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Pharmacodynamics of Aspirin Through Gestation: Predictors of Aspirin Response and Association With Pregnancy Outcome, a Prospective Cohort Study

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ABSTRACT

Low-dose aspirin is recommended for prevention of hypertensive disorders of pregnancy (HDP) and preterm birth (PTB) in high-risk pregnancies. There is limited data on factors impacting aspirin response in pregnancy. We aimed to evaluate predictors of aspirin response and association with pregnancy outcome with a prospective study of high-risk pregnancies taking 81 mg aspirin daily. Aspirin response was evaluated with Platelet Function Assay-100 (PFA-100) epinephrine closure time at baseline (< 16 weeks' gestation), follow-up 1 (2–4 weeks after aspirin initiation), and follow-up 2 (28–32 weeks gestation). Multivariable regression was used to identify factors associated with PFA-100 at each visit, and results presented with beta coefficient (B) and confidence interval. The median difference (MD) in PFA-100 in those with and without HDP or PTB was compared. Results included 108 who completed follow-up 1 and 96 who completed both visits with > 75% adherence. PFA-100 was increased from baseline at follow-ups 1 and 2 (MD 37 (27–49); MD 26 (15.5–38.5) respectively). At follow-up 1, obesity (B = −30 (−53 to −7) seconds), diabetes (B = −39 (−75 to −2) seconds), and age (B = 2.2 (0.3–4.0) seconds per year increased) were associated with PFA-100 response. Those with HDP in the current pregnancy versus not had similar aspirin response, but those with PTB versus term birth in the current pregnancy had reduced aspirin response at 28–32 weeks (MD −27 (−54 to −3) seconds). A daily dose of 81 mg aspirin results in platelet inhibition throughout gestation. Obesity, diabetes, and younger age are associated with reduced aspirin response in pregnancy.

JEL Classification: DEI

1 | Introduction

Low-dose aspirin reduces the risk of preeclampsia and perinatal morbidity in selected high risk pregnancies [1–3]. The efficacy of low-dose aspirin in preeclampsia prevention may vary by individual factors [4], with 20%–30% experiencing preeclampsia despite aspirin use [5]. Currently the United States Preventative Services Task Force (USPSTF) recommends 81 mg aspirin daily dosing for patients with risk factors for preeclampsia [6], however meta-analyses are conflicting regarding the role of higher dose in aspirin efficacy [1, 7]. In non-pregnant adults, there is well established individual variability in platelet response to low-dose aspirin [8, 9], this may contribute to efficacy of higher versus lower doses in specific individuals in pregnancy as well. There exists a need to better quantify the pharmacologic response to aspirin in the pregnant population.

Summary

- What is the current knowledge on the topic?
  - Non-pregnant adults demonstrate significant variability in response to aspirin which has implications for clinical care and dosing; however, there is a limited understanding of aspirin response in pregnancy, which has important implications for clinical efficacy.
- What question does this study address?
  - We sought to evaluate predictors of aspirin pharmacodynamics in pregnancy, measured by a commercially available assay, platelet inhibition through PFA-100 epinephrine closure time (Siemens), and assess whether aspirin response was associated with pregnancy outcome.
- What does this study add to our knowledge?
  - A daily dose of 81 mg aspirin results in measurable and sustained platelet inhibition throughout pregnancy, as measured by PFA-100 epinephrine closure time, although this declines as pregnancy progresses.
  - Pre-gestational diabetes, and baseline obesity (BMI ≥ 30) were independently associated with reduced initial response to aspirin in pregnancy.
  - There was no difference in aspirin response in those who developed a hypertensive disorders of pregnancy versus not, however those who had a preterm birth had a reduced response to aspirin at 28–32 weeks compared to those with a term birth.
- How might this change clinical pharmacology or translational science?
  - We identified important covariates (obesity, diabetes, age) that influence aspirin response through pregnancy and that a commercially available assay, PFA-100 (Siemens) is useful for assessment of aspirin pharmacodynamics in pregnancy.
  - Our findings have important implications for the design of future dose–response studies in pregnancy taking into consideration individual characteristics and gestational age.
  - Furthermore, our findings suggest further research is warranted on the relationship between aspirin pharmacodynamics and pregnancy outcomes such as preterm birth.

The mechanism of action of aspirin in preeclampsia prevention is not well established. Prior work has demonstrated how early platelet activation and placental vascular hypo-perfusion plays in the development of preeclampsia later in pregnancy [10, 11]. It is postulated aspirin inhibits platelet activity, and subsequent placental vasculopathy [12]. Aspirin inhibits platelet activity through inhibition of cyclooxygenase-1, which leads to suppression of thromboxane A2, a necessary substrate from platelet activation, which ultimately leads to reduced platelet reactivity [13, 14].

In non-pregnant adults, non-response to low-dose aspirin, as measured by platelet activity, is associated with increased risk of cardiovascular related morbidity in patients recommended to take aspirin for preventative purposes [13, 14]. There are a number of different ways to assess platelet activity in response to aspirin. The gold standard is usually considered to be light aggregometry, however this is time intensive and laboratory specific, limiting its use as a generalizable assay for clinical use [14]. There are commercially available assays that have been validated against light aggregometry including Platelet Function Assay-100 (PFA-100, Siemens). Inadequate response to low-dose aspirin as measured by Platelet Function Assay-100 (Siemens, PFA-100) closure time is associated with significantly increased cardiovascular morbidity [13–15] in non-pregnant adults.

A similar relationship between individual aspirin response and clinical efficacy has not been well studied in pregnancy. Given the known inter-individual variability in aspirin response in non-pregnant adults [14, 16], the impact aspirin response measured by Platelet Function Assay-100 (Siemens, PFA-100) closure time has on risk of subsequent cardiovascular morbidity [13], the overlapping pathophysiological pathways in non-pregnant cardiovascular disease and preeclampsia [17] and preterm birth [18, 19], and the benefit of aspirin in risk reduction in both clinical scenarios, it stands to reason that similar markers of platelet response to aspirin therapy may be relevant to pregnancy outcome. Our objective was to conduct a prospective cohort study of patients at high risk for preeclampsia recommended to take aspirin daily to study individual predictors of aspirin response, as measured by PFA-100 epinephrine closure time, and association of aspirin response with pregnancy outcomes.

2 | Materials and Methods

2.1 | Cohort

This is a prospective cohort study of singletons recommended low-dose aspirin (81 mg for the purposes of this study and as is standard at our site) for prevention of preeclampsia as defined by the USPSTF [6] (Table 1). During the course of the cohort study USPSTF updated their guidelines leading to a protocol update: eligible participants prior to January 2022 had to have at least one high risk factor and after 2022 had to have either a high-risk factor or 2 or more moderate risk factors (Table 1). Exclusion criteria for this study included: contraindication to aspirin, pre-existing platelet disorder, inherited thrombophilia, baseline thrombocytopenia < 150,000, current or planned use of any anticoagulant aside from aspirin. Participants were enrolled at 10–16 weeks' gestation prior to initiation of aspirin therapy and followed until delivery. A total of 81 mg enteric coated aspirin was provided by the Thomas Jefferson University pharmacy and distributed to participants. A subset of these participants ($N = 19$) were enrolled in a pharmacokinetic sub-study [20], and those were provided non-enteric coated aspirin through gestation for the purpose of that study. We aimed to first evaluate individual predictors of aspirin response in pregnancy, and then to evaluate whether there was a difference in aspirin response in those with and without hypertensive disorders of pregnancy and other adverse pregnancy outcomes. This study was approved by the Institutional Review Board prior to enrollment and all participants provided written consent.

2.2 | Study Procedures and Data Collection

Participants had four study visits, baseline visit completed prior to aspirin initiation at 10–16 weeks gestation, follow-up visit-1

TABLE 1 | Baseline characteristics and preeclampsia risk factors in study cohort of $N = 117$ singleton pregnancies.

Baseline characteristics	
Age (years)	33 (9)
Body mass index (kg/m^2)	34.3 (11.5)
Black, Non-Hispanic	69 (59.0%)
White, non-Hispanic	32 (27.4%)
Asian	4 (3.4%)
Hispanic, White	11 (9.4%)
Other	1 (0.9%)
Preeclampsia risk factor	
Chronic hypertension^	36 (30.8%)
Pre-gestational diabetes^	12 (10.3%)
Chronic kidney disease^	1 (0.9%)
Lupus or antiphospholipid Ab syndrome^	2 (1.7%)
Prior preeclampsia^	36 (30.8%)
Prior preterm preeclampsia^	12 (10.3%)
Nulliparous	37 (31.6%)
Advanced maternal age	50 (42.7%)
Long inter-pregnancy interval	8 (6.8%)
IVF pregnancy	3 (2.6%)
Family history of preeclampsia	6 (5.1%)
≥1 High risk factor (^)	75 (64.1%)
≥2 Moderate risk factor only	42 (35.9%)

Note: Data presented as *N* (%) or median [interquartile range].
Abbreviations: IVF: in vitro fertilization; ^: indicates a high risk factor.

was 2–4 weeks after aspirin initiation, follow-up visit-2 was at 28–32 weeks gestation, and a final follow-up for adherence check at 34–36 weeks. We chose to evaluate aspirin response through gestation given the potential for increased volume of distribution or platelet turnover in pregnancy [21] to impact aspirin response with advancing gestation [14]. Data collected included demographic data, preeclampsia risk factors, obstetric history, pregnancy outcomes including gestational age at delivery, and pregnancy complications. Participant history, risk factor assessment, and race were participant reported; objective factors such as obesity or BMI were verified with measured weight at baseline visit. Finally, at baseline, follow-up 1 and follow-up 2, bloodwork was collected to assess platelet count, creatinine, and PFA-100.

Aspirin adherence was assessed by both a survey of reported missed doses as well as by a percentage of doses taken/doses prescribed by pill counting at each study visit. Adequate aspirin adherence was defined as > 75% by pill count. There is not a current accepted standard for necessary aspirin adherence for efficacy. Clinical trials on low-dose aspirin have used a wide range of "acceptable" adherence, with studies in pregnancy or cardiology using thresholds of 50%–100% [22]. The lower threshold of acceptable in cardiology studies was 75%, while for obstetrics was 50% [22], thus we selected 75%. Aspirin adherence at follow-ups 1 and 2 were used to evaluate for inclusion in analyses below.

All data were entered in a REDCap database [23], hosted by Thomas Jefferson University.

2.3 | Aspirin Response

Response to aspirin was assessed with PFA-100 as a continuous measure assessed at baseline, follow-up 1 (2–4 weeks after aspirin initiation) and follow-up 2 (28–32 weeks' gestation). After ~1 weeks' of daily aspirin, steady state of platelet inhibition is expected [14]. PFA-100 is a commercially available point of care test. This test measures the time it takes for blood to clot an aperture after platelet stimulation. Aspirin results in an increased PFA-100 closure time. PFA-100 epinephrine closure time was selected because it is used commonly to assess response to low-dose aspirin [14]. Inadequate aspirin response as measured by PFA-100 is associated with adverse cardiovascular outcomes in high-risk non-pregnant adults taking aspirin prophylaxis [13, 14]. Given the overlapping pathophysiology of preeclampsia and adult cardiovascular disease [17, 24, 25], we hypothesized it would also be useful to assess for association with pregnancy outcome. Furthermore, we chose to evaluate platelet reactivity, rather than simply thromboxane suppression, because we felt this was a better reflection of the desired physiologic effect of aspirin as an anti-platelet therapy in pregnancy. There is not a single defined value of optimal PFA-100 response, but it is generally recommended to be > 150–180 s to be considered appropriate aspirin response [14, 26]; one prior study in pregnancy used a threshold of 150 s [26]. Because of the lack of a goal threshold PFA-100 result validated in pregnancy, we chose to evaluate aspirin response as a continuous outcome.

2.4 | Outcomes and Statistical Analysis

There were two primary objectives for this cohort study, first to describe aspirin response (PFA-100) through gestation and identify predictors of PFA-100 at each visit. Second, to evaluate relationship between aspirin response and pregnancy outcome, the median difference (MD) in PFA-100 at each visit in those with and without that outcome was compared.

2.4.1 | Aspirin Response

Participants included in outcome analysis were those who took 81 mg aspirin daily and had > 75% aspirin adherence by pill count at the respective follow-up visit. The primary measure of outcome response was PFA-100 (continuous) at follow-up visit-1. Secondary outcome was PFA-100 closure time at follow-up 2. Predictors of PFA-100 were assessed with multivariable logistic regression with backward selection at each follow-up visit. Predictors retained in the stepwise model had a $p < 0.10$, while $p < 0.05$ were considered significant. Predictors of aspirin response evaluated were: baseline obesity (BMI ≥ 30), chronic hypertension, pre-gestational diabetes, maternal age, and for each respective visit- platelet count and creatinine. Additional potential confounder of enteric coating (yes or no) was also included.

Predictors were evaluated with multivariable ordinary least squares model. Difference in PFA-100 between each study visit was assessed with paired sample *t*-test or paired non-parametric test as appropriate. In addition, predictors of PFA-100 and change in PFA-100 through gestation was also evaluated with multivariate generalized estimated equation (GEE) to account for repeat measures over time with predictors including maternal age, baseline obesity (BMI ≥ 30), chronic hypertension, pregestational diabetes, baseline creatinine, platelet count (at respective visit), and enteric versus non-enteric coating.

Although there is not a set threshold for adequate aspirin response in pregnancy, we evaluated it as a categorical variable with a cut-off of goal PFA-100 epinephrine > 150 s as this was previously used in another study in pregnancy [26]. It should be noted that there is no established goal threshold for aspirin response in pregnancy with any measure including PFA-100 [27].

2.4.2 | Pregnancy Outcome

Participants included in outcome analysis were those who took 81 mg aspirin daily with > 75% aspirin adherence by pill count at follow-ups 1 and 2. The primary measure of clinical outcome was hypertensive disorder of pregnancy (preeclampsia or gestational hypertension), as defined by standard clinical criteria (ACOG) [28] and determined by diagnoses documented from chart review of admission note and discharge summary from delivery admission. Secondary clinical outcomes included preterm birth (gestational age at delivery < 37 weeks', any cause), and preterm delivery due to preeclampsia. These pregnancy outcomes were selected because they have been consistently found to be reduced with low-dose aspirin use [1, 26, 27, 29].

Evaluation of PFA-100 as predictive of pregnancy outcome was assessed by comparing PFA-100 at each visit between those with and without outcome of interest with Mann Whitney *U* test. If PFA-100 closure time was different between those with and without any outcome of interest, a receiver operator characteristic curve was also planned.

2.5 | Sample Size and Power

We aimed to have 100 participants included in our outcome analysis. This would be powered to detect a mean difference of 13 s in PFA-100 closure time at follow-up visit 1 in those who did and did not develop hypertensive disorder of pregnancy or other outcome of interest, this is similar to a difference identified in those with and without preeclampsia in pregnancies not taking aspirin [30]. Given an expected 10% loss to follow-up, and 10% without adequate adherence [5], we aimed to enroll $N = 130$.

3 | Results

3.1 | Cohort Description

Participants were enrolled from August 2020—May 2022. Cohort flow diagram is presented in Figure 1. One hundred and eight participants were included in analysis relating to aspirin response in pregnancy and 96 participants included in analysis of aspirin response as a predictor of pregnancy outcome. Baseline characteristics are described in Table 1; 59% were Black, and 64% had at least one high risk factor for preeclampsia. Table 2 describes the longitudinal change in individual factors through pregnancy. Regression results include beta coefficient (B) and confidence interval.

3.2 | Response to Aspirin Therapy in Pregnancy

For this analysis we included $N = 96$ who completed follow-ups 1 and 2 with > 75% adherence. We found that there was significant inhibition of platelet activity as measured by PFA-100 epinephrine closure time following aspirin initiation at both 2–4 weeks after aspirin initiation and in the third trimester at 28–32 weeks (Figure 2). In paired comparison, there was significant increase in PFA-100 from baseline at both follow-ups 1 and 2 (MD 37 [27–49], $p < 0.001$ and MD 26 [15.5–38.5], $p < 0.001$ respectively). There was a decrease in aspirin response with advancing gestation from follow-up 1 to 2 (MD −14.5 [−27 to −2], $p = 0.025$).

3.3 | Predictors of Aspirin Response in Pregnancy

At follow-up 1 (including $N = 108$ with > 75% adherence), using multivariable linear regression with backward selection we found that obesity (B = −30 [−53 to −7], $p = 0.01$), pre-gestational diabetes (B = −39 [−75 to −2], $p = 0.04$), and age (B = 2.2 [0.3–4.0], $p = 0.02$) were associated with response to aspirin, as measured by PFA-100 epinephrine closure time 2–4 weeks after aspirin initiation (Figure 3, Table S1). Enteric coating, platelet count, creatinine were not significantly associated with PFA-100 response (Table S1).

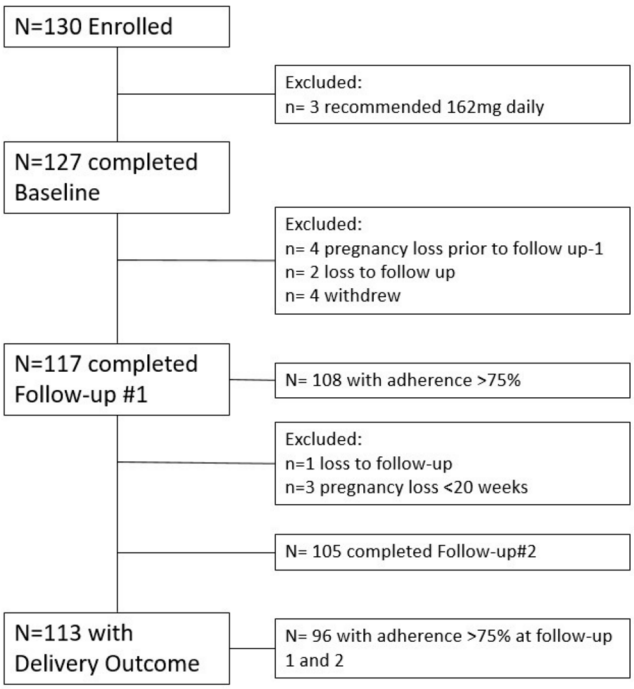

FIGURE 1 | Cohort flow diagram.

TABLE 2 | Longitudinal change in baseline characteristics.

	Baseline pre-aspirin ($N=117$)	Follow-up 1, 2–4 weeks after aspirin ($N=117$)	Follow-up 2, 28–32 weeks' gestation ($N=105$)
Gestational age (weeks)	12.8 ± 1.4	16.2 ± 2.4 MD 3.5 (3.1–3.8)*	29.6 ± 1.8 MD 16.8 (16.3–17.2)*
Weight (lbs)	204.3 ± 51.1	207.1 ± 50.3 MD 2.8 (1.5–4.2)*	215.0 ± 49.3 MD 12.8 (10.4–15.1)*
Body Mass Index (kg/m^2)	34.4 ± 8.3	35.1 ± 8.6 MD 0.7 (0.3–1.2)*	36.1 ± 7.8 MD 2.1 (1.7–2.5)*
Platelet count (100,000/μL)	270 ± 73	268 ± 75 MD −1.2 (−4.2–6.8)	248 ± 79 MD −21.8 (−30.6 to −13.0)*
Creatinine (mg/dL)	0.58	Not collected	0.57 MD −0.02 (−0.03 to 0.0)

Note: Longitudinal changes in individual characteristics in singleton pregnancies taking 81 mg aspirin daily. Statistical analysis completed with two-sample *t*-test pair-wise comparison from baseline. Data presented as mean ± standard deviation and mean difference (MD) and (95% confidence interval) among paired samples (Follow-ups 1 and 2 vs. baseline). Two-sided significance set at 0.05.
*Two-sided *p* value was < 0.001.

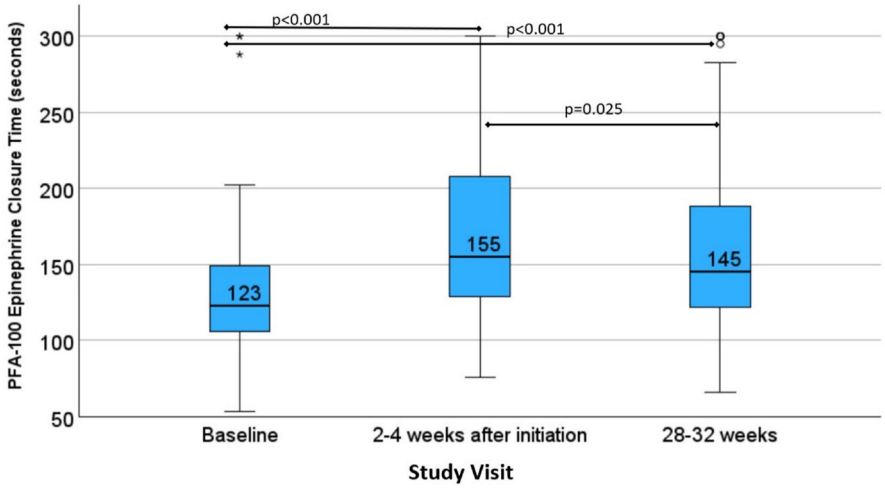

FIGURE 2 | Aspirin response as measured by platelet inhibition (PFA-100 epinephrine closure time) in high risk singletons ($N=96$) taking 81 mg aspirin daily with > 75% adherence documented each visit. Higher closure time indicates increased platelet inhibition, expected with aspirin use. $N=96$ with > 75% adherence at follow-ups 1 and 2. Paired sample comparison with related samples Wilcoxon signed rank test. $p<0.05$ considered significant. Box plot indicates interquartile range (box) and range (whiskers).

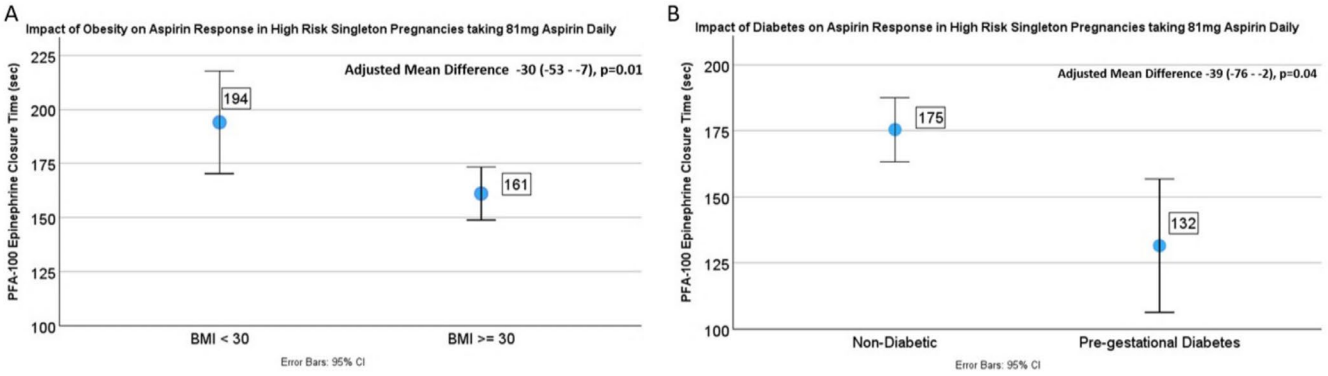

FIGURE 3 | Individual factors associated with reduced response to aspirin in pregnancy, assessed 2–4 weeks' after initiation. In multivariable regression analysis with backward selection, (A) obesity (B = −30 (−53 to −7), $p=0.01$), (B) pre-gestational diabetes (B = −39 (−76 to −2), $p=0.04$) were associated with reduced response to aspirin (lower PFA-100 epinephrine closure time). Mean and 95% confidence interval demonstrated by point and whiskers.

At follow-up 2 (28–32 weeks gestation), there were $N = 96$ who had adherence > 75%. In multivariable linear regression evaluating predictors of aspirin response at follow-up 2, only current weight was retained, although the significance was borderline (B = −0.25 [−0.49 to 0], $p = 0.05$) (Table S2A). Including PFA-100 epinephrine closure time at follow-up 1 in the model, as expected PFA-100 epinephrine closure time at follow-up 1 was strongly associated with PFA-100 at follow-up 2 (B = 0.43 [0.24–0.61], $p < 0.001$) (Table S2B).

Similar results were noted using GEE to account for repeat measures over time. For this analysis there were 332 values from 127 participants available. Results from follow-ups 1 and 2 were restricted to those with > 75% adherence by pill counting and PFA-100 geometric mean was used. We found that age (mean ratio 1.008 [1.001–1.02], $p = 0.04$), maternal obesity (mean ratio 0.90 [0.82–0.99], $p = 0.04$), and maternal diabetes (mean ratio 0.83 [0.73–0.94], $p = 0.004$) were significantly associated with PFA-100 response. There was a significant increase in PFA-100 at both follow-ups 1 and 2 compared to baseline (mean ratio: 1.31 [1.23–1.40], $p < 0.001$ and 1.23 [1.14–1.33], $p < 0.001$, respectively).

In examining aspirin response as a categorical variable as defined as PFA-100 > 150 s at follow-up 1 was 56.3% ($n = 54$) and at follow-up 2 was 45.8% ($n = 44$), although this difference was not statistically significant in paired sample comparison of proportion ($p = 0.12$). In multivariable regression analysis with binary outcome of aspirin response, only a history of diabetes was associated with an increased risk of inadequate aspirin response (adjusted odds ratio 5.1 [1.02–25.72]).

3.4 | Association With Pregnancy Outcome

Among the 113 participants with delivery outcomes available, the overall rate of hypertensive disorders of pregnancy was 26.5% ($n = 30$), of overall preterm birth < 37 weeks was 15% ($n = 17$), and of preterm birth due to preeclampsia 6.2% ($n = 7$). There were 17 preterm births, 7 due to preterm preeclampsia, 6 spontaneous preterm births, and the remaining 4 were due to fetal growth restriction ($n = 1$), oligohydramnios ($n = 1$), placenta accreta ($n = 1$), and one demise in setting of congenital anomaly ($n = 1$). $N = 96$ who maintained adherence > 75% at follow-up 2 were included in analysis of pregnancy outcome. Rate of pregnancy outcomes was similar as in the overall cohort (Table 3).

There was no difference in PFA-100 closure time at follow-up 1 or 2 in those who did or did not develop a hypertensive disorder of pregnancy (Table 3). There was a trend toward lower PFA-100 at 2–4 weeks after initiation in those with versus without a preterm birth, although this difference did not reach statistical significance (median difference −27 [−60 to −4], $p = 0.08$). There was a significantly reduced aspirin response (lower PFA-100 closure time) at 28–32 weeks gestation in those who had a preterm birth versus not (median difference −27 [−54 to −4] $p = 0.02$) (Table 3, Figure 4A). Otherwise there was no difference in PFA-100 closure time at follow-up 1 or 2 between those with preterm birth due to preeclampsia (Table 3). In a sensitivity analysis including all participants without taking adherence into consideration, the overall results were similar with a reduced PFA-100 epinephrine closure time in those with a preterm versus term birth (Table S3).

A receiver operator characteristic curve was generated to evaluate PFA-100 closure time at follow-up 2 and outcome of preterm birth (Figure 4B). Reduced PFA-100 epinephrine time was moderately predictive of preterm birth with an area under the curve of 0.71 (0.55–0.87), $p = 0.009$.

4 | Discussion

4.1 | Main Findings

We identified that baseline obesity, pre-gestational diabetes, and younger age were independently associated with significantly reduced platelet response to aspirin therapy in pregnancy. Notably, there is not an established goal threshold for aspirin response in pregnancy. Current opinion suggests aspirin dose modification based on risk for preeclampsia [31], our data suggests additionally dose modification should be considered based on individual factors predisposing to reduced aspirin response. Our results are strengthened by the focusing on those with adequate adherence and high rate of measured adherence, consistent with prior study in this population [5].

Although aspirin response was not predictive of hypertensive disorders of pregnancy, we did identify reduced platelet suppression (increased platelet activity) in the third trimester in those with preterm birth versus term birth. Aspirin response in pregnancy may be associated with risk for preterm birth despite therapy, further highlighting the need to understand response to aspirin in pregnancy for optimal dosing and management.

TABLE 3 | PFA-100 epinephrine closure time by pregnancy outcome.

Outcome	PFA-100 at Follow-up 1	PFA-100 at Follow-up 2
Hypertensive disorder of pregnancy (HDP, $n = 28$) (vs. none, $n = 68$)	158 [88] vs. 156 [73] MD 1 (−24 to 24)	152 [66] vs. 144 [74] MD −1 (−24 to 21)
Preterm birth, $n = 12$ (vs. term, $n = 84$)	140 [55] vs. 163 [78] MD −27 (−60 to 4)	121 [37] vs. 152 [79] MD −27 (−54 to −4)
Preterm birth due to HDP, $n = 6$ (vs. term birth or PTB other cause, $n = 90$)	150 [137] vs. 156 [76] MD −12 (−62 to 54)	136 [88] vs. 145 [69] MD −9 (−57 to 32)

Note: PFA-100 closure time at follow-up 1 (2–4 weeks after aspirin initiation) and follow-up 2 (28–32 weeks) by pregnancy outcome in $N = 96$ high risk singleton pregnancies taking 81 mg aspirin daily with > 75% adherence at follow-ups 1 and 2. Data presented as median [interquartile range] and median difference (MD) (95% confidence interval) in those with and without outcome of interest. Mann–Whitney *U* test used for comparison against reference group. HDP: Hypertensive disorder of pregnancy, two-sided $p < 0.05$ considered significant.

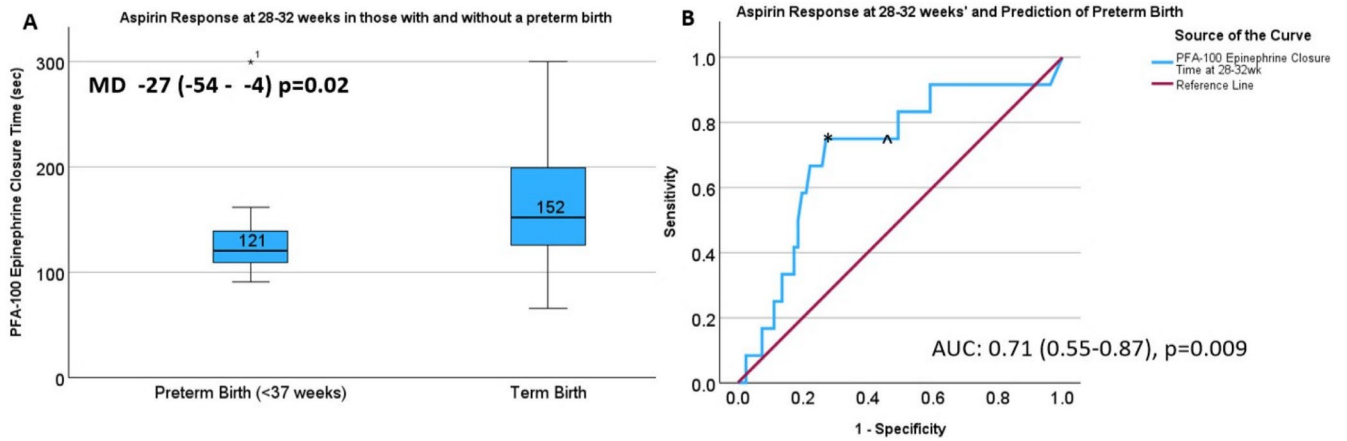

FIGURE 4 | Aspirin response and preterm birth: (A) Aspirin response measured by PFA-100 epinephrine closure time at 28–32 weeks was reduced in those with a preterm versus term birth, data presented as median difference (MD) measured by Mann–Whitney *U* test with two sided $p < 0.05$ considered significant. Mean and 95% confidence interval demonstrated by point and whiskers. (B) Reduced aspirin response (PFA-100 Epinephrine closure time) is predictive of preterm birth. Thresholds indicated are: *PFA-100 < 128: Sensitivity 75%, Specificity 73%. ^PFA-100 < 150: Sensitivity 75%, Specificity 52%.

4.2 | Results in the Context of What Is Known

Prior studies on aspirin response in pregnancy are limited. Similar to a prior study on 60 mg aspirin daily [32], we found that obesity associated with reduced aspirin response. That study evaluated thromboxane suppression, and our pharmacokinetic sub-study found a strong correlation between thromboxane suppression and platelet inhibition [20]. Our results add to this older data because we studied this prospectively in a contemporary cohort, in patients taking 81 mg daily, rather than 60 mg, evaluated multiple potential individual factors, and assessed aspirin response soon after initiation, reflective of when patients are initiating aspirin in pregnancy for preeclampsia prevention, and in the third trimester. Furthermore, we assessed aspirin response with platelet inhibition as measured by a commercially available assay PFA-100, which unlike immunologic assays for thromboxane, can be comparable across sites and laboratories. In contrast to another contemporary study assessing platelet response with the commercial assay VerifyNow [33], we did have a significant percentage of patients with what would be considered non-response to aspirin therapy. A prior study evaluated aspirin response in pregnancy with PFA-100 and found a lower rate of non-response (28.7%) compared to our study [26]. The higher rate of aspirin non-response in our study may be related to difference in baseline characteristics such as diabetes and obesity.

Consistent with studies in non-pregnant adults, we found that young age, obesity, and pre-gestational diabetes were associated with reduced platelet inhibition in response to 81 mg aspirin daily. We previously demonstrated in a pharmacokinetic substudy of this population that increasing BMI was associated with reduced plasma salicylic acid levels as well as reduced platelet response in the setting of 81 mg aspirin daily [20], so there is the initial altered systemic exposure of aspirin with increasing BMI, likely related to increased volume of distribution. Obesity is also associated with increased platelet turn-over which alters aspirin pharmacodynamics, and furthermore, oxidative stress associated with obesity leads to platelet hyperreactivity, further countering the effect of aspirin at a given dose [34]. Regarding pre-gestational diabetes, unlike obesity, it was not associated with altered aspirin pharmacokinetics in pregnancy [20]. However, similar to obesity, it is also associated with oxidative stress pathways that blunt the platelet inhibitory effect of aspirin [35]. There are limited studies on young age and platelet response, as most studies relating to aspirin are in the setting of adult cardiovascular disease. Although this was a statistically significant finding, it is may not be clinically significant given the small increase in PFA-100 with each year noted. In non-pregnant adults, one study found lower bleeding time (increased platelet activity) in response to aspirin in younger (18–22 years) versus older (48–52 years) women [36], which was postulated to be related to altered prostacylic: thromboxane ratio with aging. This is especially notable given that young age (< 18 year) is itself a risk factor for preeclampsia [37] and preterm birth [38, 39].

Similar to two prior studies [32, 33], we did not find an association between aspirin response and risk of hypertensive disorders of pregnancy, however we did find an association with preterm birth. The study by Finneran et al. [32] was limited in its ability to evaluate relationship to pregnancy outcome due to low dose of aspirin used (60 mg), and late initiation (> 16 weeks). The study by Navatram et al. [33] was limited in its ability to evaluate pregnancy outcome because of variable definition of aspirin response, and they sampled earlier in pregnancy (< 20 weeks) and again >34 weeks, so they may have missed the best time point to assess platelet response for relation to pregnancy outcome (28–32 weeks as we did here). Furthermore, they assessed aspirin response as a categorical variable, whereas we studied PFA-100 closure time as a continuous variable due to lack of data on what the goal PFA-100 closure time in pregnancy should be. Our finding of an inflection point at PFA-100 closure time > 150 associated with preterm birth outcome does align with one prior study that used PFA-100 closure time > 150 as a goal for aspirin response, although that study did not evaluate pregnancy outcome in detail [26].

It is notable that the pregnancy outcome we identified associated with platelet response to aspirin therapy was not overall

hypertensive disorders of pregnancy, but preterm birth. The majority of preterm births in our study were due to conditions related to placental insufficiency (preterm preeclampsia, fetal growth restriction, oligohydramnios). This finding is supported by previous literature identifying that (1) placental vascular pathology is related to outcomes of preterm preeclampsia, fetal growth restriction, and even spontaneous preterm birth [40], (2) Increased platelet activity has been associated with spontaneous preterm birth and preterm preelampsia [17, 41], and an activating platelet receptor genotype was associated with increased rate of preterm birth, both spontaneous and indicated [42]; (3) aspirin efficacy is predominantly in prevention of preterm preeclampsia [1, 7], and (4) aspirin is effective in prevention of preterm birth overall [3, 29], and preterm birth due to preterm preeclampsia [1, 7], and spontaneous preterm birth [2, 43]. Our findings highlight the importance of preterm birth overall as a clinical outcome when studying the impact of anti-platelet therapies, rather than focusing exclusively on hypertensive disorders of pregnancy.

In summary, we identified that young age, obesity, and diabetes are associated with reduced response to 81 mg aspirin daily in pregnancy, and may be individual factors warranting consideration for increased aspirin dose for preeclampsia prevention. Furthermore, we found there may be reduced response to aspirin identified for those who ultimately have a preterm versus term birth. These findings highlight the significance of measuring aspirin response through pregnancy, and the potential clinical utility of PFA-100 as a tool for assessing aspiring response in pregnancy. Our results are strengthened by the focusing on those with adequate adherence and high rate of measured adherence, consistent with prior study in this population [5].

4.3 | Implications for Clinical Care

The current lack of a goal metric for aspirin response in pregnancy for prevention of adverse perinatal outcomes is a critical gap in knowledge impacting clinical care, especially in the setting of the common individual characteristics we identified (age, obesity, pre-gestational diabetes) to be associated with reduced response to aspirin. This identifies a subset of patients who may specifically benefit from higher aspirin dosing. This especially notable given recent expert commentary suggesting risk-based selection of patients who may benefit from higher dose of aspirin, but without specific guidance regarding what risk factors should be used [31]. Our findings suggest further study is warranted on potential benefit (or not) of aspirin dose modification in pregnancy taking into consideration individual factors predisposing to reduced aspirin response.

4.4 | Implications for Research

We have significant individual variability in response to aspirin in pregnancy, which may contribute to differential efficacy of aspirin in prevention of adverse pregnancy outcomes. Thus, it is critical we identify markers of aspirin response that are associated with pregnancy outcome so aspirin dosing can be optimized for prevention of preeclampsia and preterm birth. PFA-100 closure time, a commercially available assay, may be an important clinical tool for identifying appropriate aspirin response and/or identifying those at risk for preterm birth despite aspirin use. The use of PFA-100 as a tool for evaluating aspirin response and prediction of preterm birth should be validated in an external cohort. Further study needs to be done to determine whether increased dosing mitigates aspirin non-response in through pregnancy and improves pregnancy outcomes.

Additional research is also needed on the relevance of the change in aspirin response through pregnancy. We found there was a reduction in aspirin response as pregnancy progresses from early second to mid third trimester; however the clinical significance of this finding is not clear.

We did not find an association with overall diagnosis of hypertensive disorders of pregnancy. Given the hypothesized differential mechanism of action of early versus late presentation of preeclampsia, future studies on aspirin response should focus on preterm birth or preterm placentally mediated outcomes, as these are more strongly impacted by aspirin use compared to term hypertensive disorders of pregnancy [12].

Of note, this study focuses on the cyclooxygenase-1 mediated pathway of aspirin response. We cannot comment on the cyclooxygenase-2 pathway of aspirin action, which involves inflammatory pathways, and how that may play a role in preeclampsia development and, subsequently, in preeclampsia/preterm birth prevention. Further study is needed on other intermediate markers of aspirin response including COX-2 pathway markers.

4.5 | Strengths and Limitations

This study has several strengths. It is prospective, studying patients at high risk for preeclampsia, taking 81 mg aspirin daily, from the first trimester through the end of pregnancy with documented adequate adherence. We assessed platelet response to aspirin therapy using a commercially available assay, allowing for reproducibility and external validity, and evaluated multiple individual factors that could impact aspirin response in pregnancy. We assessed and controlled for aspirin adherence. We studied aspirin response both in the first/early second trimester and again in the early third trimester to see if either time point was helpful in either assessing aspirin response for prediction of pregnancy outcome/residual risk for adverse perinatal outcome despite aspirin use. Finally, our study population was diverse and reflective of patients at high risk for preeclampsia in the United States.

There are some important limitations to note. First, it is possible we were underpowered to detect an association between markers of aspirin response and some pregnancy outcomes, including preterm preeclampsia. This study was powered to evaluate whether there was a difference in PFA-100 between those who did and did not have a certain pregnancy outcome, and was not designed or powered with sufficient cases to conduct multivariable regression to create a model that incorporates PFA-100 along with other individual characteristics. Ultimately, PFA-100 epinephrine closure time in the third trimester is "down-stream" of baseline characteristics, and our interest in this initial evaluation was to see if there was even any difference in PFA-100 epinephrine time in

those with and without specific pregnancy outcomes in a cohort of pregnant patients taking aspirin, as had been previously identified in patients not taking aspirin [30]. Second, we only included patients taking 81 mg aspirin daily, so we were not able to report on a dose–response relationship in pregnancy. However, our pharmacokinetic sub-study [20] did find greater plasma levels of drug were associated with improved aspirin response, supporting the hypothesis that increased dose should improve aspirin response. Third, we report on platelet inhibition assessed by PFA-100 epinephrine closure time. This is a downstream marker of aspirin effect, and can be impacted by other non-aspirin related factors [14]. We attempted to limit that effect by excluding those with thrombocytopenia or known platelet disorder or thrombophilia and controlling for other factors such as adherence, platelet count, renal function. Based on our results, it is unlikely that these other individual factors impacting PFA-100 closure time significantly impacted our findings. Additionally, we did not collect concomitant medication use and thus could not assess for drug–drug interactions. While we identified that PFA-100 response at 28–32 weeks was predictive of preterm birth, our findings should be validated in an external cohort, and are not sufficient to establish a definitive goal threshold for aspirin response in pregnancy. Finally, while adherence was measured by pill counting, we did not assess consecutive missed doses which may have a differential impact on aspirin response.

5 | Conclusion

Aspirin use in pregnancy results in platelet inhibition through gestation. There is significant individual variability in aspirin response in pregnancy, with young age, obesity, and pregestational diabetes being independent risk factors for reduced response to aspirin in pregnancy. Aspirin response through pregnancy was not associated with overall risk of hypertensive disorders of pregnancy; however, reduced response to aspirin in the early third trimester, as measured by PFA-100 epinephrine closure time, may be associated with preterm birth. Our study suggests further study is warranted on potential benefit (or not) of aspirin dose modification in pregnancy taking into consideration individual factors predisposing to reduced aspirin response and further research is needed on the relationship between aspirin response and pregnancy outcomes.

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Conflicts of Interest

RCB receives research grant funding from Covis Pharma, not related to this study. All other authors declare no conflicts of interests for this work.

Presentations

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References

1. J. T. Henderson, K. Vesco, C. Senger, R. Thomas, and N. Redmond, "Number 205 Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: An Evidence Update for the *AHRQ Publication Number 21-05274-EF-1*" 2021.

2. E. O. G. van Vliet, L. A. Askie, B. W. J. Mol, and M. A. Oudijk, "Antiplatelet Agents and the Prevention of Spontaneous Preterm Birth: A Systematic Review and Meta-Analysis," *Obstetrics and Gynecology* 129, no. 2 (2017): 327–336.

3. L. M. Askie, L. Duley, D. J. Henderson-Smart, L. A. Stewart, and PARIS Collaborative Group, "Antiplatelet Agents for Prevention of Pre-Eclampsia: A Meta-Analysis of Individual Patient Data," *Lancet* 369, no. 9575 (2007): 1791–1798.

4. C. Banala, S. Moreno, Y. Cruz, et al., "Impact of the ACOG Guideline Regarding Low Dose Aspirin for Prevention of Superimposed Preeclampsia in Women With Chronic Hypertension," *American Journal of Obstetrics and Gynecology* 223, no. 3 (2020): 419.e1–419.e16, https://doi.org/10.1016/j.ajog.2020.03.004.

5. R. Boelig, M. Wanees, T. Zhan, V. Berghella, and A. Roman, "Improving Utilization of Aspirin for Prevention of Preeclampsia in a High Risk Urban Cohort: A Prospective Cohort Study," *American Journal of Perinatology* 38, no. 6 (2021): 544–552.

6. K. W. Davidson, M. J. Barry, C. M. Mangione, et al., "Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: US Preventive Services Task Force Recommendation Statement," *JAMA: The Journal of the American Medical Association* 326, no. 12 (2021): 1186–1191.

7. S. Roberge, K. Nicolaides, S. Demers, J. Hyett, N. Chaillet, and E. Bujold, "The Role of Aspirin Dose on the Prevention of Preeclampsia and Fetal Growth Restriction: Systematic Review and Meta-Analysis," *American Journal of Obstetrics and Gynecology* 216, no. 2 (2017): 110–120.

8. M. E. Al-Sofiani, L. R. Yanek, N. Faraday, et al., "Diabetes and Platelet Response to Low-Dose Aspirin," *Journal of Clinical Endocrinology and Metabolism* 103, no. 12 (2018): 4599–4608.

9. A. Karathanos and T. Geisler, "Monitoring Aspirin and Clopidogrel Response: Testing Controversies and Recommendations," *Molecular Diagnosis & Therapy* 17, no. 3 (2013): 123–137.

10. L. H. Theilen, H. D. Campbell, S. L. Mumford, et al., "Platelet Activation and Placenta-Mediated Adverse Pregnancy Outcomes: An Ancillary Study to the Effects of Aspirin in Gestation and Reproduction Trial," *American Journal of Obstetrics and Gynecology* 223, no. 5 (2020): 741.e1–741.e12.

11. M. G. Macey, S. Bevan, S. Alam, et al., "Platelet Activation and Endogenous Thrombin Potential in Pre-Eclampsia," *Thrombosis Research* 125, no. 3 (2010): e76–e81.

12. D. L. Rolnik, K. H. Nicolaides, and L. C. Poon, "Prevention of Preeclampsia With Aspirin," *American Journal of Obstetrics and Gynecology* 226, no. 2 (2022): S1108–S1119.

13. J. L. Reny, P. de Moerloose, M. Dauzat, and P. Fontana, "Use of the PFA-100™ Closure Time to Predict Cardiovascular Events in Aspirin-Treated Cardiovascular Patients: A Systematic Review and Meta-Analysis," *Journal of Thrombosis and Haemostasis* 6, no. 3 (2008): 444–450.

14. G. J. Hankey and J. W. Eikelboom, "Aspirin resistance," *Lancet* 367, no. 9510 (2006): 606–617.

15. H. Y. Chen and P. Chou, "PFA-100-Measured Aspirin Resistance Is the Predominant Risk Factor for Hospitalized Cardiovascular Events

in Aspirin-Treated Patients: A 5-Year Cohort Study," *Journal of Clinical Pharmacy and Therapeutics* 43, no. 2 (2018): 249–255.

16. M. del Bianco-Rondeau, M. Robert-Halabi, S. Bloom, et al., "Aspirin for Primary Cardiovascular Prevention in Patients With Diabetes: Uncertainties and Opportunities," *Thrombosis and Haemostasis* 122, no. 9 (2022): 1443–1453.

17. S. Yagel, S. M. Cohen, and D. Goldman-Wohl, "An Integrated Model of Preeclampsia: A Multifaceted Syndrome of the Maternal Cardiovascular-Placental-Fetal Array," *American Journal of Obstetrics and Gynecology* 226, no. 2S (2022): S963–S972, https://doi.org/10.1016/j.ajog.2020.10.023.

18. A. Hauspurg, W. Ying, C. A. Hubel, E. D. Michos, and P. Ouyang, "Adverse Pregnancy Outcomes and Future Maternal Cardiovascular Disease," *Clinical Cardiology* 41, no. 2 (2018): 239–246.

19. M. B. Minissian, S. Kilpatrick, J. A. Eastwood, et al., "Association of Spontaneous Preterm Delivery and Future Maternal Cardiovascular Disease," *Circulation* 137, no. 8 (2018): 865–871.

20. R. C. Boelig, G. Kaushal, A. Rochani, S. McKenzie, and W. K. Kraft, "Aspirin Pharmacokinetics and Pharmacodymamics Through Gestation," *American Journal of Obstetrics and Gynecology* 231, no. 3 (2024): 344.e1–344.e16.

21. M. C. Valera, O. Parant, C. Vayssiere, J. F. Arnal, and B. Payrastre, "Physiologic and Pathologic Changes of Platelets in Pregnancy," *Platelets* 21, no. 8 (2010): 587–595.

22. K. Navaratnam, Z. Alfirevic, M. Pirmohamed, and A. Alfirevic, "How Important Is Aspirin Adherence When Evaluating Effectiveness of Low-Dose Aspirin?," *European Journal of Obstetrics & Gynecology and Reproductive Biology* 219 (2017): 1–9.

23. P. A. Harris, R. Taylor, B. L. Minor, et al., "The REDCap Consortium: Building an International Community of Software Partners," *Journal of Biomedical Informatics* 95 (2019): 103208.

24. V. R. Kay, N. Wedel, and G. N. Smith, "Family History of Hypertension, Cardiovascular Disease, or Diabetes and Risk of Developing Preeclampsia: A Systematic Review," *Journal of Obstetrics and Gynaecology Canada* 43, no. 2 (2021): 227–236.

25. I. Hromadnikova, K. Kotlabova, L. Hympanova, and L. Krofta, "Gestational Hypertension, Preeclampsia and Intrauterine Growth Restriction Induce Dysregulation of Cardiovascular and Cerebrovascular Disease Associated microRNAs in Maternal Whole Peripheral Blood," *Thrombosis Research* 137 (2016): 126–140.

26. N. Caron, G. É. Rivard, N. Michon, et al., "Low-Dose ASA Response Using the PFA-100 in Women With High-Risk Pregnancy," *Journal of Obstetrics and Gynaecology Canada* 31, no. 11 (2009): 1022–1027.

27. D. L. Rolnik, D. Wright, L. C. Poon, et al., "Aspirin Versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia," *New England Journal of Medicine* 377, no. 7 (2017): 613–622.

28. K. Lu, N. Kauff, C. B. Powell, and I. Cass, "ACOG Practice Bulletin: Gestational Hypertension and Preeclampsia," *Obstetrics and Gynecology* 133, no. 1 (2019): e1–e10.

29. M. K. Hoffman, S. S. Goudar, B. S. Kodkany, et al., "Low-Dose Aspirin for the Prevention of Preterm Delivery in Nulliparous Women With a Singleton Pregnancy (ASPIRIN): A Randomised, Double-Blind, Placebo-Controlled Trial," *Lancet* 395, no. 10220 (2020): 285–293.

30. A. Vincelot, N. Nathan, D. Collet, Y. Mehaddi, P. Grandchamp, and A. Julia, "Platelet Function During Pregnancy: An Evaluation Using the PFA-100 Analyser," *British Journal of Anaesthesia* 87, no. 6 (2001): 890–893.

31. M. Jones Pullins, K. Boggess, and T. F. Porter, "Aspirin in Pregnancy," *Obstetrics and Gynecology* 142, no. 6 (2023): 1333–1340.

32. M. M. Finneran, V. M. Gonzalez-Brown, D. D. Smith, M. B. Landon, and K. M. Rood, "Obesity and Laboratory Aspirin Resistance in High-Risk Pregnant Women Treated With Low-Dose Aspirin," *American Journal of Obstetrics and Gynecology* 220, no. 4 (2019): 385, https://doi.org/10.1016/j.ajog.2019.01.222.

33. K. Navaratnam, A. Alfirevic, A. Jorgensen, and Z. Alfirevic, "Aspirin Non-responsiveness in Pregnant Women at High-Risk of Pre-Eclampsia," *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 221 (2018): 144–150.

34. N. B. Norgard, "Obesity and Altered Aspirin Pharmacology," *Clinical Pharmacokinetics* 57, no. 6 (2018): 663–672.

35. F. Santilli, D. Lapenna, S. la Barba, and G. Davì, "Oxidative Stress-Related Mechanisms Affecting Response to Aspirin in Diabetes Mellitus," *Free Radical Biology & Medicine* 80 (2015): 101–110.

36. K. A. Jørgensen, J. Dyerberg, A. S. Olesen, and E. Stoffersen, "Acetylsalicylic Acid, Bleeding Time and Age," *Thrombosis Research* 19, no. 6 (1980): 799–805.

37. J. J. Sheen, J. D. Wright, D. Goffman, et al., "Maternal Age and Risk for Adverse Outcomes," *American Journal of Obstetrics and Gynecology* 219, no. 4 (2018): 390.e1–390.e15.

38. R. L. Goldenberg and E. M. McClure, "The Epidemiology of Preterm Birth," in *Preterm Birth Prevention and Management*, vol. 2 (Wiley Blackwell, 2010), 22–39.

39. S. E. Purisch and C. Gyamfi-Bannerman, "Epidemiology of Preterm Birth," *Seminars in Perinatology* 41, no. 7 (2017): 387–391.

40. L. M. Ernst, "Maternal Vascular Malperfusion of the Placental Bed," *APMIS* 126, no. 7 (2018): 551–560.

41. O. Erez, R. Romero, D. Hoppensteadt, et al., "Premature Labor: A State of Platelet Activation?," *Journal of Perinatal Medicine* 36, no. 5 (2008): 377–387.

42. R. C. Boelig, T. J. Cahanap, L. Ma, et al., "Platelet Protease Activated Receptor 4 (PAR 4) Receptor Genotype Is Associated With an Increased Risk of Preterm Birth," *Journal of Thrombosis and Haemostasis* 20 (2022): 2419–2428.

43. M. Andrikopoulou, S. E. Purisch, R. Handal-Orefice, and C. Gyamfi-Bannerman, "Low-Dose Aspirin Is Associated With Reduced Spontaneous Preterm Birth in Nulliparous Women," *American Journal of Obstetrics and Gynecology* 219, no. 4 (2018): 399.e1–399.e6.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.