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ASPRE trial: effects of aspirin on mean arterial blood pressure and uterine artery pulsatility index trajectories in pregnancy

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KEYWORDS: aspirin; ASPRE trial; first trimester; mean arterial pressure; pre-eclampsia; prevention; uterine artery Doppler

CONTRIBUTION

What are the novel findings of this work?
Aspirin is effective in preventing preterm pre-eclampsia, but its precise mechanism of action remains unknown. In this secondary longitudinal analysis of the ASPRE trial, aspirin had no evident effect on the trajectory of mean arterial pressure values over time but led to a steeper decline in uterine artery pulsatility index, particularly before 20 weeks of gestation.

What are the clinical implications of this work?
We found no evidence of antihypertensive effects of aspirin in pregnancy. The significant difference in uterine artery pulsatility index trajectory between high-risk women who receive aspirin compared with those who do not, particularly before 20 weeks of pregnancy, may suggest an improvement in trophoblastic invasion and uteroplacental perfusion.

ABSTRACT

Objectives *The mechanism by which aspirin prevents pre-eclampsia is poorly understood, and its effects on biomarkers throughout pregnancy are unknown. We aimed to investigate the effects of aspirin on mean arterial pressure (MAP) and mean uterine artery pulsatility index (UtA-PI) using repeated measures from women at increased risk of preterm pre-eclampsia.*

Methods *This was a longitudinal secondary analysis of the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Pre-eclampsia Prevention (ASPRE) trial using repeated measures of MAP and UtA-PI. In the trial, 1620 women at increased risk of preterm pre-eclampsia were identified using the Fetal Medicine Foundation algorithm at 11 + 0 to 13 + 6 weeks, of whom 798 were randomly assigned to receive 150 mg/day aspirin and 822 were assigned to receive placebo daily from 11–14 weeks to 36 weeks of gestation or delivery, whichever came first. MAP and UtA-PI were measured at baseline and follow-up visits at 19–24, 32–34 and 36 weeks of gestation. Generalized additive mixed models with treatment by gestational age interaction terms were used to investigate the effects of aspirin on MAP and UtA-PI trajectories over time.*

Results *Among 798 participants in the aspirin group and 822 in the placebo group, there were 5951 MAP and 5942 UtA-PI measurements. Trajectories of raw and multiples of the median (MoM) values of MAP did not differ significantly between the two groups (MAP MoM analysis:* P*-value for treatment by gestational age interaction, 0.340). In contrast, trajectories of raw and MoM values of UtA-PI showed a significantly steeper decline in the aspirin group than in the placebo group, with the difference mainly driven by a more pronounced reduction before 20 weeks of gestation (UtA-PI MoM analysis:* P*-value for treatment by gestational age interaction, 0.006).*

Conclusions *In women at increased risk of preterm pre-eclampsia, 150 mg/day aspirin initiated in the first trimester does not affect MAP but is associated with a significant decrease in mean UtA-PI, particularly before 20 weeks of gestation.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

Pre-eclampsia remains a leading cause of maternal and perinatal mortality. Traditional methods used to identify women at increased risk of pre-eclampsia rely on the presence of risk factors related to maternal characteristics and medical and obstetric history, but they fail to detect the majority of women who later develop the disease[1]. More accurate risk stratification in the first trimester of pregnancy can be achieved with the use of the Fetal Medicine Foundation (FMF) competing-risks algorithm that combines maternal characteristics and medical and obstetric history with mean arterial pressure (MAP), mean uterine artery pulsatility index (UtA-PI) on Doppler ultrasound and serum placental growth factor (PlGF) to produce individual risk estimates[1–3].

Accurate risk stratification is essential because, in the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Pre-eclampsia Prevention (ASPRE) trial, the treatment of high-risk women identified using the FMF algorithm with aspirin at a daily dose of 150 mg from the first trimester to 36 weeks led to a 62% reduction in the rate of pre-eclampsia with delivery before 37 weeks and nearly 90% reduction in the rate of very early forms of the disease (with delivery before 32 weeks of gestation)[4]. However, while appropriate treatment of high-risk women with aspirin initiated in the first trimester is associated with a significant reduction in preterm pre-eclampsia risk, the exact mechanism by which aspirin prevents pre-eclampsia remains unclear. It has been shown that aspirin delays placental aging and disease onset[5,6], and other theories include improvement in trophoblastic invasion, endothelial stabilization and reduction in inflammation[7–9], but large human studies to support such theories are lacking. The effect of aspirin on biomarkers of pre-eclampsia is also poorly understood, and its knowledge may provide insights into the mechanism of action of the drug.

This secondary analysis of the ASPRE trial data aimed to investigate the effects of aspirin on MAP and mean UtA-PI trajectories during pregnancy using repeated measures from the trial participants.

METHODS

Study design and population

This was a *post-hoc* secondary analysis of the ASPRE trial data. A longitudinal study design was used to investigate the effects of aspirin on MAP and mean UtA-PI trajectories during pregnancy using repeated measures among participants at high risk of preterm pre-eclampsia. The ASPRE trial was conducted at 13 maternity hospitals in the UK, Spain, Italy, Belgium, Greece and Israel[4]. Approval for the trial was obtained from the relevant research ethics committee and the competent authority of each country in which the trial was conducted. Quality control of screening and verification of adherence to the protocol were performed by the University College London Comprehensive Clinical Trials Unit (UCL-CCTU).

In the participating hospitals, routine screening for preterm pre-eclampsia was carried out at 11 + 0 to 13 + 6 weeks of gestation using the FMF first-trimester competing-risks algorithm that combined maternal demographic characteristics and medical and obstetric history with the measurements of MAP, UtA-PI, serum pregnancy-associated plasma protein-A (PAPP-A) and serum PlGF (1-2-3 kits, DELFIA Xpress random access platform; PerkinElmer Inc, Turku, Finland). Participants were then invited to participate in the randomized controlled trial (RCT) if they had an estimated risk of preterm pre-eclampsia greater than 1 in 100, were ≥ 18 years old, had no serious mental illness or learning difficulty and had a viable singleton pregnancy with no major fetal abnormality demonstrated on the 11–13-week ultrasound scan.

After screening 26 941 women, 1776 high-risk participants were allocated randomly in a double-blind fashion to receive treatment with 150 mg/day aspirin, at night, or matching placebo, from 11–14 weeks to 36 weeks' gestation or delivery, whichever came first. A total of 152 women (8.6%) withdrew consent during the study, four (0.2%) were lost to follow-up and the remaining 1620 participants were included in the intention-to-treat analysis. Pre-eclampsia was defined according to the 2001 International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines[10]. The primary outcome was pre-eclampsia with delivery before 37 weeks of gestation, which was reduced by 62% in the aspirin group compared with the placebo group (1.6% *vs* 4.3%; odds ratio adjusted for site and estimated risk, 0.38 (95% CI, 0.20–0.74); $P = 0.004$).

Follow-up

Telephone interviews were planned at 16 and 28 weeks of gestation and 30 days after the last aspirin dose to assess self-reported side effects and adherence to treatment, and follow-up visits were planned at 19–24, 32–34 and 36 weeks of gestation[11]. During these visits, participants underwent measurement of MAP, ultrasound examination to assess fetal biometry and UtA-PI, and optional collection of a maternal blood sample when women consented. Blood samples were stored at −80°C for measurement of PAPP-A and PlGF at a later stage. All measurements were carried out following standardized protocols by operators trained and certified by the FMF, and biomarker values were converted into multiples of the median (MoM) using previously published equations[12,13].

Self-reported side effects were recorded, and the remaining aspirin tablets were counted to estimate compliance by subtracting the number of tablets returned from the number of tablets prescribed. Adherence was deemed good if the estimated intake of tablets was 85% or more of the total number that participants were expected

to have taken between the date of randomization and the date of the visit at 36 weeks of gestation or the date of delivery if delivery occurred before 36 weeks of gestation. Adherence was good in 79.9% of the participants[4].

Statistical analysis

Repeated MAP and UtA-PI measurements, expressed as raw and MoM values, were $\log_{10}$-transformed to achieve an approximately normal distribution and stabilize the variances. Given the unbalanced repeated-measures design, with about 6% mistimed measurements (all in the third and fourth visits), multivariable generalized additive mixed models (GAMM) with unstructured variance-covariance matrices were fitted to the data using restricted maximum likelihood. Such flexible models allow for inclusion of non-linear functions of continuous predictors and account for the within-participant correlation by introducing random effects. Given the evidence of a non-linear relationship of gestational age with $\log_{10}$ MAP and UtA-PI values, the models included natural cubic spline terms for gestational age with three degrees of freedom (two knots placed at 20.3 and 32.4 weeks of gestation, dividing the data into three equally sized parts), as well as individual random intercepts and slopes. Differences in MAP and UtA-PI trajectories between the aspirin and placebo groups were investigated by including the main effects of treatment and treatment by gestational age interaction terms. To account for the baseline risk, estimates were also adjusted for the first-trimester estimated risk of preterm pre-eclampsia. Trajectories between the treatment groups were considered different when the two-sided *P*-value for the treatment by gestational age interaction term was statistically significant at the 0.05 alpha level. Trajectories were presented graphically as estimated marginal means with corresponding 95% CIs.

Model fit was assessed by visual inspection of studentized residuals *vs* fitted values plots, and the adequacy of GAMM with the abovementioned specification was compared with that of linear mixed-effects models and models with different spline function specification, by comparing adjusted R^2 and Bayesian information criterion (BIC) values obtained with maximum likelihood estimation.

To assess the robustness of the estimates, we conducted two sensitivity analyses: the first was restricted to women whose reported adherence to treatment was 90% or greater; the second was limited to women who did not develop pre-eclampsia to eliminate any possible effect of the reduction in the rate of preterm pre-eclampsia in the aspirin group on observed differences in MAP and UtA-PI trajectories. Statistical analysis was conducted using the statistical software package R[14], and the packages lme4 and gamm4 were used to fit the mixed-effects models[15,16].

RESULTS

Among 798 participants in the aspirin group and 822 in the placebo group, there were 5951 MAP and 5942 UtA-PI measurements (Table 1). A total of 160 participants developed pre-eclampsia (66/798 (8.3%) in the aspirin group and 94/822 (11.4%) in the placebo

Table 1 Estimated marginal geometric means of mean arterial blood pressure (MAP) and mean uterine artery pulsatility index (UtA-PI) at different gestational ages, expressed as raw and multiples of the median (MoM) values, in high-risk women taking aspirin or placebo for pre-eclampsia prevention

	Aspirin		*Placebo*	
Biomarker	n	*Geometric mean (95% CI)*	n	*Geometric mean (95% CI)*
MAP (mmHg)				
12 weeks	798	94.604 (94.018–95.193)	822	94.445 (93.870–95.023)
22 weeks	756	90.158 (89.615–90.703)	778	90.134 (89.599–90.673)
32 weeks	721	90.950 (90.344–91.561)	726	91.457 (90.852–92.066)
36 weeks	682	93.566 (92.937–94.200)	668	93.819 (93.190–94.453)
MAP MoM				
12 weeks	798	1.083 (1.076–1.089)	822	1.078 (1.073–1.086)
22 weeks	756	1.042 (1.036–1.048)	778	1.041 (1.035–1.047)
32 weeks	721	1.027 (1.020–1.033)	726	1.032 (1.026–1.039)
36 weeks	682	1.050 (1.043–1.056)	668	1.051 (1.044–1.058)
UtA-PI				
12 weeks	798	2.071 (2.029–2.113)	822	2.095 (2.053–2.137)
22 weeks	755	1.063 (1.043–1.083)	777	1.123 (1.102–1.144)
32 weeks	720	0.786 (0.769–0.802)	724	0.838 (0.820–0.855)
36 weeks	680	0.751 (0.736–0.767)	666	0.777 (0.761–0.793)
UtA-PI MoM				
12 weeks	798	1.234 (1.121–1.259)	822	1.249 (1.225–1.274)
22 weeks	755	1.042 (1.023–1.063)	777	1.101 (1.080–1.122)
32 weeks	720	1.055 (1.033–1.078)	724	1.126 (1.102–1.149)
36 weeks	680	1.055 (1.034–1.078)	666	1.093 (1.071–1.116)

Values were obtained using generalized additive mixed models with natural cubic spline functions of gestational age with three degrees of freedom, individual random intercepts and slopes, treatment by gestational age interaction terms and unstructured variance-covariance matrices.

group), including 48 who had preterm pre-eclampsia (13/798 (1.6%) in the aspirin group and 35/822 (4.3%) in the placebo group).

The GAMM including natural cubic spline functions of gestational age with three degrees of freedom provided a significantly better fit to the data compared to models with a different number of knots for the natural cubic spline functions and linear mixed-effects models for MAP (BIC, −24 258 with GAMM *vs* −24 009 with a linear mixed-effects model; $P < 0.001$) and for UtA-PI (BIC, −9498 with GAMM *vs* −9339 with a linear mixed-effects model; $P < 0.001$).

The number of measurements in each group at the different follow-up visits and the estimated geometric means of MAP and UtA-PI at 12, 22, 32 and 36 weeks of gestation in each group are shown in Table 1.

Trajectories of raw and MoM values of MAP did not differ significantly between the aspirin and placebo groups (MAP MoM analysis: *P*-value for overall treatment by gestational age interaction, 0.340) (Figure 1a). In contrast, trajectories of raw and MoM values of UtA-PI were significantly different between the groups, demonstrating a steeper decline in UtA blood-flow impedance in the aspirin group than in the placebo group (UtA-PI MoM analysis: *P*-value for overall treatment by gestational age interaction, 0.006) (Figure 1b). The difference was mainly driven by a more pronounced reduction in the mean UtA-PI in the first spline segment (11–20.3 weeks, *P*-value for treatment by gestational age interaction, 0.006).

Fixed effects from the GAMM for the prediction of MAP MoM and UtA-PI MoM values are shown in Tables 2 and 3, respectively. Estimates and inference for MAP MoM values did not differ significantly on the sensitivity analysis restricted to 1143 women with compliance of 90% or greater or on the sensitivity analysis excluding 160 women who developed pre-eclampsia (*P*-values for overall treatment by gestational age interaction, 0.270 and 0.640, respectively). Estimates and inference for UtA-PI MoM values were also similar on the sensitivity analyses (*P*-values for treatment by gestational age first spline interaction, 0.037 and 0.024, respectively).

DISCUSSION

Main findings

In this study of repeated measurements of MAP and UtA-PI from participants of the ASPRE trial who were at increased risk of preterm pre-eclampsia, we found no significant effect of aspirin on MAP. MAP trajectories followed a U-shaped curve, which is characteristic of the physiological changes expected in pregnancy and did not differ between the aspirin and placebo groups, with largely overlapping curves. Conversely, women taking aspirin had a significantly more pronounced decline in UtA impedance, particularly before 20 weeks of gestation.

Interpretation and clinical implications

In pregnancy, cardiac output increases substantially, with a peak of 1.5 L/min in the early third trimester, accompanied by a decrease in systemic vascular resistance[17]. The physiological reduction in vascular resistance is a consequence of decreased vascular responsiveness to the pressor effects of angiotensin-II and norepinephrine, leading to vasodilation and creation of a high-flow, low-resistance circuit in the uteroplacental circulation[18,19]. Such changes incur a well-known U-shaped relationship between MAP and gestational age, mainly driven by a reduction in diastolic blood pressure (BP) in the second trimester and a return to prepregnancy levels during the third trimester[20].

Pre-eclampsia is thought to be caused by defective trophoblastic invasion, leading to increased resistance to blood flow in the UtAs that is present several weeks before disease onset and is recognizable during the first trimester[21]. A more recent theory suggests that pre-eclampsia may be caused by suboptimal maternal cardiovascular performance or adaptation to pregnancy, which leads to impaired placental perfusion[22]. In hemodynamic studies, women who develop pre-eclampsia have been found to have increased peripheral vascular resistance[23]. It is plausible that pre-eclampsia is a result of placental hypoperfusion, which may occur due to abnormal trophoblastic invasion or failure of the cardiovascular system to meet the fetoplacental demand, ultimately leading to angiogenic imbalance and endothelial dysfunction, responsible for the symptoms and signs that characterize the disease.

Although aspirin is highly effective in preventing preterm pre-eclampsia and appears to defer disease onset by delaying placental aging[5,6], the precise mechanism by which the disease is prevented remains poorly understood. Initial studies in the 1980s were triggered by evidence of increased placental thromboxane and reduced prostacyclin levels in pre-eclamptic pregnancies, and by the then-recent discovery that aspirin selectively inhibits thromboxane synthesis without affecting prostacyclin production[24]. This selective inhibition of thromboxane synthesis by aspirin may result in placental vasodilation and improved UtA blood flow. Other suggested mechanisms include improvement in trophoblastic invasion, endothelial stabilization, reduction in inflammation and possible antihypertensive effects of aspirin[7–9].

In our study, while high-risk women had higher-than-expected MAP, their patterns of change in MAP across gestation were similar compared with those expected from the general population. Nonetheless, MAP trajectories were similar in women who were treated with aspirin and those who were not. Similarly, a previous non-invasive maternal cardiac function study demonstrated that women who develop pre-eclampsia have a pathological cardiac adaptation to pregnancy and that aspirin may not alter this profile[25]. A RCT by Hermida *et al.*, including 240 pregnant women, showed that 100 mg/day aspirin had no significant effect on BP when given in

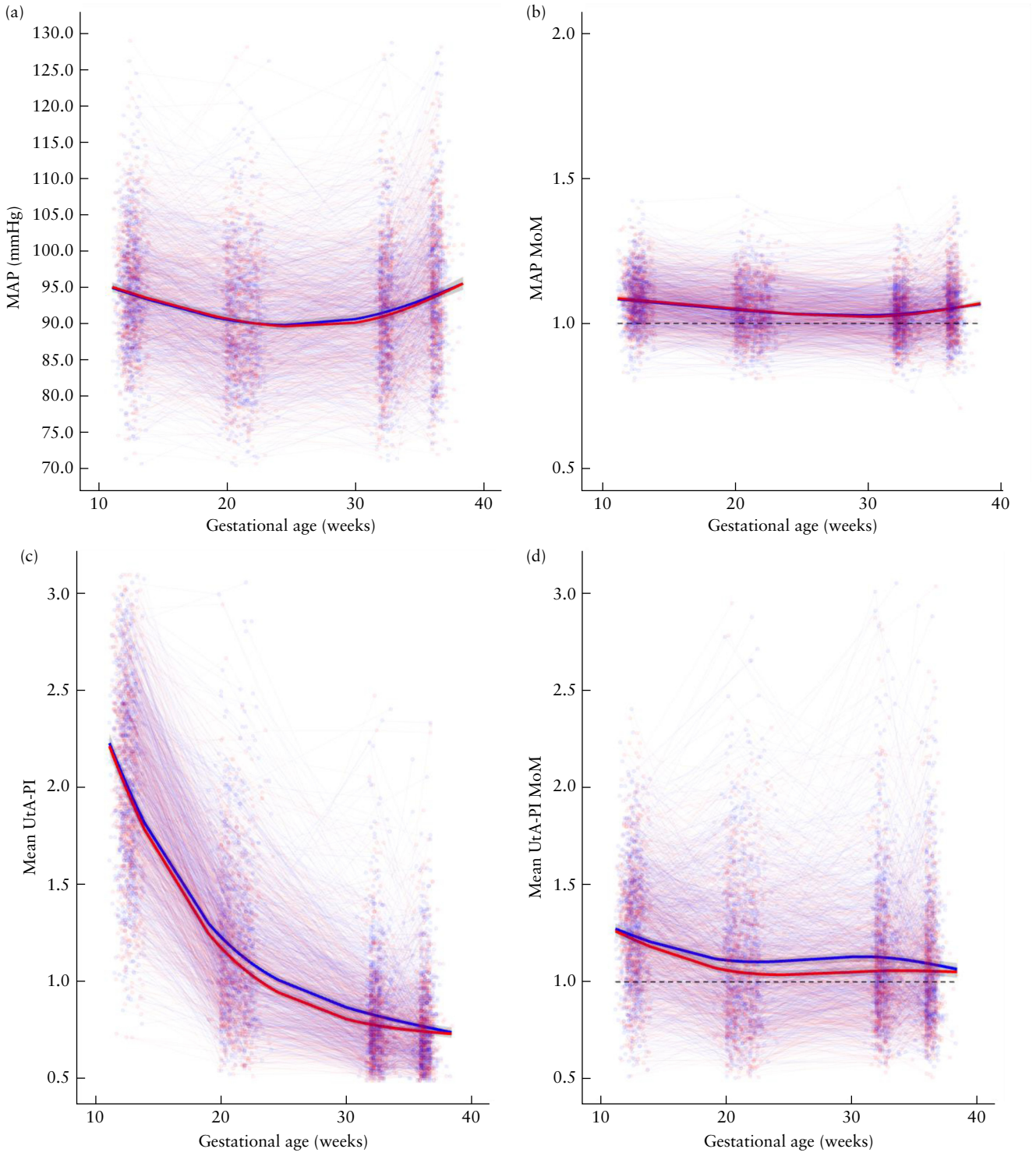

Figure 1 Estimated marginal means of repeated mean arterial pressure (MAP) (a,b) and mean uterine artery pulsatility index (UtA-PI) (c,d) measurements, expressed as raw (a,c) and multiples of the median (MoM) (b,d) values, among women at increased risk of preterm pre-eclampsia randomly allocated to receive 150 mg/day aspirin (——) or placebo (——) in the ASPRE trial[4], with 95% CI (gray-shaded areas on either side of lines). Faint red and blue dots and connecting lines represent individual participant measurements and trajectories. Estimates were obtained using generalized additive mixed models with natural cubic spline functions of gestational age at testing with three degrees of freedom (two equally spaced knots at 20.3 and 32.4 weeks of gestation). For MAP MoM analysis: *P*-value for overall treatment by gestational age interaction, 0.340; adjusted R^2, 0.065. For UtA-PI MoM analysis: *P*-value for overall treatment by gestational age interaction, 0.006; adjusted R^2, 0.074.

the morning but was associated with a BP reduction compared with placebo when given in the afternoon or at bedtime[26]. Studies in non-pregnant healthy adults and in those at increased risk of cardiovascular disease remain inconclusive about the possible effects of aspirin on BP[27,28].

Whilst no effects of aspirin on MAP were observed, aspirin initiated in the first trimester led to a more pronounced decrease in UtA resistance before 20 weeks of gestation compared with placebo. This finding is in line with those of two previous smaller studies[8,29]. Conversely, a previous RCT of 150 mg aspirin *vs* placebo including 155 participants with UtA-PI > 95th percentile at 11–14 weeks published before the ASPRE trial showed no significant changes in UtA-PI at 28 weeks of gestation[30]. The trial was criticized for not reaching its intended sample size (240 participants), reporting on overall, rather than preterm, PE and selecting participants based on UtA Doppler resistance alone, a poor predictor of disease in isolation, which is reflected by the low (4.5%) incidence of pre-eclampsia in the 'high-risk' group[31].

The effect of aspirin on UtA resistance may suggest that it prevents pre-eclampsia by improving trophoblastic invasion and spiral artery remodeling and/or inducing placental vasodilation, thereby improving perfusion, rather than by exerting systemic effects on BP or inflammation. Further research on the impact of aspirin on serum angiogenic and antiangiogenic biomarkers (such as PlGF and soluble fms-like tyrosine kinase-1, respectively) may help clarify whether trophoblastic invasion is improved and whether aspirin has a significant impact on endothelial function.

Our results provide insight into the possible mechanisms by which aspirin prevents pre-eclampsia. Still, the variability in the data is likely too large to allow clinical management decisions, such as when to cease treatment based on individual changes in UtA-PI.

Table 2 Fixed effects in prediction of $\log_{10}$ mean arterial pressure multiples of the median values

Term	*Coefficient*	*SE*	P
Intercept	0.03060	0.00151	< 0.001
Aspirin	0.00114	0.00204	0.577
GA spline 1	−0.02525	0.00235	< 0.001
GA spline 2	−0.02636	0.00323	< 0.001
GA spline 3	0.00379	0.00180	0.035
Pre-eclampsia risk	0.08592	0.00962	< 0.001
Aspirin × GA spline 1	−0.00579	0.00333	0.082
Aspirin × GA spline 2	−0.00070	0.00460	0.880
Aspirin × GA spline 3	−0.00065	0.00254	0.799

Estimates obtained using generalized additive mixed model including natural cubic spline function of gestational age (GA) at blood sampling with three degrees of freedom and knots placed at 20.3 and 32.4 weeks of gestation, treatment by GA spline interaction terms and unstructured variance-covariance matrix. Random intercepts and slopes for GA were modeled as random effects for 1620 participants with a total of 5951 mean arterial pressure measurements. Adjusted R^2, 0.065; Akaike information criterion, −24 345; Bayesian information criterion, −24 258; *P*-value for overall treatment by GA interaction, 0.340. SE, standard error.

Table 3 Fixed effects in prediction of $\log_{10}$ mean uterine artery pulsatility index multiples of the median values

Term	*Coefficient*	*SE*	P
Intercept	0.09054	0.00505	< 0.001
Aspirin	−0.00376	0.00684	0.582
GA spline 1	−0.01765	0.00847	0.037
GA spline 2	−0.13904	0.01143	< 0.001
GA spline 3	−0.02404	0.00631	< 0.001
Pre-eclampsia risk	0.28200	0.03074	< 0.001
Aspirin × GA spline 1	−0.03309	0.01198	0.006
Aspirin × GA spline 2	−0.02462	0.01628	0.130
Aspirin × GA spline 3	0.01000	0.00890	0.261

Estimates obtained using generalized additive mixed model including natural cubic spline function of gestational age (GA) at blood sampling with three degrees of freedom and knots placed at 20.3 and 32.4 weeks of gestation, treatment by GA spline interaction terms and unstructured variance-covariance matrix. Random intercepts and slopes for GA were modeled as random effects for 1620 participants with a total of 5942 mean uterine artery pulsatility index measurements. Adjusted R^2, 0.074; Akaike information criterion, −9585; Bayesian information criterion, −9498; *P*-value for overall treatment by GA interaction, 0.006. SE, standard error.

Strengths and limitations

The main strength of this study is its large sample size, with nearly 6000 MAP and UtA-PI measurements. Previous studies on the effects of aspirin on BP and UtA blood flow in pregnant women were smaller and reached variable conclusions. We used modern regression techniques that appropriately account for the repeated-measures design and non-linear trends in the data. Using data from a large RCT with balanced baseline characteristics between the groups implies unconditional exchangeability; therefore, any observed effects of aspirin on biomarker trajectories can be assumed to be causal. We also conducted sensitivity analyses to evaluate the effects of compliance and pre-eclampsia on the estimates obtained.

The main limitations of the study include smaller numbers of participants in subsequent follow-up visits, leading to unbalanced group sizes, and the presence of mistimed observations in about 6% of the participants. However, both issues are addressed by mixed-effects models, which treat gestational age as a continuous, rather than categorical, variable. The declining number of participants during follow-up was similar between the aspirin and placebo groups and is also expected in a longitudinal follow-up, as some women delivered preterm, with or without pre-eclampsia. The findings are generalizable to women at increased risk of preterm pre-eclampsia identified by the FMF competing-risks algorithm and who receive 150 mg/day aspirin from the first trimester. However, they may not apply to low-risk women, those at increased risk identified by other means and those who take aspirin at lower doses or start taking aspirin after the first trimester.

Conclusion

In women at increased risk of preterm pre-eclampsia, 150 mg/day aspirin initiated in the first trimester has no effect on MAP but is associated with a decrease in mean UtA-PI, particularly before 20 weeks of gestation. These findings suggest possible improvements in trophoblastic invasion and UtA blood flow.

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