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RESEARCH ARTICLE

General obstetrics

Mid-trimester uterine artery Doppler for aspirin discontinuation in pregnancies at high risk for preterm pre-eclampsia: Post-hoc analysis of StopPRE trial

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Abstract

Objective: To assess whether aspirin treatment can be discontinued in pregnancies with normal uterine artery pulsatility index (≤90th percentile) at 24–28 weeks.

Design: Post-hoc analysis of a clinical trial.

Setting: Nine maternity hospitals in Spain.

Population or Sample: Pregnant individuals at high risk of pre-eclampsia at 11–13 weeks and normal uterine artery Doppler at 24–28 weeks.

Methods: All participants received treatment with daily aspirin at a dose of 150 mg. Participants were randomly assigned, in a 1:1 ratio, either to continue aspirin treatment until 36 weeks (control group) or to discontinue aspirin treatment (intervention group), between September 2019 and September 2021. In this secondary analysis, women with a UtAPI >90th percentile at 24–28 weeks were excluded. The non-inferiority margin was set at a difference of 1.9% for the incidence of preterm pre-eclampsia.

Main outcome measures: Incidence of preterm pre-eclampsia.

Results: Of the 1611 eligible women, 139 were excluded for UtAPI >90th percentile or if UtAPI was not available. Finally, 804 were included in this post-hoc analysis. Preterm pre-eclampsia occurred in three of 409 (0.7%) women in the aspirin discontinuation group and five of 395 (1.3%) women in the continuation group (−0.53; 95% CI −1.91 to 0.85), indicating non-inferiority of aspirin discontinuation.

Conclusions: Discontinuing aspirin treatment at 24–28 weeks in women with a UtAPI ≤90th percentile was non-inferior to continuing aspirin treatment until 36 weeks for preventing preterm pre-eclampsia.

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KEYWORDS
aspirin, Doppler, pre-eclampsia, salicylic acid, screening, uterine artery

1 | INTRODUCTION

Pre-eclampsia (PE) is a serious multisystem disorder which typically develops as new-onset hypertension and proteinuria after 20 weeks of gestation. It affects 2–4% of pregnancies[1] and accounts for more than 70 000 maternal deaths and 500 000 fetal deaths worldwide annually.[2] The exact pathogenesis of PE is not well understood and various maternal and placental factors may be involved; nevertheless, impaired placentation is believed to be a primary factor contributing to early-onset and preterm cases.[1,3] In normal pregnancies, maternal spiral arteries convert from narrow muscular vessels into wide non-muscular channels, and the impedance to flow in the uterine arteries (UtA) decreases between 6 and 24 weeks.[4] Increased pulsatility index (PI) in UtA reflects their maladaptation to pregnancy changes, which is more frequently found in pregnant women who will develop preterm PE.[1,4] By contrast, normal mid-trimester UtAPI has a negative predictive value (NPV) >96% to exclude the development of PE.[5] Impaired placentation also results in uteroplacental ischaemia,[6] with the ensuing excess of anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), and decrease of pro-angiogenic factors, such as placental growth factor (PlGF).[7] Therefore, the sFlt-1/PlGF ratio is increased several weeks before clinical onset of PE.[8] UtAPI and PlGF can be used in the first-trimester screening for PE,[9,10] which indicates the initiation of aspirin treatment before 16 weeks, thereby decreasing the incidence of preterm PE by 62%.[11] First-trimester screening detects 60–70% of women who will develop preterm PE at a 10% false-positive rate.[9,10] However, as the incidence of preterm PE in high-risk women is around 4%,[11] more than 95% of women classified as being at risk of PE would be false-positive cases and will receive unnecessary treatment with aspirin. In a previous clinical trial, we showed that a normal sFlt-1/PlGF ratio (≤38) at 24–28 weeks can detect false positives and makes it possible to identify patients for whom aspirin can be discontinued without increasing the incidence of preterm PE (1.48% versus 1.73%, risk difference −0.25 [−1.86 to 1.36]).[12] Unfortunately, the sFlt-1/PlGF ratio might not be available in all settings. As previous studies have shown a good correlation between angiogenic factors and UtAPI,[13] we aimed to assess whether aspirin treatment can be discontinued in patients with a normal UtAPI at 24–28 weeks without increasing the incidence of preterm PE.

2 | METHODS

2.1 | Population

This is a post-hoc analysis of the StopPRE trial, which was conducted at nine maternity units across Spain between September 2019 and September 2021. The study protocol has been described previously.[12] The StopPRE trial is registered with ClinicalTrials.gov (NCT03741179) and clinicaltrialsregister.eu (2018–000811-26). All participants provided their written informed consent. In the StopPRE trial, all pregnant women with a high risk of PE at the 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, either to continue aspirin treatment (control group) or to discontinue aspirin treatment (intervention group). All 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 whether they continued aspirin treatment. The non-inferiority margin was set at a 1.9% difference between both groups for the incidence of preterm PE; therefore, non-inferiority was met if the upper limit of the 95% confidence interval (CI) for the difference between both groups in preterm PE incidence was <1.9%.

Inclusion criteria in the StopPRE trial were singleton pregnancy, maternal age ≥18 years, gestational age between 24^{+0} and 27^{+6} (24–28) weeks, live fetus, high risk of preterm PE (≥1/170) during the first trimester (11^{+0} to 13^{+6} weeks) according to the screening algorithm,[9,14] treatment with daily aspirin at a dose of 150 mg initiated ≤16^{+6} weeks until randomisation 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, fetus with known congenital abnormalities, von Willebrand's disease, antiphospholipid syndrome, peptic ulceration and any condition or factor that, according to the investigator, might prevent adherence to the protocol. All participants provided written informed consent.

2.2 | Study variables and outcomes

UtAPI >95th percentile and >90th percentile perform similarly to assess the risk of PE; however, the 90th percentile has

a greater specificity and NPV to exclude the development of PE.[15] Thus, for the purposes of this post-hoc analysis, the 90th percentile was considered more appropriate and we excluded those patients with an abnormal UtAPI (>90th percentile) or without an assessment of UtAPI at enrolment. In this post-hoc analysis, we included all cases of the original study as well as all the cases excluded for having an sFlt-1/PlGF ratio ≥38. However, as all participants with an sFlt-1/PlGF ratio ≥38 also had an abnormal UtAPI, these participants were finally excluded from analysis. Among patients with a normal UtAPI (≤90th percentile) at 24–28 weeks, we compared pregnancy outcomes for patients allocated to aspirin discontinuation and patients allocated to aspirin continuation until 36 weeks. The primary outcome was delivery due to PE before 37 weeks (preterm PE). Secondary outcomes were 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, SGA, spontaneous delivery without PE and stillbirth were considered other adverse outcomes. SGA was defined as a birthweight below the 10th percentile according to customised local charts.[16] PE was defined according to the guidelines of the American College of Obstetricians and Gynecologists: new-onset high blood pressure (SBP >140 mmHg and/or DBP >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/mcl, serum creatinine >1.1 mg/dl or pulmonary oedema.[17] 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.[18] Immediate delivery was indicated in women with pulmonary oedema, placental abruption, persistent hypertension despite appropriate antihypertensive therapy, persistent cerebral or visual disturbances, oliguria (≤500 ml in 24 hours or <20 ml/hour) or eclampsia. Other secondary outcomes were minor antepartum bleeding complications (nose and/or gum bleeding), major antepartum bleeding complications (digestive and/or vaginal bleeding, haemoptysis), maternal intracranial haemorrhage; postpartum haemorrhage, stillbirth, neonatal death, low birthweight (below the 3rd or 10th percentile),[16] neonatal complications, and neonate requiring therapy.

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

2.3 | Statistical analysis

Categorical data were reported as frequency and percentage and comparisons between groups were estimated by 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, and intervention effect for the primary and secondary outcomes was quantified as the absolute difference between groups in incidences, the relative risk (RR) and the 95% confidence interval (95% CI). Statistical significance level was set at $P < 0.05$. The non-inferiority margin was set at a difference of 1.9% between both groups for incidence of preterm PE, as in the original study. Statistical analyses were performed on an intention-to-treat basis using the STATA Statistical Software (StataCorp 2017. Stata Statistical Software: Release 15. StataCorp LLC.).

3 | RESULTS

Between 5 March 2019 and 15 May 2021, a total of 13 983 women were screened for PE; of these, 1984 (14.2%) were identified as being at a high risk of preterm PE and were prescribed daily aspirin at a dose of 150 mg to be taken at bedtime until 36 weeks. However, 373 of these women (18.8%) did not meet the eligibility criteria (Figure 1). Of the 1611 eligible women (1604 had an sFlt-1/PlGF ratio <38 as in the StopPRE trial, and seven had an sFlt-1/PlGF ratio ≥38), 139 were excluded in this study due to UtAPI >90th percentile or when UtAPI was not available. All cases with an sFlt-1/PlGF ≥38 had a UtAPI >90th percentile and were therefore excluded from this study. Finally, 836 agreed to participate and were randomised in two groups, from 20 August 2019 through 15 September 2021. After randomisation, three women withdrew consent and 29 were lost to follow-up. For 804 women (96.2%) data were available for the primary and secondary outcomes. Baseline characteristics of women included and excluded in this study can be seen in Table 1 and Table S1.

Preterm PE occurred in three of 409 women (0.7%) in the intervention group and five of 395 women (1.3%) in the control group (absolute difference −0.53; 95% CI −1.91 to 0.85). Median (interquartile range) gestational age at delivery for cases with PE <37 weeks was 35.1 (34.0–35.3) weeks in the intervention group and 36.3 (34.7–36.6) weeks in the control group ($P = 0.297$). More details can be found in Figure 2. There were no significant differences between groups in terms of incidence of other adverse outcomes with delivery <37 weeks or any adverse outcome with delivery <34 weeks. The incidence of adverse outcomes at ≥37 weeks of gestation did not differ significantly between groups. Median (interquartile range) gestational age at delivery for cases with PE at ≥37 weeks was 38.7 (37.9–39.4) weeks in the intervention group and 38.3 (37.3–39.6) weeks in the control group ($P = 0.509$).

The incidence of minor antepartum haemorrhage was 7.6% in the intervention group and 13.2% in the control group (absolute difference −5.59; 95% CI −9.79 to −1.38). At least one bleeding complication occurred in 33 of 409 participants (8.1%) in the intervention group and 54 of 409

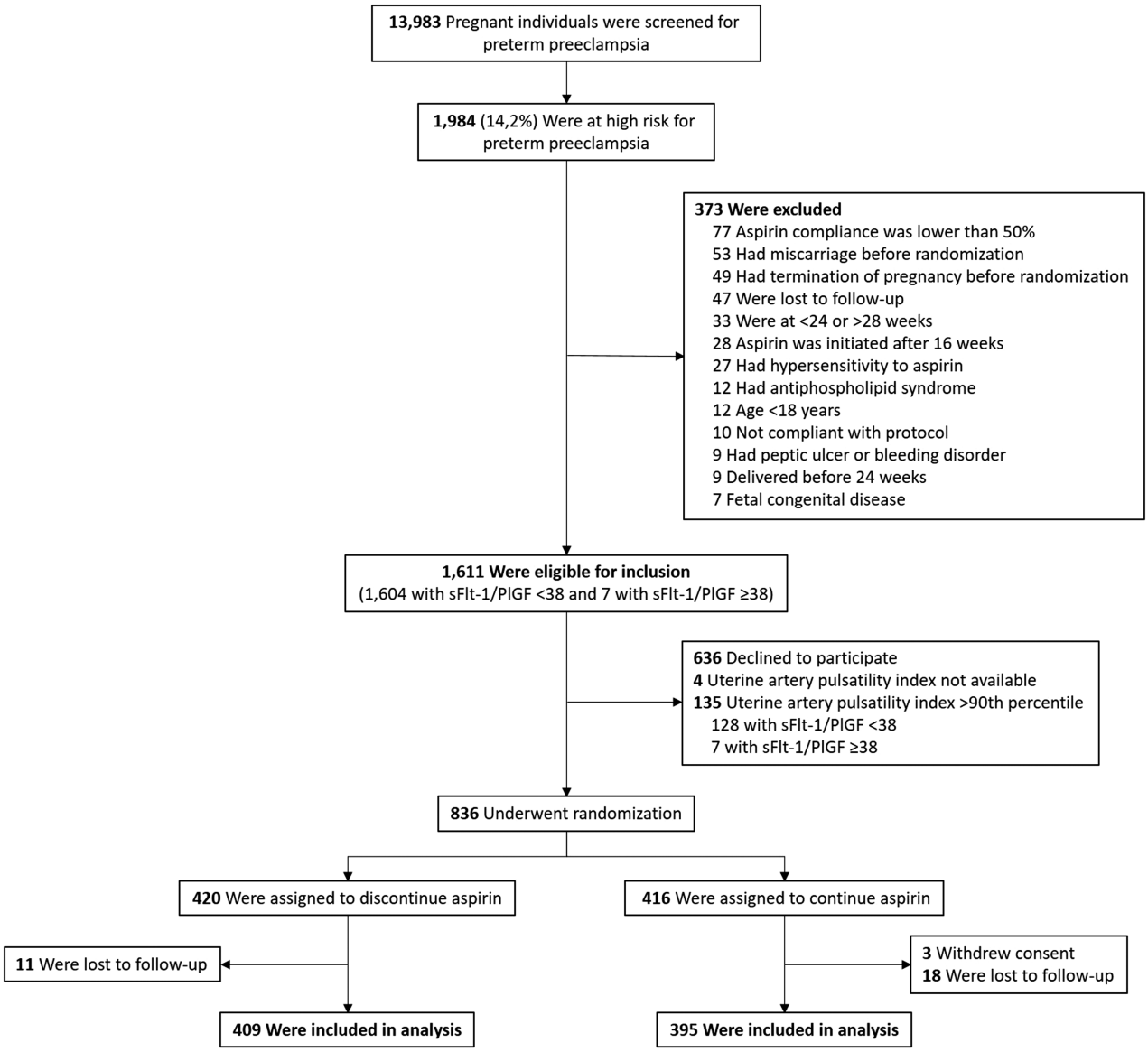

FIGURE 1 Flowchart.

participants (13.7%) in the control group (absolute difference −5.60; 95% CI −9.90 to −1.31). The incidence of other bleeding complications or adverse neonatal events (Figure 2) did not differ significantly between groups; however, the incidence of placental abruption at <37 weeks of gestation (no cases versus three [0.8%] cases, $P = 0.077$) and neonatal distress syndrome (6 [1.5%] cases versus 13 [3.3%] cases, $P = 0.089$) tended to be greater in participants that continued aspirin treatment until 36 weeks. Figure 2 shows a forest plot for all outcomes.

Despite being assigned to the intervention group, four participants (0.98%) continued aspirin treatment with a median (interquartile range) tablet intake of 100% (100–100). In the control group, aspirin treatment compliance could not be verified by tablet counts in six of 395 participants (1.5%). Among the 389 women for whom aspirin treatment compliance was verified, tablet intake was ≥90% in all visits for ≥81% of participants.

4 | DISCUSSION

4.1 | Main findings

Aspirin discontinuation in women with normal UtAPI (≤90th percentile) at 24–28 weeks is non-inferior to aspirin continuation until 36 weeks for preventing preterm PE and other pregnancy complications. Additionally, women in the intervention group had significantly fewer minor bleeding complications and tended to have less placental abruption at <37 weeks and neonatal respiratory distress syndrome than women in the control group.

TABLE 1 Characteristics of the trial participants.

Characteristic	Intervention group ($n=409$)	Control group ($n=395$)
Gestational age at randomisation, weeks	26.1 (25.7–26.7)	26.3 (25.9–26.6)
Age, years	32.6 (28.1–36.5)	32.8 (27.9–36.3)
Body mass index, kg/m^2	28.0 (24.6–32.3)	28.4 (24.6–32.6)
Race or ethnic group[a]		
White	384 (93.9)	363 (91.9)
Black	15 (3.7)	14 (3.5)
South Asian	3 (0.7)	9 (2.3)
East Asian	2 (0.5)	2 (0.5)
Mixed race	5 (1.2)	7 (1.8)
Method of conception		
Natural	400 (97.8)	389 (98.5)
Assisted by use of ovulation drugs	1 (0.2)	1 (0.3)
In vitro fertilisation	8 (2.0)	5 (1.2)
Cigarette smoking	33 (8.1)	39 (9.9)
Medical history		
Chronic hypertension	16 (3.9)	13 (3.3)
Systemic lupus erythematosus	0 (0)	0 (0)
Diabetes mellitus type 1 or 2	16 (3.9)	11 (2.8)
Renal disease	0 (0)	0 (0)
Obstetrical history		
Nulliparous	217 (53.1)	200 (50.6)
Multiparous without pre-eclampsia	164 (40.1)	177 (44.8)
Multiparous with pre-eclampsia	28 (6.8)	18 (4.6)
Risk of preterm pre-eclampsia as assessed at screening at 11–13 weeks[b], %	2.0 (1.0–6.0)	2.0 (1.0–5.0)
Gestational age for sFlt-1/PlGF measurement at randomisation, weeks	25.1 (24.8–25.8)	25.3 (24.9–25.9)
sFlt-1/PlGF at randomisation	3.89 (2.55–5.89)	3.77 (2.43–5.64)
Estimated fetal weight at randomisation, grams	931.0 (860.0–1024.0)	923.0 (847.0–1009.0)
Estimated fetal weight <10th percentile at randomisation	3 (0.7)	2 (0.5)
Uterine artery pulsatility index at randomisation	0.81 (0.69–0.94)	0.82 (0.70–0.95)

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

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

[b]Risk of preterm pre-eclampsia 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.[9]

4.2 | Strengths and limitations

The main strength of this study is its prospective design in a large cohort of women at a high risk of PE. Additionally, we provide novel evidence that a UtAPI ≤90th percentile is a good alternative to an sFlt-1/PlGF ≤38, which can be used alone or in combination with the sFlt-1/PlGF ratio to identify patients for whom aspirin treatment can be discontinued, thereby reducing exposure time to aspirin treatment and aspirin-related complications during pregnancy.

This study also has several limitations. First, it is a post-hoc analysis of a previous clinical trial and its results should therefore be interpreted with caution. Secondly, it shares the limitations of the original trial: Physicians and participants were aware of group assignment, and placebo was not used in the intervention group, as PE is not a subjective outcome measure and because the researchers aimed to simulate a real clinical setting. Thirdly, the trial was not powered enough to assess the effect of aspirin treatment discontinuation for rarer complications. Finally, the incidence of all adverse outcomes was low and for this reason, the participating site could not be used as a cluster variable in analysis, which may have lowered standard errors and the possibilities of reaching the non-inferiority margin. Nevertheless, E-values were calculated to assess the robustness of our findings to unmeasured confounding, showing that in most cases considerable unmeasured confounding would be needed to explain away the results of this study (see Table S2).

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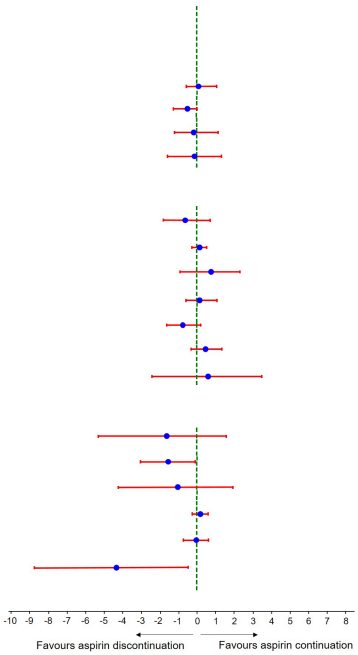
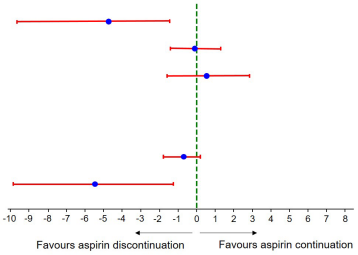
A. Secondary outcomes according to gestational age	Stop aspirin group [n= 409]	Control group [n= 395]	Relative risk [95% CI]	Incidence difference [95%CI]
Adverse outcomes at <34 weeks of gestation				
Preeclampsia	0	0	-	-
Gestational hypertension	0	0	-	-
Small-for-gestational-age*	0	0	-	-
Stillbirth	2 [0.5]	1 [0.3]	1.93 [0.18-21.22]	0.24% [-0.60 to 1.07]
Placental abruption	0	2 [0.5]	-	-0.51% [-1.21 to 0.19]
Spontaneous delivery without preeclampsia	3 [0.7]	3 [0.8]	0.97 [0.20-4.76]	-0.03% [-1.22 to 1.16]
Any	5 [1.2]	5 [1.3]	0.97 [0.28-3.31]	-0.04% [-1.58 to 1.49]
Adverse outcomes at <37 weeks of gestation				
Preeclampsia	3 [0.7]	5 [1.3]	0.58 [0.14-2.41]	-0.53% [-1.91 to 0.85]
Gestational hypertension	1 [0.2]	0	-	0.24% [-0.23 to 0.72]
Small-for-gestational-age*	6 [1.5]	2 [0.5]	2.90 [0.59-14.27]	0.96% [-0.40 to 2.32]
Stillbirth	2 [0.5]	1 [0.3]	1.93 [0.18-21.22]	0.24% [-0.60 to 1.07]
Placental abruption	0	3 [0.8]	-	-0.76% [-1.62 to 0.10]
Spontaneous delivery without preeclampsia	11 [2.7]	9 [2.3]	1.18 [0.49-2.82]	0.49% [-0.19 to 1.17]
Any	21 [5.1]	18 [4.6]	1.13 [0.61-2.08]	0.58% [-2.39 to 3.54]
Adverse outcomes at ≥37 weeks of gestation				
Preeclampsia	25 [6.1]	31 [7.8]	0.78 [0.47-1.29]	-1.74% [-5.26 to 1.79]
Gestational hypertension	2 [0.5]	8 [2.0]	0.24 [0.05-1.13]	-1.54% [-3.08 to -0.01]
Small-for-gestational-age*	20 [4.9]	24 [6.1]	0.80 [0.45-1.43]	-1.19% [-4.34 to 1.96]
Stillbirth	1 [0.2]	0	-	0.24% [-0.23 to 0.72]
Placental abruption	1 [0.2]	1 [0.3]	0.97 [0.06-15.39]	-0.01% [-0.70 to 0.68]
Any	46 [11.2]	61 [15.4]	0.73 [0.51-1.04]	-4.20% [-8,89 to -0.50]



B. Bleeding complications	Stop aspirin group [n= 409]	Control group [n= 395]	Relative risk [95% CI]	Incidence difference [95%CI]
Minor antepartum hemorrhage†	31 [7.6]	52 [13.2]	0.58 [0.38-0.88]	-5,59% [-9,79 to -1.38]
Major antepartum hemorrhage‡	4 [1.0]	4 [1.0]	0.97 [0.24-3.83]	-0.03% [-1.41 to 1.34]
Postpartum hemorrhage ≥1000 mL	13 [3.2]	10 [2.5]	1.26 [0.56-2.83]	0.65% [-1,65 to 2.95]
Maternal intracerebral hemorrhage	0	0	-	-
Neonatal intraventricular hemorrhage grade ≥III	0	0	-	-
Placental abruption	1 [0.2]	4 [1.0]	0.24 [0.03-2.15]	-0.77% [-1.87 to 0.33]
Any	33 [8.1]	54 [13.7]	0.59 [0.39-0.89]	-5.60% [-9.90 to -1.31]



C. Neonatal outcomes	Stop aspirin group [n= 409]	Control group [n= 395]	Relative risk [95% CI]	Incidence difference [95%CI]
Death or complications				
Stillbirth or death	4 [1]	1 [0.3]	3.86 [0.43 to 34.41]	0.72% [-0.35 to 1.80]
Intraventricular hemorrhage of grade ≥II	0	0	-	-
Sepsis with confirmed bacteremia in cultures	2 [0.5]	5 [1.3]	0.39 [0.08 to 1.98]	-0.78% [-2.07 to 0.52]
Respiratory distress syndrome	6 [1.5]	13 [3.3]	0.45 [0.17 to 1.16]	-1.82% [-3.93 to 0.29]
Necrotizing enterocolitis resulting in surgery	1 [0.2]	0	-	0.24% [-0.23 to 0.72]
Any	12 [2.9]	17 [4.3]	0.68 [0.33 to 1.41]	-1.37% [-3.95 to 1.21]
Therapy				
Admission to intensive care unit	24 [5.9]	25 [6.4]	0.93 [0.54 to 1.60]	-0.44% [-3.78 to 2.90]
Ventilation or intubation	9 [2.2]	10 [2.5]	0.87 [0.36 to 2.12]	-0.33% [-2.43 to 1.77]
Any	24 [5.9]	26 [6.6]	0.89 [0.52 to 1.53]	-0.71% [-4.06 to 2.63]
Poor fetal growth				
Birth weight <3rd percentile*	11 [2.7]	6 [1.5]	1.77 [0.66 to 4.74]	1.17% [-0.81 to 3.15]
Birth weight <10th percentile*	26 [6.4]	26 [6.6]	0.97 [0.57 to 1.63]	-0.23% [-3.63 to 3.18]

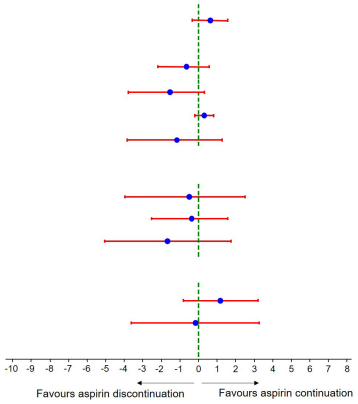


FIGURE 2 Pregnancy outcomes. Data are number of events (%), relative risk (95% CI) and incidence difference (95% CI). *The status of being small for gestational age was defined as a birthweight below the 10th percentile. Birthweight percentiles were calculated according to gestational age at birth by customised charts.[16] †Minor antepartum haemorrhage: nose and/or gum bleeding. ‡Major antepartum haemorrhage: haemoptysis, digestive and/or vaginal bleeding.

4.3 | Interpretation

Two meta-analyses showed that a greater prevention of PE was achieved when aspirin was initiated before 16 weeks and that a daily dose ≥100 mg initiated after 16 weeks may be associated with an increased relative risk of placental abruption and other bleeding complications.[19,20] For this reason, aspirin treatment should be initiated in the first trimester and discontinued at term or before onset of labour. Despite the safety concerns associated with aspirin treatment during pregnancy, discontinuation of aspirin treatment before term has been evaluated in only one study.[21] In that study, a Japanese cohort study, aspirin treatment was discontinued at 28 weeks following the Japanese national recommendations for aspirin use in pregnancy, and the study compared the incidence of PE with that of untreated historical controls. The authors Kawaguchi et al.[21] found no reduction in PE incidence; nevertheless, participants were selected according to maternal risk factors and not by a multivariable algorithm. The the incidence of preterm PE was surprisingly high in both groups (12.0 versus 13.1%), the daily dose of aspirin was only 100 mg, and compliance in the aspirin group was not reported. For these reasons, those authors concluded that further studies were needed to determine when aspirin treatment should be discontinued during pregnancy. The Stop-PRE trial showed that aspirin treatment discontinuation in patients with an sFlt-1/PlGF ratio ≤38 at 24–28 weeks was non-inferior to prevent preterm PE compared with continuing aspirin treatment until 36 weeks.[12] Several studies have demonstrated that a normal UtAPI in the second and third trimesters has an NPV above 90% for excluding PE.[15] However, no previous studies have evaluated the usefulness of UtA Doppler for deciding whether to discontinue aspirin treatment in women at a high risk of PE. In the Stop-PRE trial, the screen-positive rate at 24–28 weeks according to the sFlt-1/PlGF ratio (i.e. patients with sFlt-1/PlGF>38) was 0.7% (7/975) and, according to this, aspirin treatment could be discontinued in 99.3% (968/975) of pregnant women at a high risk of PE. By contrast, in the present post-hoc analysis, the screen-positive rate based on the UtAPI (i.e. patients with a UtAPI >90th percentile) was 13.9% (135/971) and therefore, aspirin treatment could be safely discontinued in 86.1% (836/971) of participants. Thus, aspirin discontinuation based on the UtAPI may be more convenient and cost-effective for some settings than aspirin discontinuation based on the sFlt-1/PlGF ratio. On the other hand, aspirin treatment would be discontinued in a lower proportion of patients when using the UtAPI alone (99.3 versus 86.1%).

Additionally, in this study we show that aspirin discontinuation in pregnant women with normal UtAPI did not increase the risk of preterm PE, which supports the hypothesis that an abnormal placentation can be identified by Doppler studies and is a major cause of PE, especially in its earlier forms.

4.4 | Clinical and research implications

This study has important clinical implications, as it provides evidence that aspirin can be safely discontinued in those women at a high risk of PE who have a normal UtAPI at 24–28 weeks, which may reduce the risk of bleeding and potentially other iatrogenic complications of aspirin treatment such as neonatal respiratory distress syndrome and placental abruption when discontinued in larger populations. Therefore, the results of the current study may be used as an alternative to use of the sFlt-1/PlGF ratio in those settings where this value is not available. Additionally, our findings

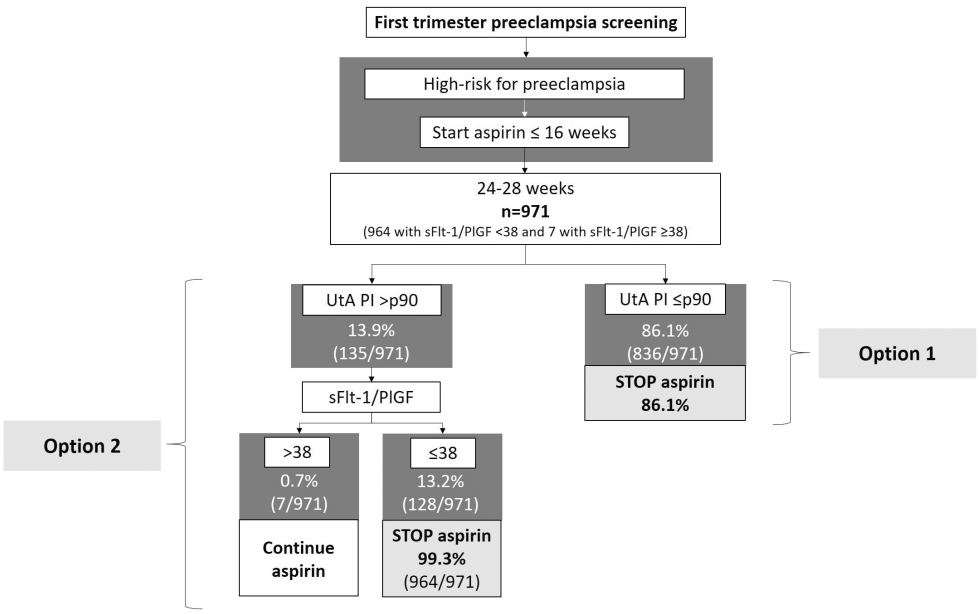


FIGURE 3 Options for aspirin discontinuation based on mean uterine artery pulsatility index.

may complement those of the Stop-PRE trial, and one potential management protocol may be done in two steps, as follows: in the first step, aspirin may be discontinued in the 804 (86.1%) women with UtAPI ≤90th percentile. In the second step, aspirin may be discontinued in the remaining 132 (13.9%) women with UtAPI >90th percentile and normal sFlt-1/PlGF (≤38). This two-step approach would allow discontinuation of aspirin in the same proportion of women as in the Stop-PRE trial and would therefore have the same outcomes as those of the Stop-PRE trial but with the difference that sFlt-1/PlGF measurement would be performed in a smaller proportion of patients (13.9% instead of 100%). (Figure 3).

5 | CONCLUSION

Discontinuing aspirin treatment at 24–28 weeks in women at a high risk of PE with a UtAPI ≤90th percentile was non-inferior to continuing aspirin treatment until 36 weeks for preventing preterm PE and other related disorders. Therefore, a UtAPI ≤90th percentile may be used alone or in combination with the sFlt-1/PlGF ratio to identify patients for whom aspirin treatment can be discontinued, which could reduce bleeding risk and other iatrogenic complications of aspirin treatment.

AUTHOR CONTRIBUTIONS

Conceptualisation: MM and AS. Methodology: MM, EB, PG-M and AS. Data collection: All authors. Statistical analysis: MM. Data interpretation: MM, EB, PG-M and AS. Drafting of the article: EB and PG-M. Article review and editing: All authors.

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CONFLICT OF INTEREST STATEMENT

MM 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. Completed disclosure of interests forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study protocol was approved by the institutional review board at each participating centre and by the Spanish Agency for Medicines and Medical Devices (AEMPS). Participants provided written informed consent.

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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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