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ORIGINAL RESEARCH

Placental growth factor at 24–28 weeks for aspirin discontinuation in pregnancies at high risk for preterm preeclampsia: Post hoc analysis of StopPRE trial

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Abstract

Introduction: This study aims to evaluate the safety of discontinuing aspirin treatment at 24–28 weeks in women at high risk after first-trimester combined screening for preeclampsia (PE) and normal placental growth factor (PlGF) levels at 24–28 weeks of gestation.

Material and Methods: This is a post hoc analysis of the StopPRE trial, conducted at nine Spanish maternity hospitals from September 2019 to September 2021. In the StopPRE trial, all high-risk single pregnancies identified during first-trimester screening for PE were treated with 150 mg of daily aspirin. Out of 1604 eligible women with a soluble fms-like tyrosine kinase-1 to PlGF ratio (sFlt-1/PlGF) ≤38 at 24–28 weeks, 968

Abbreviations: CI, confidence interval; NPV, negative predictive values; PE, preeclampsia; PlGF, placental growth factor; RR, relative risk; sFlt-1, soluble fms-like tyrosine kinase-1.

Anna Suy and Manel Mendoza are joint last authors.

were randomly assigned in a 1:1 ratio to either continue aspirin until 36 weeks (control group) or discontinue it (intervention group). In this secondary analysis, only women with PlGF ≥100 pg/mL at 24–28 weeks were included. As in the StopPRE trial, the non-inferiority margin was set at a 1.9% difference in preterm PE incidence between the groups.

Results: Among the 13 983 screened pregnant women, 1984 (14.2%) were deemed high-risk for preterm PE, of which 397 (20.0%) were ineligible, 636 declined participation, and 32 were excluded. Ultimately, 919 women with PlGF >100 pg/mL were randomized and included in this analysis. Preterm PE occurred in 0.9% of the intervention group (4 out of 465) and 1.5% of the control group (7 out of 454), indicating non-inferiority of aspirin discontinuation. There were no significant differences between the groups in adverse pregnancy outcomes before 37 weeks, at <34 weeks, or ≥37 weeks. Minor antepartum hemorrhage incidence was significantly lower in the intervention group (absolute difference, −5.96; 95% CI, −10.10 to −1.82).

Conclusions: Discontinuation of aspirin treatment at 24–28 weeks in women with PlGF levels ≥100 pg/mL was non-inferior to continuing until 36 weeks for preventing preterm PE. However, these findings should be interpreted with caution, as they originate from a subanalysis of the StopPRE trial.

KEYWORDS
aspirin, PlGF, preeclampsia, salicylic acid, screening preeclampsia

1 | INTRODUCTION

Preeclampsia (PE) is a severe condition affecting 2%–4% of pregnancies, characterized by new-onset hypertension and proteinuria after 20 weeks of gestation, leading to increased maternal and perinatal morbidity and mortality.[1,2] Its exact cause remains unclear, but impaired placentation, resulting from deficient spiral artery remodeling and abnormal trophoblast invasion during the first trimester, is thought to be a primary factor contributing to early-onset and preterm cases. This leads to the second stage of the disease, which involves placental hypoxia and the release of anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1). sFlt-1 binds to and inhibits the activity of pro-angiogenic factors, such as placental growth factor (PlGF). This results in an angiogenic imbalance characterized by decreased PlGF levels and increased sFlt-1 (and sFlt-1/PlGF ratio) levels, which induces endothelial dysfunction and ultimately causes the clinical features of PE.[3,4]

While PE has no treatment, early prediction and identification of high-risk pregnancies allow for the application of preventive measures.[1] Combined screening for PE has the highest detection rates when using algorithms that include maternal risk factors, measurements of mean arterial pressure, serum PlGF, and mean uterine artery pulsatility index.[5] High-risk women identified in this screening should commence nightly aspirin treatment before 16 weeks' gestation, (150 mg) until 36 weeks, reducing the risk of preterm PE by 62%.[6]

Key message

Discontinuing aspirin at 24–28 weeks of gestation was non-inferior to continuing aspirin until 36 weeks of gestation for preventing preterm preeclampsia in individuals at high risk of preeclampsia and placental growth factor ≥ 100 pg/mL.

The drawback of first-trimester screening is that 10%–15% of pregnancies will be classified as high risk, and since the incidence of preterm PE in high-risk women is around 4%, more than 95% of pregnancies will be false positives and unnecessarily treated swith aspirin.[6] Low-dose aspirin is relatively safe in pregnancy; however, it may be associated with an increased risk of placental abruption,[7] perinatal hemorrhagic complications,[8,9] and hearing disorders in children with in utero exposure.[10] In a previous clinical trial,[11] we showed that sFlt-1 to PlGF ratio ≤38 at 24–28 weeks can detect false positives from the first-trimester screening, allowing for aspirin treatment discontinuation without increasing the incidence of preterm PE. PlGF and the sFlt-1/PlGF ratio are inversely correlated, and different studies suggest that PlGF alone performs comparably to sFlt-1/PlGF in predicting early-onset and preterm PE.[12] However, no previous studies have compared their efficacy in deciding aspirin discontinuation for high-risk individuals. Hence, this secondary analysis aims to determine whether PlGF alone could be used instead of

sFlt-1/PlGF for deciding aspirin treatment discontinuation in women at high risk of PE.

2 | MATERIAL AND METHODS

This is a post hoc analysis of the StopPRE trial, conducted at nine maternity centers in Spain from September 2019 to September 2021. The trial protocol has been previously described.[11] The trial was registered on ClinicalTrials.gov, under NCT03741179 (https://clinicaltrials.gov/study/NCT03741179) in October 2018. All participants provided written informed consent. In the StopPRE trial, all single pregnancies at high risk of PE based on first-trimester screening were treated with daily aspirin at a dose of 150 mg. Cases with an sFlt-1/PlGF ratio ≤38 at 24–28 weeks were randomly assigned, in a 1:1 ratio, to either continue aspirin treatment (control group) or discontinue aspirin treatment (intervention group). Participants were followed up every 4 weeks, and all data and pregnancy outcomes were prospectively recorded in an electronic database. The primary outcome of the StopPRE trial was to demonstrate that the incidence of preterm PE in patients with an sFlt-1/PlGF ratio ≤38 was similar, regardless of continuing aspirin treatment. Non-inferiority was defined with a 1.9% difference in the incidence of preterm PE between groups, with non-inferiority met if the upper limit of the 95% confidence interval (CI) for this difference was less than 1.9%.

Inclusion criteria in the StopPRE trial were singleton pregnancy, maternal age ≥18 years, gestational age between 24 + 0 and 27 + 6 weeks, a live fetus, high risk of preterm PE (≥1/170) during the first trimester (11 + 0 to 13 + 6 weeks) according to the screening algorithm,[13,14] treatment with daily aspirin at a dose of 150 mg initiated ≤16 + 6 weeks until randomization with a compliance of at least 50%, and an sFlt-1/PlGF ratio ≤38 between 24 and 28 weeks. Exclusion criteria were aspirin intolerance or allergy, a fetus with known congenital abnormalities, von Willebrand's disease, antiphospholipid syndrome, peptic ulceration, and any condition or factor that, according to the investigator, may prevent adherence to the protocol.

PlGF ≥100 pg/mL and sFlt-1/PlGF ≤38 have similar negative predictive values (NPV) for excluding PE and other placental-related disorders in women with suspected PE.[12] This post hoc analysis included all cases from the original study and those excluded for having an sFlt-1/PlGF ratio >38. However, participants with an sFlt-1/PlGF ratio >38 were ultimately excluded from this analysis as all cases had also a PlGF <100 pg/mL. Among patients with a normal PlGF (≥100 pg/mL) at 24–28 weeks, pregnancy outcomes were compared between those allocated to aspirin discontinuation and those allocated to aspirin continuation until 36 weeks. The primary outcome was delivery due to PE before 37 weeks (preterm PE). Secondary outcomes included PE or other adverse pregnancy outcomes before 34 weeks, any other adverse pregnancy outcomes <37 weeks, and PE or other adverse pregnancy outcomes at ≥37 weeks. Gestational hypertension, placental abruption, spontaneous delivery without PE, and stillbirth were considered other adverse outcomes. PE was defined according to the guidelines of the American College of Obstetricians and Gynecologists: new-onset high blood pressure (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg), or worsening of previous high blood pressure in addition to new-onset proteinuria (protein to creatinine ratio >300 or dipstick+), or worsening of previous proteinuria, or at least one of the following signs and symptoms: cerebral or visual symptoms, elevation of liver enzymes to twice the normal level, platelet count <100 000/μL, serum creatinine >1.1 mg/dL, or pulmonary edema.[15] Elective delivery was recommended at ≥37 weeks in women with PE without severe features and at ≥34 weeks in women with PE with severe features and/or HELLP syndrome.[16] Immediate delivery was indicated in women with pulmonary edema, placental abruption, persistent hypertension despite appropriate antihypertensive therapy, persistent cerebral or visual disturbances, oliguria (≤500 mL in 24 h or <20 mL/h), or eclampsia. Other secondary outcomes were minor antepartum bleeding complications (nose and/or gum bleeding); major antepartum bleeding complications (digestive and/or vaginal bleeding, hemoptysis); maternal intracranial hemorrhage; postpartum hemorrhage; stillbirth; neonatal death; neonatal complications; and neonate requiring therapy.

No patients were involved in the development of the research study. No core outcome set has been used as an outcome in this study.

2.1 | Statistical analyses

Categorical data were reported as frequency and percentage, and comparisons between groups were estimated using the χ^2 or Fisher tests, as appropriate. Continuous variables were reported as the mean and standard deviation or as the median and interquartile range. The intervention effect for primary and secondary outcomes was quantified as the absolute difference between groups in incidences, the relative risk (RR), and the 95% CI. Statistical significance was set at $p < 0.05$. The non-inferiority margin was set at a difference of 1.9% between both groups for the incidence of preterm PE. Statistical analyses were performed on an intention-to-treat basis using Stata Statistical Software (StataCorp. 2017. Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC).

3 | RESULTS

From March 5, 2019, to May 15, 2021, a total of 13 983 women underwent screening for PE. Among them, 1984 (14.2%) were identified as being at high risk for preterm PE and were prescribed daily aspirin 150 mg at bedtime until 36 weeks. However, 397 of these women (20.0%) did not meet the eligibility criteria, with 24 of them having a PlGF <100 pg/mL (7 with an sFlt-1/PlGF >38 and 17 with an sFlt-1/PlGF ≤38). Of the 1587 eligible women, 636 declined to participate. Finally, 951 were randomized into two groups from August 20, 2019, through September 15, 2021. After randomization, three

women withdrew consent, and 29 were lost to follow-up. Data for the primary and secondary outcomes were available for 919 women (96.6%) (Figure 1). Baseline characteristics of women included and excluded in this study are presented in Table 1 and Table S1.

Preterm PE occurred in four out of 465 women (0.9%) in the intervention group and seven out of 454 women (1.5%) in the control group (absolute difference −0.68; 95% CI, −2.10 to 0.73). Adverse outcomes with delivery before 37 weeks of gestation were not significantly different between the two groups; however, participants in the intervention group tended to have less placental abruption at <37 weeks (3 [0.7%] vs. 0 cases; absolute difference −0.60%; CI, −0.66 to 0.08, $p = 0.079$). There were no significant differences between groups for the incidence of adverse outcomes with delivery <34 weeks or ≥37 weeks. Further details can be found in Figure 2.

Four participants (0.9%) in the intervention group and two participants (0.4%) in the control group experienced stillbirth or neonatal death (absolute difference, 0.42% [95% CI, −0.62% to 1.46%]). However, none of these events occurred in participants with PE, and only one case of neonatal death due to intraventricular hemorrhage and sepsis occurred in a pregnancy with fetal growth restriction in the control group (Table S2).

The incidence of minor antepartum hemorrhage was 7.6% in the intervention group and 12.2% in the control group (absolute difference, −4.61; 95% CI, − 8.47 to −0.75). At least one bleeding complication occurred in 40 of 465 participants (8.6%) in the intervention group and 66 of 454 participants (14.6%) in the control group (absolute difference, −5.96; 95% CI, −10.10 to −1.82). The incidence of other bleeding complications or adverse neonatal events did not differ significantly between groups (Figure 2).

4 | DISCUSSION

Discontinuing aspirin in women with PlGF levels ≥100 pg/mL at 24–28 weeks was non-inferior to continuing aspirin until 36 weeks for preventing preterm PE and other pregnancy complications. Additionally, women in the intervention group experienced

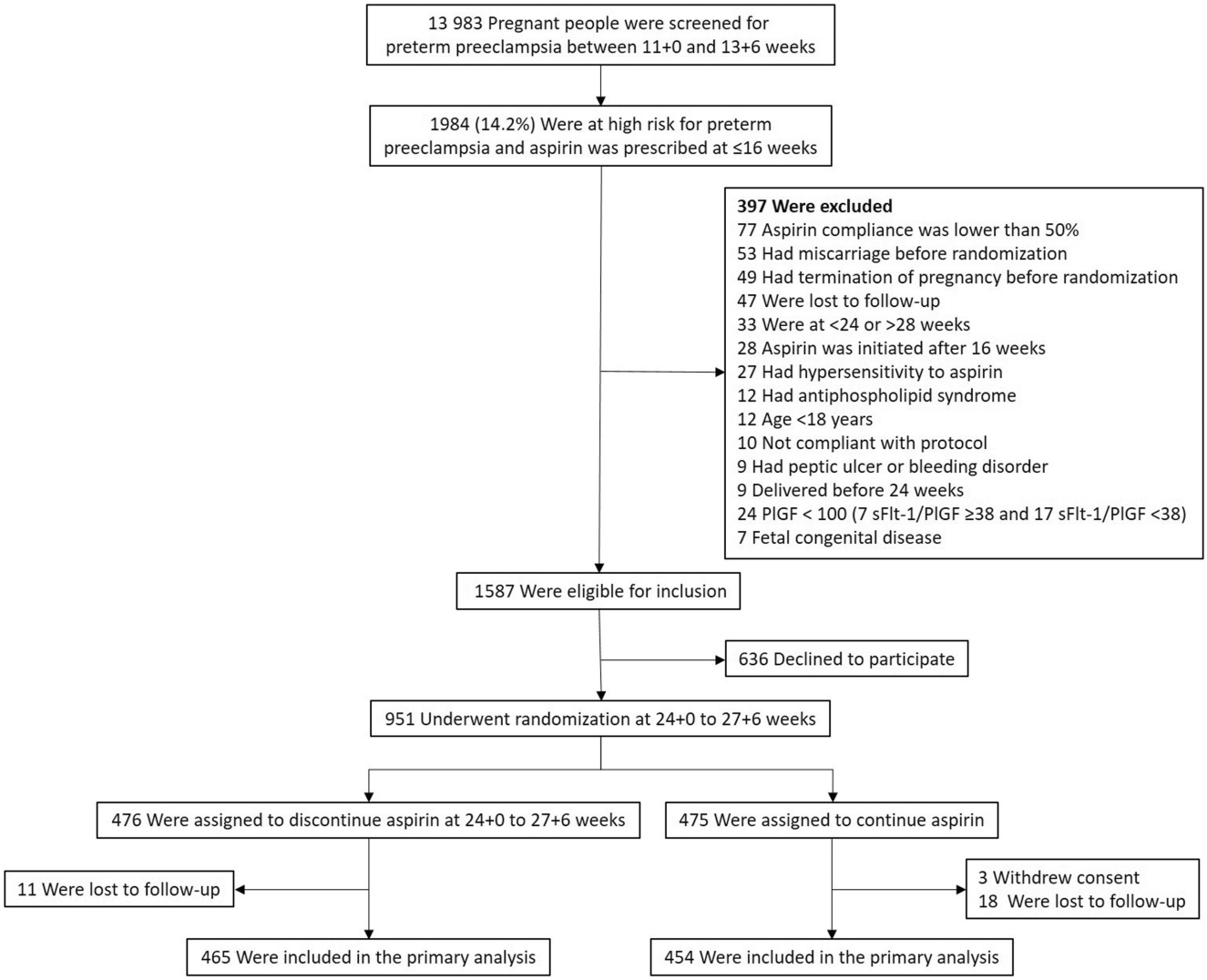


FIGURE 1 Flowchart. PlGF, placental growth factor.

TABLE 1 Characteristics of the trial participants.

Characteristic	Intervention group ($n=465$)	Control group ($n=454$)	p
Gestational age at randomization, weeks	26.1 (25.7–26.7)	26.1 (25.7–26.7)	0.999
Age, years	32.8 (28.1–36.4)	32.8 (28.3–36.8)	0.763
Body-mass index, kg/m^2	28.1 (24.7–32.3)	28.3 (24.7–32.4)	0.908
Race or ethnic group[a]			0.644
White	436 (93.8%)	418 (92.1%)	
Black	16 (3.4%)	16 (3.5%)	
South East Asian	4 (0.9%)	9 (2.0%)	
Oriental Asian	2 (0.4%)	2 (0.4%)	
Mixed race	7 (1.5%)	9 (2.0%)	
Cigarette smoking	39 (8.4%)	46 (10.1%)	0.426
Medical history			1.0
Chronic hypertension	25 (5.4%)	25 (5.5%)	
Autoimmune disease	4 (0.9%)	3 (0.7%)	
Diabetes mellitus type 1 or 2	16 (3.4%)	16 (3.5%)	
Renal disease	1 (0.2%)	1 (0.2%)	
Obstetrical history			0.810
Nulliparous	240 (51.6%)	225 (49.6%)	
Multiparous without preeclampsia	193 (41.5%)	198 (43.6%)	
Multiparous with preeclampsia	32 (6.9%)	31 (6.8)	
Risk of preterm preeclampsia as assessed at screening at 11–13 weeks. Median (IQR)	0.02 (0.01–0.05)	0.02 (0.01–0.05)	0.962
sFlt-1/PlGF at randomization	3.88 (2.57–6.01)	3.79 (2.43–5.70)	0.505
Estimated fetal weight at randomization, grams	928 (853–1017)	917 (842–1000)	0.160
Uterine artery pulsatility index at randomization	0.86 (0.70–1.01)	0.87 (0.72–1.03)	0.381

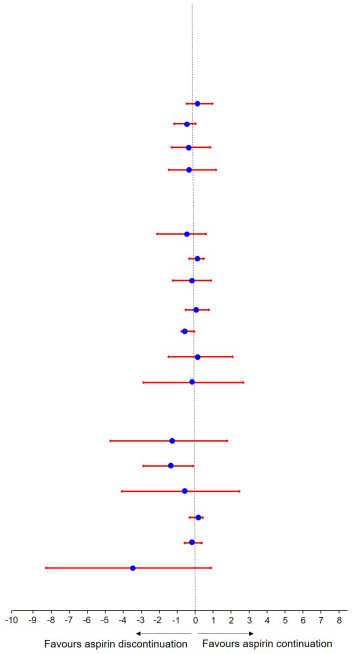
Note: Data are number of events (%) or median (IQR).

[a]Race and ethnicity was self-reported by participants from predefined categories.

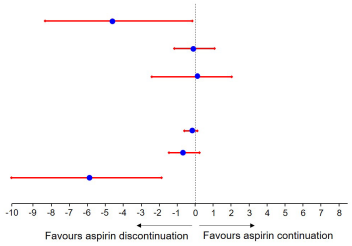
significantly fewer minor bleeding complications and tended to have less placental abruption at <37 weeks.

Two meta-analyses have concluded that the most effective treatment protocol to prevent PE consists of a daily dose of aspirin of 100 mg or more, initiated before 16 weeks of gestation.[7,17] However, low-dose aspirin has been associated with a higher RR of experiencing placental abruption and other bleeding complications[7–9] that could be mitigated by discontinuing aspirin treatment at 36 weeks.[5,18] Additionally, low-dose aspirin during pregnancy has been associated with some long-term offspring complications such as hearing defects and asthma.[10,19] Despite the high proportion of cases unnecessarily treated with aspirin and the safety concerns associated with its use during pregnancy, discontinuation of aspirin treatment before term has been evaluated in only one previous study.[20] In that cohort study, aspirin treatment was discontinued at 28 weeks following Japanese national recommendations, and the incidence of PE was compared with that of untreated historical controls. Kawaguchi H, et al. found no reduction in PE incidence; however, participants were selected based on maternal risk factors rather than a multivariable algorithm, the incidence of preterm PE was surprisingly high in both groups (12.0% vs. 13.1%), and compliance in the aspirin group was not reported. For these reasons, they concluded that further studies were needed to determine when aspirin treatment should be discontinued during pregnancy. The StopPRE trial showed that discontinuation of aspirin treatment in patients with an sFlt-1/PlGF ratio ≤38 at 24–28 weeks was non-inferior to continuing treatment until 36 weeks in preventing preterm PE.[11] In that trial, the sFlt-1/PlGF ratio was used as a selection criterion due to its high NPV for excluding PE in high-risk women after first-trimester screening.[21] Low values of sFlt-1/PlGF ratio and high values of PlGF have shown similar NPV for excluding PE in women with suspected PE.[12] In the Pelican Study, women were classified based on maternal serum PlGF concentration into different groups: PlGF ≥100 pg/mL (normal values), PlGF 12–99 pg/mL (low values), and PlGF <12 pg/mL (very low values). That study showed that normal PlGF concentrations in women with suspected PE had a high NPV (98%) for excluding the

(A) Perinatal outcomes according to gestational age	Stop aspirin group (*n*= 465)	Control group (*n*= 454)	Relative risk (95% CI)	Incidence difference (95%CI)
Adverse outcomes at <34 weeks of gestation				
Preeclampsia	0	0	-	-
Gestational hypertension	0	0	-	-
Small-for-gestational-age*	0	0	-	-
Stillbirth	2 (0.4%)	1 (0.2%)	1.95 (0.18-21.4)	0.21% (-0.53 to 0.95)
Placental abruption	0	2 (0.4%)	-	-0.44% (-1.05 to 0.17)
Spontaneous delivery without preeclampsia	3 (0.6%)	4 (0.4%)	0.73 (0.16- 3.25)	-0.24% (-1.37 to 0.89)
Any	5 (1.1%)	6 (1.3%)	0.81 (0.25-2.65)	-0.25% (-1.66 to 1.17)
Adverse outcomes at <37 weeks of gestation				
Preeclampsia	4 (0.9%)	7 (1.5%)	0.56 (0.16-1.89)	-0.68% (-2.10 to 0.73)
Gestational hypertension	1 (0.2%)	0	-	0.22% (-0.21 to 0.64)
Small-for-gestational-age*	4 (0.9%)	4 (0.9%)	0.98 (0.25-3.88)	-0.02% (-1.23 to 1.19)
Stillbirth	2 (0.4%)	1 (0.2%)	1.95 (0.18-21.4)	0.20% (-0.53 to 0.95)
Placental abruption	0	3 (0.7%)	-	-0.60% (-0.66 to 0.08)
Spontaneous delivery without preeclampsia	12 (2.6%)	11 (2.4%)	1.06 (0.47-2.39)	0.16% (-1.87 to 2.19)
Any	23 (5.0%)	23 (5.1%)	0.98 (0.56-1.71)	-0.12% (-2.95 to 2.71)
Adverse outcomes at ≥37 weeks of gestation				
Preeclampsia	30 (6.5%)	36 (8.0%)	0.81 (0.51-1.30)	-1.49% (-4.84 to 1.87)
Gestational hypertension	3 (0.6%)	10 (2.2%)	0.29 (0.08-1.06)	-1.56% (-3.10 to -0.02)
Small-for-gestational-age*	33 (7.1%)	36 (8.0%)	0.89 (0.57-1.41)	-0.84% (-4.26 to 2.59)
Stillbirth	1 (0.2%)	0	-	0.22% (-0.21 to 0.64)
Placental abruption	1 (0.2%)	1 (0.2%)	-	-0.10% (-0.65 to 0.60)
Any	63 (11.2%)	78 (15.4%)	0.79 (0.58-1.07)	-3.65% (-8.33 to -1.03)



(B) Bleeding complications	Stop aspirin group (*n*= 409)	Control group (*n*= 395)	Relative risk (95% CI)	Incidence difference (95%CI)
Minor antepartum hemorrhage†	35 (7.6%)	55 (12.2%)	0.62 (0.41-0.93)	-4.61% (-8.47 to -0.75)
Major antepartum hemorrhage‡	4 (0.9%)	4 (0.9%)	0.97 (0.24-3.83)	-0.02% (-1.23 to 1.19)
Postpartum hemorrhage ≥1000 mL	14 (3.0%)	13 (2.9%)	1.05 (0.50-2.21)	0.15% (-2.40 to 2.34)
Maternal intracerebral hemorrhage	0	0	-	-
Neonatal intraventricular hemorrhage grade ≥III	0	1 (0.2%)	-	-0.22% (-0.65 to 0.19)
Placental abruption	1 (0.2%)	4 (0.9%)	0.24 (0.03-2.18)	-0.67% (-1.63 to 0.29)
Any	40 (8.6%)	66 (14.6%)	0.59 (0.41-0.86)	-5.96% (-10.10 to -1.82)



C. Neonatal outcomes	Stop aspirin group (*n*= 465)	Control group (*n*= 454)	Relative risk (95% CI)	Incidence difference (95%CI)
Death or complications				
Any	14 (3.0%)	18 (4.0%)	0.76 (0.38 -1.51)	-0.96 (-3.34 to 1.43)
Stillbirth or death	4 (0.9%)	2 (0.4%)	1.95 (0.36 -10.61)	0.42 (-0.62 to 1.46)
Intraventricular Hemorrhage > III	0	1(0.2%)	-	-0.22 (-0.65 to 0.21)
Sepsis	3 (0.6%)	6 (1.3%)	0.49 (0.12-1.94))	-0.68 (-2.1 to 0.60)
Respiratory distress syndrome	8 (1.7%)	14 (3.1%)	0.56 (0.24-1.32)	-1.37 (-3.36 to 0.62)
Necrotizing enterocolitis resulting in surgery	1 (0.2%)	0.	-	0.22 (-0.21 to 0.64)
Therapy				
Any	28 (6.0%)	35 (7.7%)	0.78 (0.48-1.26)	-1.74 (-4.98 to 1.59)
Admission to Intensive Care Unit	28 (6.0%)	34 (7.6%)	0.93 (0.54-1.60)	-1.46 (-4.76 to 1.83)
Ventilation with positive airway pressure or intubation	10 (2.2%)	11 (2.4%)	0.89 (0.38-2.07)	- 0.27 (-2.22 to 1.67)

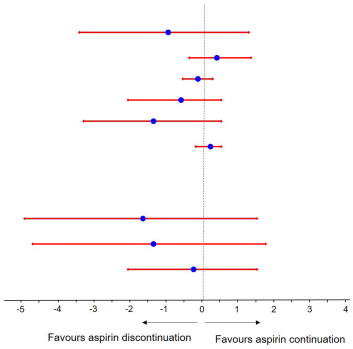


FIGURE 2 Perinatal and neonatal outcomes according to trial group. *Minor antepartum hemorrhage: nose and/or gum bleeding. †Major antepartum hemorrhage: haemoptysis, digestive and/or vaginal bleeding.

occurrence of PE that required delivery within 14 days.[22] However, no previous studies have investigated whether a normal PlGF in the third trimester could be used to discontinue aspirin treatment in asymptomatic women at high risk for PE.

The main strength of this study is its prospective design in a large cohort of women at high risk of PE. Additionally, we provide novel evidence that PlGF ≥100 pg/mL alone is a good alternative to sFlt-1/PlGF ≤38, which can be used to identify 98.2% (919/936) of patients for whom aspirin treatment can be safely discontinued, thereby reducing costs (use of one biomarker instead of two), exposure time to aspirin treatment, and aspirin-related complications during pregnancy. However, this study has several limitations. First, it is a post

hoc analysis of a previous clinical trial, and its results should be interpreted with caution. Second, it is subject to the same limitations as the original trial: physicians and participants were aware of group assignments, and placebo was not used in the intervention group. This decision was made due to PE not being a subjective outcome measure and because the researchers aimed to simulate real clinical conditions by avoiding any potential placebo effect. Third, the trial was not powered enough to assess the effect of aspirin treatment discontinuation for rarer complications. Fourth, more than 80% of participants were of white origin, which could reduce the external validity of our findings. Fifth, the incidence of all adverse outcomes was low, and data could not be analyzed stratified by participating site or by other possible confounders. Finally, the selection of an absolute difference of 1.9% for the primary outcome might be considered relatively high given the low expected rate of preterm PE in the control group[23]; however, this difference adheres to the recommendations of the European Medicines Agency guidelines for designing non-inferiority trials. According to these guidelines, the choice of a wider margin is justified in cases where some loss of efficacy may be acceptable in exchange for safety benefits or lower costs, thereby reinforcing the validity of our findings.[24,25]

This study has important clinical implications, as it provides evidence that aspirin can be safely discontinued in those women at high risk of PE who have a PlGF ≥100 pg/mL at 24–28 weeks, which may reduce the risk of bleeding and potentially other iatrogenic complications of aspirin treatment, such as placental abruption, when discontinued in larger populations. Therefore, the results of the current study show that PlGF may be used as an alternative to the sFlt-1/PlGF ratio for deciding on aspirin discontinuation in 98.2% of cases from the original trial. Hence, the results of this study offer a safer treatment regimen, particularly beneficial for false-positive cases (which correspond to >95% of screened women) and could result in reduced maternal anxiety, treatment and biomarker expenses, ultrasound scans, and iatrogenic interventions.

Given that shorter treatment duration showed some potential benefits without increasing the risk of PE and other pregnancy complications, future research should investigate other treatment regimens in more ethnically diverse populations to find the optimal duration of aspirin treatment for preventing PE, aiming to maximize its preventive effect while minimizing harms.

5 | CONCLUSION

In this secondary analysis of the StopPRE trial, discontinuing aspirin treatment in women at high risk for preterm PE and PlGF ≥100 pg/mL at 24–28 weeks was non-inferior to continuing aspirin treatment until 36 weeks for preventing preterm PE.

AUTHOR CONTRIBUTIONS

Manel Mendoza conceptualized the study and provided supervision to study design; Manel Mendoza and Marta Ricart did the statistical analysis; Manel Mendoza and Anna Suy acquired funding; Manel Mendoza and Marta Ricart wrote the original draft of the report; and Manel Mendoza and Anna Suy wrote, reviewed, and edited the manuscript. All authors critically reviewed and approved the final version. Anna Suy and Manel Mendoza accessed and verified data. All authors confirm that they had full access to all the study data and accept responsibility to submit for publication.

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CONFLICT OF INTEREST STATEMENT

Manel Mendoza has received lecture fees from Roche Diagnostics outside the submitted work. The other authors report that they have no other conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The trial protocol was approved by the Institutional Review Board at each trial center (EudraCT: 2018-000811-26) on August 31, 2018. A pseudonymised dataset was used and stored according to the European General Data Protection Regulation. All participants provided their written informed consent. No patients or patient associations were involved in the design of the study. ClinicalTrials.gov: NCT03741179; October 25, 2018. First patient enrolled: March 5, 2019. https://clinicaltrials.gov/study/NCT03741179.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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