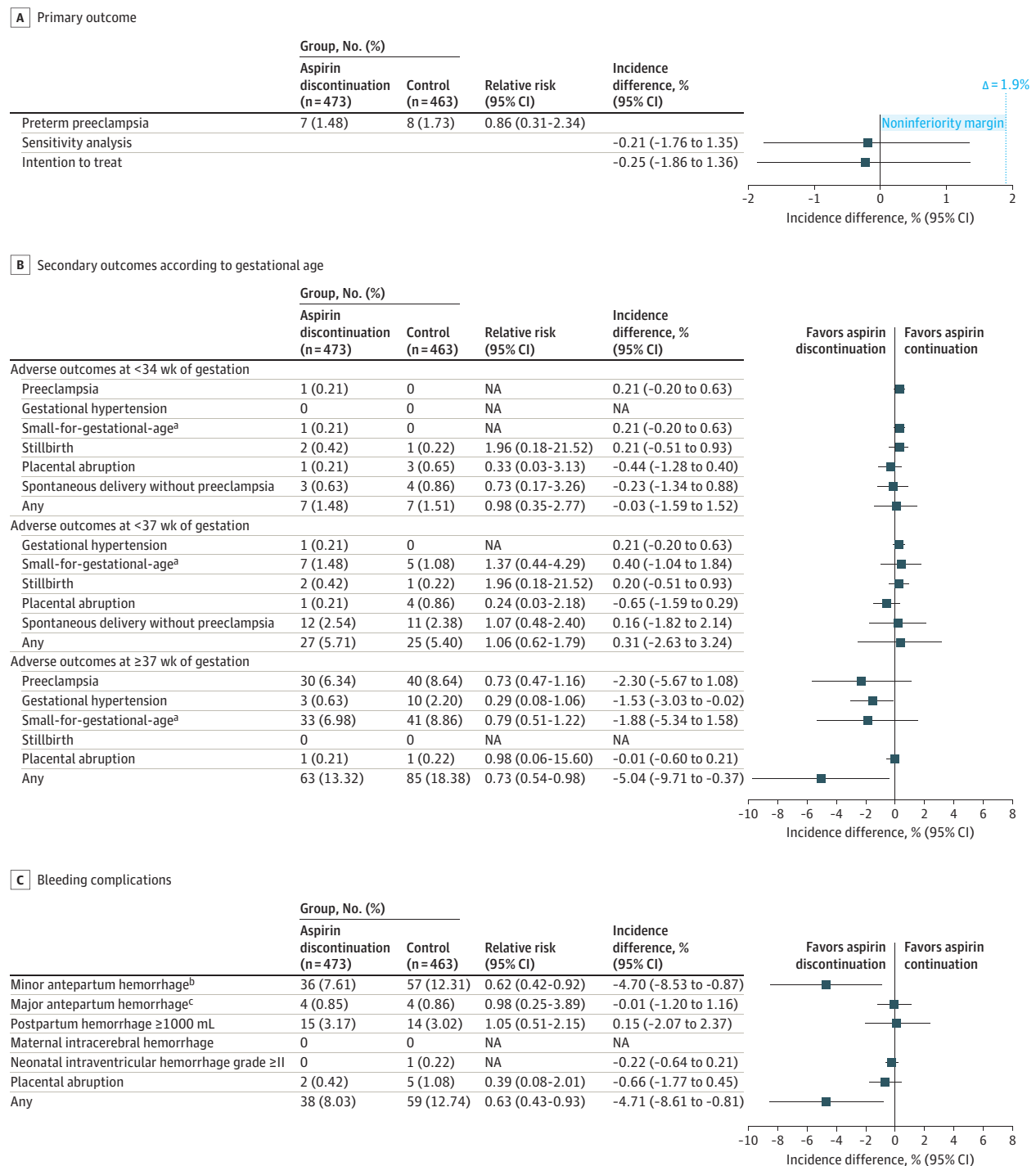
Despite being assigned to the intervention group, 5 participants (1.1%) continued aspirin treatment. In the control group, aspirin treatment adherence could not be verified by tablet counts in 6 of 463 participants (1.3%). Among the 457 participants for whom aspirin treatment adherence was verified, tablet intake was 90% or greater in all visits in more than 83% of participants (eTable 4 and eTable 5 in Supplement 2).

Discussion

Discontinuing aspirin at 24 to 28 weeks of gestation was non-inferior to continuing aspirin until 36 weeks of gestation for preventing preterm preeclampsia in individuals who had a high risk of preeclampsia in the first trimester of pregnancy and an sFlt-1:PLGF ratio of 38 or less between 24 and 28 weeks of gestation. In addition, aspirin discontinuation might reduce the risk of minor bleeding complications or pregnancy complications at 37 weeks or more of gestation.

Two meta-analyses have shown that the highest prevention of preeclampsia is achieved with a daily dose of aspirin of 100 mg or more initiated before 16 weeks of gestation.^{11,30} However, a daily dose of aspirin of 100 mg or more initiated after 16 weeks of gestation may be associated with an increased relative risk of placental abruption and other bleeding

Figure 2. Pregnancy Outcomes



Data are number of events (%), relative risk (95% CI), or incidence difference (95% CI). NA indicates not applicable.

^a The status of being small for gestational age was defined as a birth weight below the 10th percentile according to gestational age at birth by customized charts.²⁷

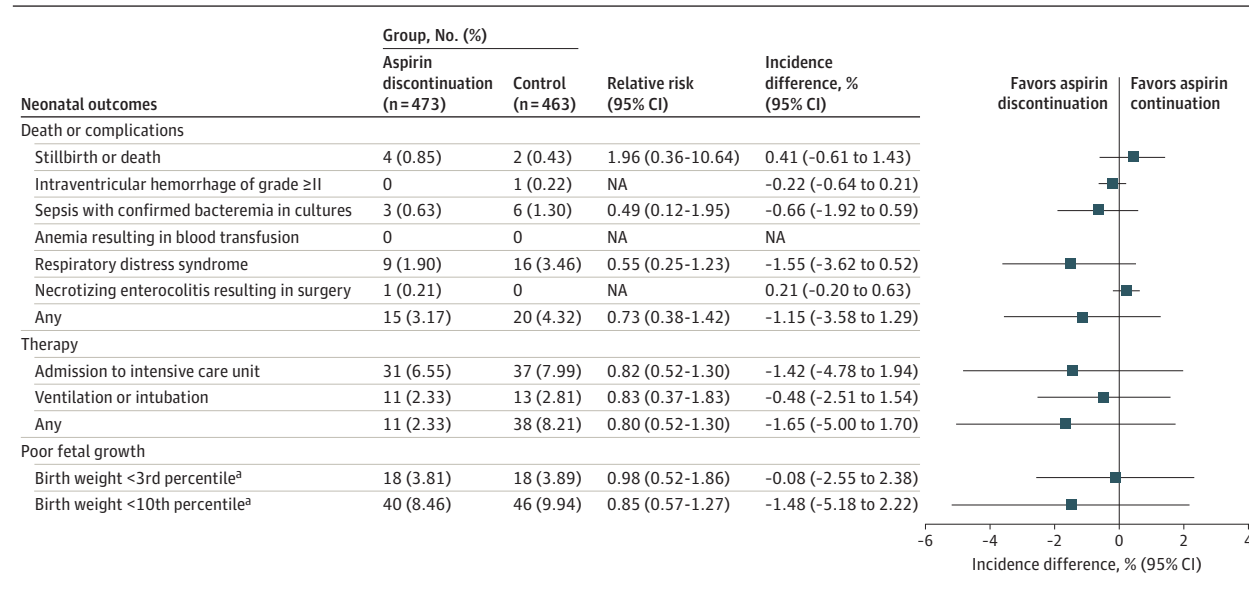
^b Nose and/or gum bleeding.

^c Hemoptysis and digestive and/or vaginal bleeding.

complications.^{16,17,29} For this reason, most guidelines recommend to discontinue aspirin at term and before onset of labor,^{15,31} which is the time where the risk of bleeding is great-

est in pregnant individuals. To reduce the percentage of individuals exposed to aspirin during pregnancy, guidelines also advise to set the threshold for classifying women at high risk

Figure 3. Neonatal Outcomes



Data are number of events (%), relative risk (95% CI), or incidence difference (95% CI).

^a Birth weight percentiles were calculated according to gestational age at birth by customized charts.²⁷

of preeclampsia in the first trimester to a maximum screen positive rate of 10% to 15%. Despite the safety concerns associated with aspirin treatment throughout pregnancy, recommendations regarding when to stop aspirin are not consistent.³¹ Discontinuation of aspirin before term has been evaluated in only 1 study,³² where aspirin was discontinued at 28 weeks of gestation. The researchers compared the incidence of preeclampsia with a group of untreated historical controls, showing no reduction in preeclampsia rates.³² Nevertheless, the study had several weaknesses and the researchers concluded that further studies were needed to determine when aspirin should be discontinued during gestation.

In the present study, aspirin at a dose of 150 mg was used. Because this is one of the highest doses recommended for preventing preeclampsia, discontinuing aspirin in this trial may have led to a significant reduction in severe bleeding complications. However, an association between earlier discontinuation of aspirin treatment and a reduction in rarer bleeding complications, such as placental abruption, maternal intracranial hemorrhage, postpartum hemorrhage, and/or neonatal intraventricular hemorrhage, was not observed. These findings could be due to several reasons; first, this study was not powered enough to assess these rare outcomes and larger studies should be conducted to address this topic, and second, aspirin was discontinued before labor in both groups, thereby reducing the chances of finding differences in the rates of postpartum and neonatal hemorrhages.

The most unexpected result of this study was the greater incidence of pregnancy complications at 37 weeks of gestation or more in the control group. Aspirin is believed to delay the onset of preeclampsia, thereby converting what would be, without treatment, preterm preeclampsia into term preeclampsia.³³ For this reason, it would have been reason-

able to expect that the incidence of term preeclampsia was greater in the intervention group and not the opposite. All participants in this trial had an sFlt-1:PlGF ratio of 38 or less and, therefore, a low risk of preterm preeclampsia. Thus, one possible explanation could be that, in pregnant individuals who are no longer at risk of preeclampsia, aspirin during the second half of pregnancy may be detrimental, in the same way that aspirin initiated after 16 weeks of gestation may increase the risk of placental abruption. However, the results of this study do not allow to confirm this hypothesis. In light of these results, aspirin treatment should be restricted to pregnant individuals at actual high risk of preeclampsia and administered during the shortest possible time. Nevertheless, this is the first study designed to investigate the safety of earlier discontinuation of aspirin and, given the low incidence of complications in both groups, the clinical implications of different doses and durations of treatment should be investigated in further studies.

The main strength of this study was that the novel evidence suggests that it may be unnecessary to continue aspirin until 36 weeks of gestation in all cases. Earlier discontinuation could ultimately reduce the risk of bleeding complications and pregnancy complications at term. It could also reduce maternal anxiety, treatment costs, number of visits, ultrasound scans, and iatrogenic interventions in a cohort of healthy pregnant individuals in which more than 95% of cases are actually false-positives and, therefore, are taking a drug unnecessarily. Furthermore, this study was conducted following current clinical practices and using the same follow-up protocol as in nonparticipants, which may increase the external validity of these results; nevertheless, these findings should be confirmed in other populations with different characteristics.

Limitations

This study had several limitations. First, it was an open-label trial; thus, physicians and participants were aware of the group assignment, which could potentially have led to bias in reporting patient symptoms. The nocebo effect of aspirin treatment should also be considered. Placebo was not used in the intervention group because the aim was to simulate a real clinical scenario by avoiding the placebo effects in the intervention group.

Second, this trial was not adequately powered to assess the effect of aspirin discontinuation in rarer complications, such as pregnancy complications at less than 34 weeks of gestation or certain bleeding complications.

Third, early termination of the trial following interim analysis according to the prespecified stopping rules and to the recommendations of the European Medicines Agency³⁴ may have influenced the results due to the low incidence of the primary and secondary outcomes. Nevertheless, it is very unlikely that the results would have been significantly different if the remaining 144 participants had been recruited.

Fourth, in this study, more than 92% of participants were White. The lack of racial and ethnic diversity limits the applicability of these results, especially among Black and South Asian individuals, who have a higher incidence of preeclampsia.

ability of these results, especially among Black and South Asian individuals, who have a higher incidence of preeclampsia.

Fifth, the choice of an absolute difference of 1.9% for the primary outcome rate might be relatively high given the low expected rate of preterm preeclampsia in the control group. According to previous studies, a noninferiority threshold of 1.6% would have been more appropriate. However, the decision to increase this threshold was made because the reduction of preterm preeclampsia rates may be lower in this population than in previous studies,⁶ given that screening for preeclampsia is less accurate in White pregnant individuals³⁵ and that aspirin treatment adherence would not be supervised between prescription and randomization.

Conclusions

Aspirin discontinuation at 24 to 28 weeks of gestation was noninferior to aspirin continuation for preventing preterm preeclampsia in pregnant individuals at high risk of preeclampsia and a normal sFlt-1:PlGF ratio.

ARTICLE INFORMATION

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