Low-dose aspirin is associated with reduced spontaneous preterm birth in nulliparous women

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BACKGROUND: Preterm birth is one of the leading causes of perinatal morbidity and mortality. Clinical data suggest that low-dose aspirin may decrease the rate of overall preterm birth, but investigators have speculated that this is likely due to a decrease in medically indicated preterm birth through its effect on the incidence of preeclampsia and other placental disease. We hypothesized that low-dose aspirin may also have an impact on the mechanism of spontaneous preterm labor.

OBJECTIVE: Our objective was to determine whether low-dose aspirin reduces the rate of spontaneous preterm birth in nulliparous women without medical comorbidities.

STUDY DESIGN: This is a secondary analysis of a randomized, placebo-controlled trial of low-dose aspirin for the prevention of preeclampsia in healthy, low-risk, nulliparous women. Low-risk women were defined by the absence of hypertension, renal disease, diabetes, other endocrine disorders, seizures, heart disease, or collagen vascular disease. Our study was limited to singleton, nonanomalous gestations. Women were eligible if they had prior pregnancy terminations but not prior spontaneous pregnancy loss <20 weeks. Current pregnancies that resulted in a loss or termination <20 weeks or antepartum stillbirth or had missing follow-up data were excluded. The treatment intervention was 60 mg of aspirin, initiated at 13–25 weeks' gestation or matching placebo. The primary outcome was spontaneous preterm birth <34 weeks' gestation. Secondary outcomes included spontaneous preterm birth <37 weeks and overall preterm birth <37 and <34 weeks. Baseline demographics and primary and secondary outcomes were compared between treatment groups. A logistic regression model was used to adjust for confounders related to spontaneous preterm birth.

RESULTS: Of 2543 included women, 1262 (49.6%) received low-dose aspirin and 1281 (50.4%) placebo. Baseline characteristics were similar between groups, except for marital status. The rate of spontaneous preterm birth <34 weeks was 1.03% (n = 13) and 2.34% (n = 30) in the low-dose aspirin and placebo group, respectively (odds ratio, 0.43, 95% confidence interval, 0.26–0.84). Additionally, the rate of spontaneous preterm birth <37 weeks was 6.58% (n = 83) in the low-dose aspirin group and 7.03% (n = 90) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.71–1.33), and the rate of overall preterm birth <37 weeks was 7.84% (n = 99) in the low-dose aspirin group and 8.2% (n = 105) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.72–1.31). After adjustment for variables that were clinically relevant or statistically significant, including body mass index, race, tobacco use, marital status, and education level, there was a significant reduction in spontaneous preterm birth <34 weeks in the low-dose aspirin group (adjusted odds ratio, 0.46, 95% confidence interval, 0.23–0.89). The rates of overall preterm birth <34 and <37 weeks and spontaneous preterm birth <37 weeks were similar in women who received low-dose aspirin compared with placebo.

CONCLUSION: Low-dose aspirin is associated with a substantial decrease in spontaneous preterm birth <34 weeks in healthy nulliparous women without comorbidities. These findings suggest a new therapeutic option for preterm birth prevention that requires further study.

Key words: low-dose aspirin, nulliparous, placental disease, platelet aggregation, preeclampsia, preterm birth, spontaneous preterm birth, uteroplacental ischemia

Preterm birth (PTB) is a challenging problem in obstetrics and one of the leading causes of perinatal morbidity and mortality, with the incidence reaching 9.6% in the United States.[1] Preterm births include both spontaneous deliveries that are preceded by preterm labor, preterm spontaneous rupture of membranes, or cervical insufficiency and account for approximately two-thirds of all PTBs. The remainder of preterm birth is iatrogenic or medically indicated.[2,3]

The pathophysiology of PTB remains multifactorial with infection or inflammation, uterine overdistention, or endocrine and immunological disorders playing important roles.[2] Uteroplacental ischemia and vascular disorders have also been shown to contribute in the pathogenesis of PTB.[4,5]

Low-dose aspirin has primarily been studied for the prevention of preeclampsia and fetal growth restriction.[6–14] Clinical data also suggest that low-dose aspirin may decrease the rate of overall PTB, but investigators have speculated that this is likely due to a decrease in medically indicated PTB.[15]

Clinical evidence suggests that low-dose aspirin may be a useful intervention for spontaneous PTB, but the data are either inconclusive or limited to special populations.[16–18] Silver et al[16] performed a secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial and studied the association of low-dose aspirin (81 mg) with the risk of spontaneous PTB in women with a history of pregnancy loss.[16,17] They found an almost 50% reduction in the risk of spontaneous PTB in women who received low-dose aspirin compared with placebo (1.1% vs 2.2%), but this finding did not reach statistical significance (relative risk, 0.51, 95% confidence interval [CI], 0.19–1.34).

Also, a recent meta-analysis of 17 randomized controlled trials evaluating the risk of spontaneous PTB

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AJOG at a Glance

Why was this study conducted?

To determine whether low-dose aspirin reduces the rate of spontaneous preterm birth in nulliparous women without medical comorbidities.

Key findings

Low-dose aspirin is associated with a substantial decrease in spontaneous preterm birth <34 weeks in nulliparous women without medical comorbidities.

What does this add to what is known?

This study suggests a promising intervention that may decrease spontaneous preterm birth in an even broader population than previously reported, independent of preeclampsia.

in women taking low-dose aspirin-dipyridamol vs placebo for preeclampsia prevention showed that women at risk for preeclampsia assigned to antiplatelet treatment had a significantly lower risk of spontaneous PTB <37 and <34 weeks.[18] The authors concluded there was a benefit in reduction of spontaneous PTB in women at risk for preeclampsia.

Low-dose aspirin is well known for its antiinflammatory and platelet aggregation inhibition properties through cyclooxygenase inhibition. It is speculated that it may affect both the inflammatory and uteroplacental ischemia pathways of PTB, leading to the reduction of contractility and inflammation and thus reduction of spontaneous PTB.[19]

Given the burden of spontaneous preterm birth, the promising existing literature, and the availability, low cost, and biological plausibility of the intervention, our objective was to determine whether low-dose aspirin reduces the rate of spontaneous PTB in healthy nulliparous women with no medical comorbidities. We hypothesized that low-dose aspirin would lead to a reduction of spontaneous PTB.

Material and Methods

This is a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units' randomized placebo-controlled trial of low-dose aspirin (60 mg) for the prevention of preeclampsia in women at low risk.[20] Women at low risk, defined by nulliparity and the absence of medical comorbidities, which included chronic hypertension, renal disease, diabetes mellitus, other endocrine disorders, seizures, heart disease, or collagen vascular disease, were eligible for the parent trial.

From 1989 to 1991, women between 13 and 25 weeks of gestation were enrolled from 7 clinical centers across the country. Women were randomized 1:1 to receive low-dose aspirin or placebo in an effort to assess the effect of low-dose aspirin on the incidence of preeclampsia and received treatment until delivery.

The primary outcome of the parent trial was incidence of preeclampsia, and investigators found no statistically significant difference between women who received aspirin compared with placebo.[20] PTB was a secondary outcome of the parent trial, and investigators did not find a difference in overall PTB by treatment assignment; however, spontaneous preterm birth was not assessed. Complete details of the study design and methods have been previously reported.[20] The study data are publicly available and deidentified and was therefore exempt from institutional review board review at our institution.

The current study focused on spontaneous preterm birth and was limited to singleton, nonanomalous gestations. Women were also eligible if a prior pregnancy was terminated at less than 20 weeks' gestation. Women with spontaneous pregnancy losses less than 20 weeks were excluded because we could not distinguish between those with prior first-trimester vs prior second-trimester losses in the data set, and those with prior second-trimester loss would have been at increased risk for spontaneous preterm birth.[21] Antepartum stillbirth or subjects with missing follow-up data were also excluded.

Women were then divided into 2 exposure groups based on their treatment assignment, low-dose aspirin vs placebo. The primary outcome was spontaneous PTB less than 34 weeks' gestation. PTB included both women with premature rupture of membranes or preterm delivery with intact membranes. Secondary outcomes included spontaneous PTB less than 37 weeks, overall PTB <37 and <34 weeks, amount of blood loss during delivery, postpartum hemorrhage, and placental abruption rates (diagnosed according to clinical findings [uterine tenderness and vaginal bleeding] or placental examination).

Maternal demographics, clinical characteristics, and primary and secondary outcomes were compared between the 2 groups. The χ^2 test was used for the analysis of categorical variables and Wilcoxon or Student *t* test for continuous variables, as appropriate. We fit a logistic regression model to adjust for confounders that were clinically related to spontaneous PTB or statistically different at baseline with a value of $P < .2$ (body mass index [BMI], race, tobacco use, marital status, and education level).

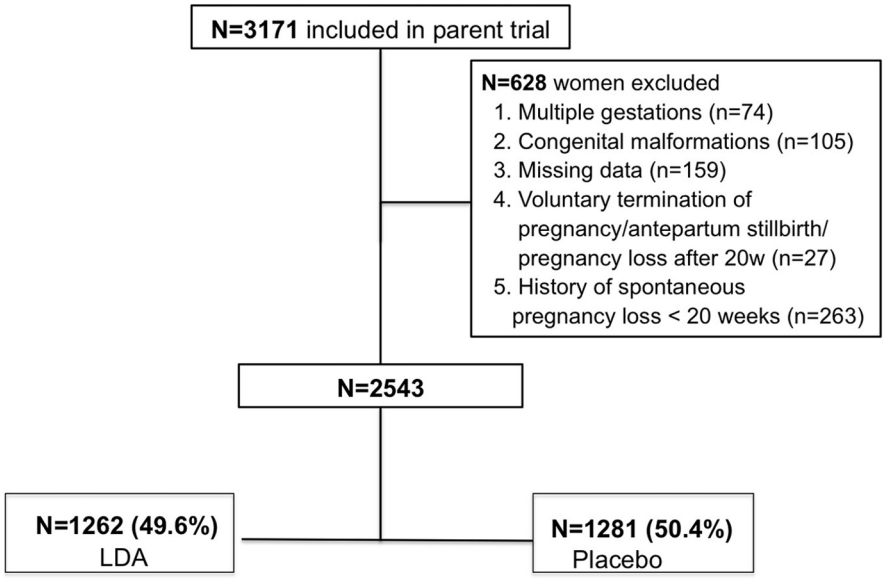
A sensitivity analysis was also performed excluding all cases of preeclampsia to eliminate the impact of preeclampsia on our outcomes. Level of significance for the primary outcome was set to a value of $P < .05$. All analyses were performed with SAS, version 9.4 (Cary, NC).

Results

Of 3171 subjects in the parent study, a total of 2543 women were included in this analysis. Details for excluded patients are listed in Figure 1. A total of 1262 (49.6%) received low-dose aspirin, and 1281 (50.4%) received placebo. Baseline characteristics were similar between groups, except for marital status (Table 1).

The rate of the primary outcome, spontaneous PTB <34 weeks, was 1.03%

FIGURE 1
Population for analysis



Flow diagram of study participants.

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(n = 13) and 2.34% (n = 30) in the low-dose aspirin and placebo groups, respectively, and was significantly lower in women who received low-dose aspirin (odds ratio [OR], 0.43, 95% confidence interval [CI], 0.26−0.84). The rate of spontaneous PTB <37 weeks was 7.03% (n = 90) and 6.58% (n = 83) in the placebo and low-dose aspirin group and was similar between the 2 groups (OR, 1.04, 95% CI, 0.78−1.39) (Figure 2). Overall PTB, which included both spontaneous and indicated preterm deliveries, at <34 and <37 weeks, was not significantly different between the low-dose aspirin and placebo groups (OR, 0.98, 95% CI, 0.79−1.21, and OR, 1.64, 95% CI, 0.93−2.87, respectively).

After adjusting for variables that were clinically relevant or statistically significant, including BMI, race, tobacco use, marital status, and education level, there was still a statistically significant reduction in spontaneous PTB <34 weeks in the low-dose aspirin group compared with women who received placebo (adjusted odds ratio, 0.46, 95% CI, 0.23−0.89). The rates of overall PTB <34 and <37 weeks and spontaneous PTB <37 weeks remained similar between groups (Table 2).

We performed several sensitivity analyses. A stratified analysis was performed of the time of aspirin initiation before or after 16 weeks as proxied by time of randomization. Limiting to those who initiated low-dose aspirin at ≥16 weeks gestational age, there still remained a statistically significant reduction of spontaneous preterm birth before 34 weeks (OR, 2.17, 95% CI, 1.05−4.45), suggesting that the time of the initiation of low-dose aspirin did not have an impact on our results. Similarly, when including women with prior loss prior to 20 weeks or stillbirth in the current pregnancy, there was still a significant reduction of spontaneous preterm birth before 34 weeks in women who received low-dose aspirin (OR, 1.82, 95% CI, 1.01−3.31).

We then excluded patients who developed preeclampsia, and there remained a statistically significant reduction of spontaneous PTB <34 weeks (adjusted odds ratio, 0.48, 95% CI, 0.24−0.95). Stratifying by preeclampsia status, in the group of women without preeclampsia, there was still a statistically significant reduction of spontaneous preterm birth <34 weeks in women who received low-dose aspirin (OR, 2.18, 95% CI, 1.12−4.23). However, there were too few women in the group who developed preeclampsia (n = 2) to draw any conclusions.

Consistent with the results of the parent trial, although low for both groups (0.72% vs 0.08%), placental

TABLE 1
Demographic comparison by treatment randomization

Variables	Low-dose aspirin (n = 1262)	Placebo (n = 1281)	*P* value
Age, y	19 [17,23]	19 [17, 23]	.5
BMI, kg/m^2	22.5 [20.2, 25.6]	22.7 [20.2, 25.9]	.4
Black race	645 (51.1)	645 (50.3)	.8
Tobacco use	276 (21.9)	246 (19.2)	.3
Alcohol use	39 (3.1)	29 (2.3)	.2
Married	222 (17.5)	278 (21.7)	< .01
Education (school years)	12 [9, 12]	11 [9,12]	.2
Previous pregnancy termination	190 (15.0)	213 (16.6)	.2
Gestational age at randomization, wks	20.3 [17.6, 23.1]	20.4 [17.4, 23.6]	.4

Categorical data are presented as n (percentage) and continuous data as median [interquartile range]. *P* values were determined by χ^2 test (categorical data) and Wilcoxon test (continuous data).

BMI, body mass index.

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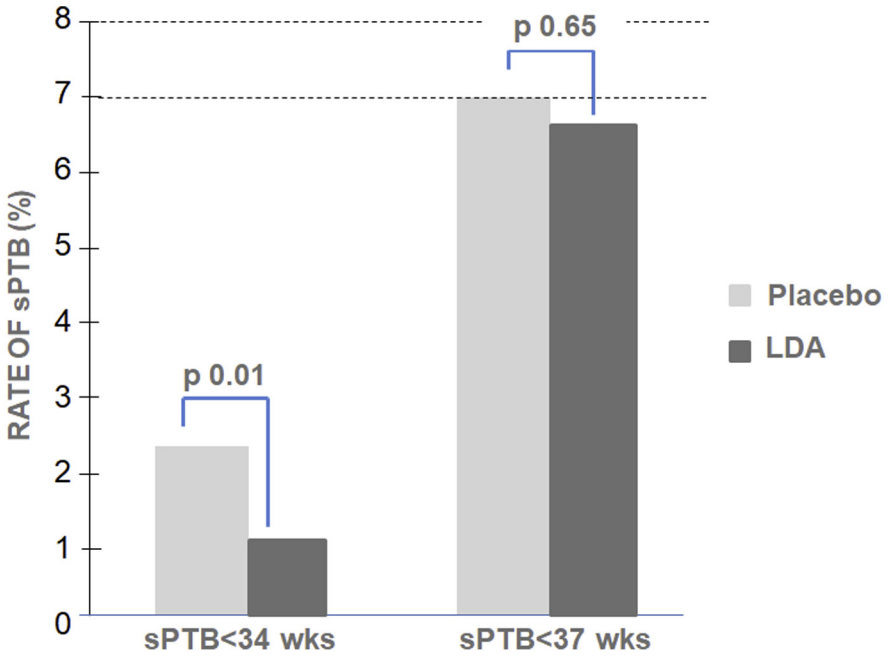
FIGURE 2
sPTB rates in women treated with low-dose aspirin vs placebo



Results of analysis of patients on low-dose aspirin vs placebo.

sPTB, spontaneous preterm birth.

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abruption was more common in women who received low-dose aspirin compared with placebo (OR, 10.0, 95% CI, 1.16−100.0) (Table 3). However, the amount of blood loss during delivery and postpartum hemorrhage rates were similar between the 2 groups (Table 3). The rate of postpartum hemorrhage was 6.8% for the low-dose aspirin group and 7.1% for the placebo group.

Comment

Principal findings

Our study shows that the administration of low-dose aspirin in nulliparous women without comorbidities is associated with a greater than 50% reduction in the odds of spontaneous PTB less than 34 weeks. While there is growing evidence that aspirin reduces overall PTB, to our knowledge, this is the first study that shows a reduction in spontaneous PTB in nulliparous low-risk women, without comorbidities and independent of preeclampsia.

TABLE 2
Rates of PTB in women treated with low-dose aspirin vs placebo

Variables	Low-dose aspirin (n = 1262)	Placebo (n = 1281)	aOR [95% CI]
sPTB <34 wks	13 (1.03)	30 (2.34)	0.46 (0.23−0.89)
PTB <34 wks	20 (1.58)	33 (2.58)	0.62 (0.35−1.12)
sPTB <37 wks	83 (6.58)	90 (7.03)	0.97 (0.71−1.33)
PTB <37 wks	99 (7.84)	105 (8.20)	0.97 (0.72−1.31)

Rate of PTB was by treatment group, n (percentage). Adjusted odds ratio was adjusted for body mass index, race, tobacco use, marital status, and education level.

aOR, adjusted odds ratio; *CI*, confidence interval; *PTB*, preterm birth; *sPTB*, spontaneous preterm birth.

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Results in the context of what is known

Despite advances in perinatal medicine, PTB remains one of the most challenging problems in obstetrics. Many studies have investigated the role of placental insufficiency and vascular disorders in the pathogenesis of PTB. Disorders of deep placentation have not only been associated with preeclampsia and intrauterine growth restriction but also with spontaneous PTB.[22,23]

Kim et al[24] studied the placental bed of patients who presented in preterm labor and demonstrated a higher degree of transformation failure of spiral arteries in myometrium and decidua in women who ultimately delivered preterm. Another study by Kelly et al[25] reported an association between various placental vascular lesions with medically indicated and spontaneous PTB.

Studies like these may explain why abnormal uterine artery Dopplers have been associated with PTB.[24−26] Because abnormal Dopplers have been related to both uteroplacental ischemia and spontaneous PTB, it is possible that low-dose aspirin may affect spontaneous PTB through the same pathway that would cause a decrease in preeclampsia.[27]

Clinical implications

Several studies have examined the risk of spontaneous PTB in women receiving aspirin, but they are either limited to a high-risk population or were underpowered to show a benefit.[16,18,28,29] As previously noted, Van Vliet et al[18] found a reduction in spontaneous PTB, but this was limited to women at risk for preeclampsia, and Silver et al[16] found a large, but nonsignificant reduction in spontaneous PTB in women with prior pregnancy loss. In contrast, our study included nulliparous women without medical comorbidities or previous poor obstetrical history, and we demonstrated a benefit to low-dose aspirin.

Others have assessed aspirin for preeclampsia and not found a decrease in spontaneous preterm birth. Rolnik

TABLE 3
Rates of bleeding during vaginal delivery, cesarean delivery, postpartum hemorrhage, and abruption in women treated with low-dose aspirin vs placebo

Variables	Low-dose aspirin	Placebo	OR [95%CI]
Abruption	9/1241 (0.72%)	1/1207 (0.08%)	10 (1.16−100.0)
PP hemorrhage	82/1205 (6.8%)	86/1207 (7.1%)	1.05 (0.76−1.43)
			P value
Blood loss VD[a]	400 [300, 500]	400 [300, 500]	.21
Blood loss CD[a]	850 [700, 1000]	800 [650, 1000]	.40

Categorical data are presented as n (percentage) and continuous data as median [interquartile range].

CD, cesarean delivery; *CI*, confidence interval; *OR*, odds ratio; *PP* postpartum; *VD*, vaginal delivery.

[a] Blood loss is in milliliters.

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et al,[29] in a multicenter, randomized trial of 150 mg of aspirin vs placebo in pregnancies of high-risk preeclampsia, found no difference in spontaneous PTB less than 34 weeks (OR, 1.07, 95% CI, 0.37−3.10) or less than 37 weeks (OR, 0.83, 95% CI, 0.47−1.47). However, women identified as high risk had serum screening for pregnancy-associated plasma protein A and placental growth factor; it is unclear whether these findings would be generalizable to a US population.[29]

In a study performed in parallel to the parent trial for this analysis, Allshouse et al[28] assessed the risk for spontaneous PTB in the Maternal-Fetal Medicine Unit low-dose aspirin trial in women who were at high risk for preeclampsia. Their group also reported a trend toward fewer PTBs because of spontaneous PTB and preterm premature rupture of membranes in women who received low-dose aspirin compared with placebo, but this finding did not reach statistical significance (OR, 0.82, 95% CI, 0.62−1.09).

We also found a curious increase in the risk of abruption. There are multiple studies in the literature that have demonstrated that aspirin during pregnancy does not increase maternal, fetal, or neonatal risks.[30−32] Although we found an increase in abruption in the group exposed to aspirin, the absolute risk of abruption was low, <1%, in both groups.

These results are similar to the parent randomized control trial, which reported a higher rate of placental abruption in the aspirin group but no higher rates of hemorrhage or need for blood transfusion.[20] The difference between the 2 groups is likely attributed to the extremely low absolute risk of abruption in the placebo group because the rate of abruption in the low-dose aspirin group was the normally expected rate.[33,34]

Many studies have shown no higher risk of abruption after aspirin use in pregnancy. The CLASP multicenter randomized trial of low-dose aspirin for the prevention and treatment of preeclampsia among 9364 pregnant women showed no increase incidence of placental abruption or maternal bleeding in women who received low-dose aspirin (60 mg).[30]

Additionally, a meta-analysis of Askie et al, [35] which included a large cohort of 32,217 women from 31 randomized controlled trials, showed similar risks of antepartum bleeding, postpartum bleeding, and placental abruption between women who received 1 or more antiplatelet agents (aspirin, dipyridamole, or other agents) vs placebo. We believe that our findings are more remarkable for the low rate of abruption in the placebo group because there is robust evidence to demonstrate the safety of aspirin, even in larger doses.[32,36,37]

Research implications

Because of the accumulating evidence of a possible benefit, there are ongoing clinical trials to further investigate the impact of low-dose aspirin in the reduction of indicated as well as spontaneous PTB. The APRIL randomized trial (Nederlands trial register 5675) investigates the role of aspirin for prevention of spontaneous and indicated PTB in women with a history of preterm birth.[38] Additionally, the ASPRIN trial (NCT02409680) assesses the role of low-dose aspirin in nulliparous women in preventing PTB in 7 low- and middle-income countries.[39]

Strengths and limitations

The strengths of this study are that our analysis included a large number of well-characterized patients from a randomized trial with rigorous data collection. Preterm birth was a secondary outcome of the original study, and information on types of PTB, whether spontaneous or indicated, were collected prospectively. The main weakness of the study is that it represents a secondary analysis of an older data set. We were unable to differentiate patients with recurrent pregnancy loss 16−20 weeks, who may have been at a higher risk for spontaneous preterm birth, so all spontaneous losses <20 weeks were excluded. Our results are only generalizable to nulliparous women without comorbidities, such as the type of women enrolled in the trial. Lastly, the study population had a low BMI, which may differ from a contemporary pregnant population.

Conclusion

Our study showed association of low-dose aspirin with significant reduction of spontaneous PTB <34 weeks in nulliparous women with no significant medical or obstetric history, suggesting that low-dose aspirin could be used in an even broader range of patients than currently endorsed.[32,40,41] This opens a new horizon of the use of low-dose aspirin as a safe, cost-effective measure of prevention of spontaneous PTB independent of preeclampsia. However, large randomized trials are needed to confirm these results, particularly because the absolute risks are low. Until then, these findings suggest that low-dose aspirin is a promising intervention that may decrease spontaneous PTB in an even broader population than previously reported. ■

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