Review

Antiplatelet Agents and the Prevention of Spontaneous Preterm Birth

A Systematic Review and Meta-analysis

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OBJECTIVE: Spontaneous preterm birth is an important cause of neonatal mortality and morbidity. An increasing body of evidence suggests that uteroplacental ischemia plays an important role in the etiology of spontaneous preterm birth. We aimed to study whether antiplatelet agents reduce the risk of spontaneous preterm birth.

DATA SOURCES: We included data from an individual participant data meta-analysis of studies that had evaluated the effect of antiplatelet agents to reduce preeclampsia (Perinatal Antiplatelet Review of International Studies Individual Participant Data).

METHODS OF STUDY SELECTION: The meta-analysis included 31 studies that randomized women to low-dose aspirin–dipyridamole or placebo–no treatment as a primary preventive strategy for preeclampsia. For the current study we analyzed data from 17 trials (28,797 women) that supplied data on type of delivery (spontaneous compared with indicated birth).

TABULATION, INTEGRATION, AND RESULTS: Primary endpoints were spontaneous preterm birth at less than 37 weeks, less than 34 weeks, and less than 28 weeks of gestation. We analyzed outcomes for each trial separately using χ^2 statistics and combined in an individual participant data meta-analysis using a binary logistic regression model. Women assigned to antiplatelet treatment compared with placebo or no treatment had a lower risk of spontaneous preterm birth at less than 37 weeks (relative risk [RR] 0.93, 95% confidence interval [CI] 0.86–0.996) and less than 34 weeks of gestation (RR 0.86, 95% CI 0.76–0.99). The RR of having a spontaneous preterm birth at less than 37 weeks of gestation was 0.83 (95% CI 0.73–0.95) for women who have had a previous pregnancy and 0.98 (95% CI 0.89–1.09) for women in their first pregnancy. The treatment effect was stable in all other prespecified subgroups.

CONCLUSION: Antiplatelet agents reduce spontaneous preterm birth in pregnant women at risk for preeclampsia.

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Preterm birth is one of the most challenging obstetric problems worldwide and occurs in approximately 5–12% of all deliveries. Preterm birth accounts for 70% of perinatal mortality and 40% of severe neurologic morbidities.[1] Preterm birth can be classified as spontaneous or iatrogenic. Spontaneous preterm birth starts with spontaneous labor with intact membranes or prelabor premature rupture of the membranes (PROM). In iatrogenic preterm birth, pregnancy is prematurely interrupted for maternal or fetal indications, often as a result of preeclampsia or fetal growth restriction.[2] In industrialized high-resourced countries, spontaneous preterm birth accounts for two thirds of all preterm births and is

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Each author has indicated that he or she has met the journal's requirements for authorship.

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considered a heterogeneous syndrome in which different pathologic processes prematurely activate the mechanisms of labor.[3,4] Myometrial contractions are activated by an interplay between mechanical and endocrine mechanisms and immune system responses.[4] Intrauterine infections are thought to play a major role in spontaneous preterm birth, because inflammatory cytokines stimulate prostaglandin release, thus contributing to preterm myometrial contractions. Furthermore, cytokines and toxins initiate neutrophil activation, leading to the release of metalloproteases that weaken the membranes and cervix.[5] Signs of infection and inflammation are however not always present in spontaneous preterm birth.

An increasing body of evidence suggests that uteroplacental ischemia also plays a role in the etiology of spontaneous preterm labor, analogous to its role of preeclampsia. Placental vascular pathology is found in at least one third of the placentas of women with spontaneous preterm labor or prelabor PROM.[6,7] In placental bed biopsies of women with spontaneous preterm labor, similarities have been found with biopsies of the placentas of women with preeclampsia. Failure of physiologic transformation of the spiral arteries, necessary for normal placental blood flow, is found in one third of women with preterm labor and prelabor PROM.[7–10] Women with spontaneous preterm birth have been shown to have abnormal angiogenic–antiangiogenic plasma profiles, comparable with those found in women with preeclampsia.[11] In addition, women with increased resistance at midtrimester Doppler measurements of uterine artery flow, indicative of disordered placentation, are at increased risk for both spontaneous and iatrogenic preterm birth.[12] Furthermore, women with a history of preeclampsia have an increased risk of spontaneous preterm birth and vice versa.

The Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis, which combined the data of 32,217 women who were randomized to antiplatelets (principally low-dose aspirin) or placebo, showed that, in women at risk for preeclampsia, the use of antiplatelet agents during pregnancy is associated with a moderate reduction in the risk of preeclampsia (relative risk [RR] 0.90, 95% confidence interval [CI] 0.84–0.97).[13] This study also showed a significant reduction in preterm birth at less than 34 weeks of gestation in women treated with antiplatelet agents (RR 0.90, 95% CI 0.83–0.98). In view of the overlapping underlying mechanisms of preeclampsia and spontaneous preterm birth, it would be relevant to know whether this reduction comprises a reduction in iatrogenic preterm birth (eg, through lowering the incidence of preeclampsia) or also in a reduction of spontaneous preterm birth. In view of the scarcity of effective preventive measures for spontaneous preterm birth, this information would be very relevant.

The aim of this additional analysis of the Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis was therefore to evaluate the efficacy of low-dose aspirin for the prevention of spontaneous preterm birth in women at risk for preeclampsia and to explore the effect in prespecified subgroups.

SOURCES

We included data from an individual participant data meta-analysis of studies that had evaluated the effect of antiplatelet agents to reduce preeclampsia, the Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis.

The Perinatal Antiplatelet Review of International Studies Collaboration conducted an Individual Participant Data meta-analysis, which included 31 randomized trials of antiplatelet agents for the prevention of preeclampsia.

STUDY SELECTION

The Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis included studies that randomized women to low-dose aspirin–dipyridamole or placebo–no treatment as a primary preventive strategy for preeclampsia. The studies included women at risk for preeclampsia, gestational hypertension, or intrauterine growth restriction, including nulliparous women. The risk classification was based on previous pregnancy history, pre-existing medical condition (eg, renal disease, diabetes, immune disorder, chronic hypertension), or obstetric risk factors early in the current pregnancy (eg, being primigravida, having a multiple pregnancy). The search strategy for this meta-analysis was described elsewhere[13] but involved extensive searching of bibliographic databases such as MEDLINE. Details on the search strategy and study selection have been published previously.[13]

The current analyses are based on data from the 17 Perinatal Antiplatelet Review of International Studies Individual Participant Data trials that supplied data on type of delivery (ie, spontaneous compared with induction–nonlabor cesarean delivery). The Perinatal Antiplatelet Review of International Studies Steering Committee granted permission for the use of the data for these analyses. We studied three main outcome measures: 1) spontaneous preterm birth of

a liveborn neonate between 20 and 37 weeks of gestation; 2) spontaneous preterm birth of a liveborn neonates between 20 and 34 weeks of gestation; and 3) spontaneous preterm birth of a liveborn neonate between 20 and 28 weeks of gestation. Preterm birth was defined as spontaneous when it followed prelabor PROM or spontaneous labor with intact membranes (ie, no induced labor and no nonlabor cesarean delivery). Because the interest of the effectiveness of antiplatelet agents is mainly focused on preterm birth, we assessed the time between 20 weeks of gestation to 1) spontaneous preterm delivery, 2) iatrogenic preterm delivery, and 3) any preterm delivery by performing a Kaplan-Meier analysis for those women with a spontaneous preterm birth who started treatment before 20 weeks of gestation.

We calculated RRs and 95% CIs for the main outcome measures. Outcomes were analyzed for each trial separately using χ^2 statistics and combined in an individual participant data meta-analysis to calculate an overall effect using a binary logistic regression model. Clustering of data within trials was taken into account by including the trial as a covariate in the model. We calculated numbers needed to treat for statistically significant outcomes. Relative risk ratios were calculated from odds ratios based on the prevalence of the outcome in the nonexposed group.

To explore the effect by trial-level characteristics, we prespecified subgroups based on gestational age at trial entry (less than 16 weeks of gestation compared with 16 weeks of gestation or greater and less than 20 weeks of gestation compared with 20 weeks of gestation or greater) and intended aspirin dose (75 mg per day or less compared with greater than 75 mg per day, based on aspirin-only trials, n=15 trials with 26,893 women). To explore the effects by participant-level characteristics, we prespecified subgroups based on 1) risk factors based on medical history, including parity, pre-existing renal disease, diabetes, hypertensive disorders, and previous small-for-gestational-age neonate; and 2) risk factors in the current pregnancy, including maternal age, pregnancy type (singleton compared with multiple gestations), and neonatal sex. Furthermore, we tested whether the treatment effect was different within women who developed preeclampsia in the current pregnancy compared with women who did not develop preeclampsia. Subgroup effects were analyzed using an interaction term between subgroup and treatment group and calculating the effect of antiplatelet treatment in different strata of the subgroups. Sensitivity analyses were performed for only those studies including a placebo arm and for studies that used aspirin as an antiplatelet agent. Analyzes were performed in IBM SPSS Statistics 22. *P* values <.05 were considered to indicate statistical significance.

The funding source had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. Funding for the data collection within the original Perinatal Antiplatelet Review of International Studies Collaboration is described elsewhere.[13] The Perinatal Antiplatelet Review of International Studies Individual Participant Data Collaboration meta-analysis was granted an exemption from ethics review by the Central Sydney Area Health Service Ethics Committee in December 2002. Permission for the additional analyses of the Perinatal Antiplatelet Review of International Studies data set undertaken in this study was granted by the Perinatal Antiplatelet Review of International Studies Steering Committee after review of the proposal in November 2014.

RESULTS

This article presents the results from 17 randomized trials (August P, Helseth G, Edersheid TG, Milton Hutson J, Druzin M. Sustained release, low-dose aspirin ameliorates but does not prevent preeclampsia [PE] in a high risk population [abstract]. Abstracts from the IXth Congress of the International Society for the Study of Hypertension in Pregnancy. Hypertens Preg 1994;13:303–78.),[14–29] comprising 28,797 women, that contained data on type of delivery. Because gestational age at delivery was unknown for 1,287 women (4.5%), data from 27,510 women were included in our analysis. Of these women, 13,825 were randomly assigned to antiplatelet treatment and 13,685 women to placebo or no treatment. Overall, 57% of the women were in their first pregnancy, 96% had a singleton pregnancy, and 62% were aged 20–35 years. Aspirin alone was given in 15 trials (n=13,294 women) in a dose ranging from 60 to 150 mg per day. One trial[21] gave aspirin in combination with dipyridamole and one trial gave dipyridamole alone.[25] Overall, 9.7% (n=2,670) of women had a spontaneous preterm birth before 37 weeks of gestation, 2.8% (n=773) before 34 weeks of gestation, and 0.5% (n=151) of the women had a spontaneous preterm birth before 28 weeks of gestation.

Antiplatelet agents were associated with a significant reduction in the risk of spontaneous preterm birth before 37 weeks of gestation (9.3% compared with 10.1%, RR 0.93, 95% CI 0.86–0.996) and before 34 weeks of gestation (2.6% compared with 3.1%, RR 0.86, 95% CI 0.76–0.99) compared with the control

group (Table 1). For spontaneous preterm birth before 28 weeks of gestation, the RR was reduced by 19%, although this effect was not significant (0.49% compared with 0.61%, RR 0.81, 95% CI 0.59–1.1). Corresponding numbers needed to treat to prevent one case of spontaneous preterm birth was 139 for spontaneous preterm birth at less than 37 weeks of gestation and 242 for spontaneous preterm birth at less than 34 weeks of gestation.

Time to delivery analyses showed that for women with a spontaneous preterm birth, there was no difference between the two treatment groups in time from 20 weeks of gestation to delivery (log-rank test: χ^2 1.80, P=.18). Furthermore, we performed time to delivery analyses for iatrogenic preterm birth and any preterm birth (iatrogenic or spontaneous preterm birth) and found no significant differences for women who received antiplatelet agents compared with those who received placebo–no treatment (all P values >.10).

For the outcome measure "spontaneous preterm birth at less than 37 weeks of gestation," there was a significant interaction with parity status (P value for interaction .04; Table 2). The RR of having a spontaneous preterm birth at less than 37 weeks of gestation was 0.83 (95% CI 0.73–0.95) for women who have had a previous pregnancy and 0.98 (95% CI 0.89–1.09) for women in their first pregnancy. There was no evidence that women in any of the other subgroups benefited more or less with antiplatelet treatment (Tables 3 and 4). Sensitivity analyses based on trials using aspirin only (n=15; 28,266 women) and on only those trials with a placebo group (n=15; 28,374 women) showed comparable results (Table 5).

DISCUSSION

This study, based on the individual participant data of 27,510 women, shows that antiplatelet agents in pregnant women at risk for preeclampsia reduces the RR of spontaneous preterm birth by approximately 7%. The effect on spontaneous preterm birth at less than 37 weeks of gestation is larger (17% RR reduction) in women with a second or subsequent pregnancy. For the outcome of spontaneous moderate to very preterm birth, defined as birth at less than 34 weeks of gestation, antiplatelet agents also significantly reduced the risk of spontaneous preterm birth (14% RR reduction), and this risk did not differ significantly between primiparous and multiparous women. There was no clear evidence that the treatment was more or less effective in any of the other subgroups, although the incidence of events in some subgroups was low.

The current study did not find a significant reduction in spontaneous preterm birth at less than 28 weeks of gestation. Because the incidence of spontaneous preterm birth at less than 28 weeks of gestation was low (0.5%) and the treatment effect was modest (RR 0.81), the lack of statistical significance may be the result of insufficient power. However, it could also be hypothesized that placental vascular pathology mainly plays a role at moderate to late preterm birth, when very preterm birth is mainly affected by infection–inflammation. Indeed, previous studies have found a higher incidence of placental infection–inflammatory lesions compared with placental vascular lesions in very preterm birth.[30–32]

Previous studies suggested that vascular lesions might play a role in spontaneous preterm birth. The current findings support this hypothesis. Most women in the Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis were at low to moderate risk for preeclampsia.[13] The risk profile of the participants was quite diverse, varying from being primigravid to having a history of previous preeclampsia. Our subgroup analysis revealed no difference in the treatment effect between women at high or low risk for preeclampsia. Therefore, the current findings might be applicable to a broader population of pregnant women. Because there is a paucity of preventive strategies for spontaneous preterm birth, we suggest that the use of antiplatelet agents may be a promising intervention for women who have a history of spontaneous preterm birth.

One of the main concerns in the administration of medication during pregnancy is safety.

The Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis[13] revealed no difference in the incidence of antepartum hemorrhage (RR 1.02, 95% CI 0.90–1.15), placental abruption (RR 1.13, 95% CI 0.87–1.48), or neonatal bleeding (RR 0.93, 95% CI 0.80–1.09) between women who received antiplatelet agents and those who did not. Postpartum hemorrhage (500 mL or greater if supplied or trialists' definition) was more frequent, but this difference was of borderline significance (RR 1.06, 95% CI 1.00–1.13). The reduction in spontaneous preterm birth found in the current study and the reduction in preeclampsia found in the original Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis[13] should be balanced against this potential higher risk of postpartum hemorrhage. Long-term follow-up within individual trials revealed no effect on infant outcomes at 12 and 18 months[33] and there are suggestions of reduced neurobehavioral difficulties at

Table 1. Spontaneous Preterm Birth at Less Than 37, Less Than 34, and Less Than 28 Weeks of Gestation

Trial Reference	Antiplatelets	Control	RR (95% CI)
Spontaneous preterm birth at less than 37 wk of gestation			
14	1/44	2/48	0.78 (0.34–1.77)
15	1/52	2/50	0.73 (0.32–1.66)
16	0/32	1/29	0.47 (0.36–0.61)
17	165/1,816	167/1,814	0.99 (0.89–1.11)
18	3/40	5/44	0.82 (0.46–1.47)
19	3/118	3/75	0.77 (0.34–1.75)
20	152/3,397	180/3,373	0.91 (0.83–1.01)
21	9/156	5/74	0.89 (0.43–1.86)
22	172/1,629	161/1,632	1.04 (0.93–1.17)
23	0/43	1/43	0.50 (0.40–0.61)
24	416/3,018	429/3,024	0.98 (0.92–1.06)
25	13/159	9/142	1.17 (0.70–1.95)
26	16/276	19/278	0.92 (0.67–1.26)
27	15/301	19/301	0.89 (0.65–1.21)
28	97/1,470	105/1,492	0.97 (0.84–1.11)
29	1/23	2/25	0.77 (0.33–1.79)
30	228/1,251	268/1,241	0.90 (0.82–0.99)
Total	1,292/13,825	1,378/13,685	0.93 (0.86–0.996)
Spontaneous preterm birth at less than 34 wk of gestation			
14	0/44	0/48	
15	1/52	0/50	
16	0/32	0/29	
17	51/1,816	53/1,814	0.98 (0.81–1.19)
18	0/40	0/44	
19	1/118	1/75	0.77 (0.19–3.13)
20	40/3,397	40/3,373	1.00 (0.80–1.24)
21	3/156	1/74	1.29 (0.23–7.13)
22	14/1,629	20/1,632	0.85 (0.64–1.13)
23	0/43	1/43	0.49 (0.40–0.61)
24	124/3,018	126/3,024	0.99 (0.88–1.13)
25	4/159	2/142	1.42 (0.46–4.44)
26	4/276	6/278	0.83 (0.50–1.39)
27	5/301	3/301	1.34 (0.54–3.29)
28	24/1,470	44/1,492	0.77 (0.65–0.93)
29	1/23	0/25	
30	88/1,251	116/1,241	0.87 (0.76–0.98)
Total	360/13,825	413/13,685	0.86 (0.76–0.99)
Spontaneous preterm birth at less than 28 wk of gestation			
14	0/44	0/48	
15	0/52	0/50	
16	0/32	0/29	
17	9/1,816	7/1,814	1.14 (0.63–1.99)
18	0/40	0/44	
19	0/118	0/75	
20	4/3,397	5/3,373	0.90 (0.50–1.61)
21	0/156	0/74	
22	1/1,629	5/1,632	0.60 (0.42–0.86)
23	0/43	0/43	
24	21/3,018	24/3,024	0.94 (0.71–1.23)
25	1/159	0/142	
26	1/276	1/278	1.00 (0.25–4.02)
27	0/301	0/301	
28	11/1,470	11/1,492	1.01 (0.66–1.53)
29	0/23	0/25	
30	20/1,251	30/1,241	0.83 (0.66–1.04)
Total	68/13,825	83/13,685	0.81 (0.59–1.12)

Data are n/N unless otherwise specified.
CI, confidence interval; RR, relative risk.

Table 2. Effect in Prespecified Subgroups on Spontaneous Preterm Birth at Less Than 37 Weeks of Gestation

	Antiplatelets	Control	RR (95% CI)	Interaction *P*
Trial factors				
Gestational age at start of treatment (wk)				
Less than 16	284/3,374	313/3,348	0.90 (0.76–1.06)	.72
16 or greater	1,007/10,445	1,064/10,333	0.93 (0.85–1.02)	
Less than 20	668/7,748	710/7,706	0.93 (0.83–1.04)	.84
20 or greater	624/6,071	667/5,975	0.91 (0.81–1.02)	
Intended aspirin dose (mg)*				
ASA 75 or less	1,076/11,293	1,173/11,289	.91 (0.83–0.99)	.40
ASA greater than 75	194/2,174	190/2,137	1.00 (0.81–1.24)	
Obstetric and medical history				
Previous pregnancy				
Yes	469/5,819	549/5,777	0.83 (0.73–0.95)	.04
No	823/7,968	828/7,873	0.98 (0.89–1.09)	
1st pregnancy				
With high risk	117/1,052	121/1,044	0.96 (0.73–1.25)	.05
Without high risk	706/6,916	707/6,829	0.98 (0.88–1.10)	
2nd or subsequent pregnancy				
With high risk	357/4,442	432/4,351	0.79 (0.68–0.91)	.07
Without high risk	112/1,377	117/1,426	0.99 (0.75–1.29)	
Pre-existing renal disease				
Yes	13/212	11/181	1.03 (0.45–2.38)	.77
No	859/10,331	918/10,293	0.92 (0.84–1.02)	
Pre-existing diabetes				
Yes	42/392	44/407	0.99 (0.63–1.55)	.24
No	1,058/11,407	1,153/11,308	0.90 (0.82–0.98)	
Pre-existing hypertensive disease				
Yes	71/1,266	94/1,252	0.73 (0.53–0.999)	.26
No	1,030/10,584	1,105/10,512	0.92 (0.84–1.004)	
Previous SGA neonate				
Yes	78/1,403	89/1,273	0.78 (0.57–1.07)	.32
No	930/10,388	957/10,387	0.97 (0.88–1.06)	
No previous neonate	823/7,968	828/7,873	0.98 (0.89–1.09)	
Current pregnancy				
Maternal age (y)				
Younger than 20	414/2,786	404/2,792	1.03 (0.89–1.20)	
20–35	500/5,199	574/5,146	0.85 (0.75–0.97)	.16
Older than 35	29/314	32/327	0.94 (0.55–1.59)	
Pregnancy type				
Singleton	1,074/12,985	1,131/12,848	0.93 (0.85–1.02)	.31
Multiple	218/839	247/835	0.86 (0.69–1.08)	
Fetal sex				
Male	568/6,624	590/6,542	0.95 (0.84–1.07)	.70
Female	494/6,195	523/6,117	0.92 (0.81–1.05)	
Preeclampsia				
Women with preeclampsia	63/1,039	75/1,126	0.90 (0.64–1.28)	.45
Women without preeclampsia	1,226/12,762	1,301/12,533	0.92 (0.85–0.996)	

RR, relative risk; CI, confidence interval; ASA, acetylsalicylic acid; SGA, small for gestational age.
Data are n/N unless otherwise specified.
* Aspirin-only trials.

5 years of age among neonates who were exposed to aspirin in utero.[34] The administration of antiplatelet agents such as aspirin during pregnancy is considered a safe intervention as a recent review commissioned by the U.S. Preventive Services Task Force concluded.

This study has some limitations. First, because this study presents analyses additional to the prespecified main Perinatal Antiplatelet Review of International Studies analysis, the results should be interpreted with caution. Because multiple analyses have been performed, the risk of a type I error

Table 3. Effect in Prespecified Subgroups on Spontaneous Preterm Birth at Less than 34 Weeks of Gestation

	Antiplatelets	Control	RR (95% CI)	Interaction *P*
Trial factors				
Gestational age at start of treatment (wk)				
Less than 16	82/3,374	89/3,348	0.91 (0.67–1.23)	.67
16 or greater	278/10,445	324/10,333	0.85 (0.72–0.99)	
Less than 20	168/7,748	199/7,706	0.84 (0.68–1.03)	.74
20 or greater	192/6,071	214/5,975	0.88 (0.72–1.07)	
Intended aspirin dose (mg)*				
ASA 75 or less	332/11,293	382/11,289	0.87 (0.75–1.00)	.67
ASA greater than 75	21/2,174	27/2,137	0.77 (0.43–1.36)	
Obstetric and medical history				
Previous pregnancy				
Yes	155/5,819	189/5,777	0.81 (0.65–1.003)	.55
No	205/7,968	224/7,873	0.90 (0.74–1.09)	
1st pregnancy				
With high risk	44/1,052	47/1,044	0.93 (0.61–1.41)	.47
Without high risk	161/6,916	177/6,829	0.90 (0.72–1.11)	
2nd or subsequent pregnancy				
With high risk	117/4,442	152/4,351	0.74 (0.58–0.95)	.52
Without high risk	38/1,377	37/1,426	1.07 (0.67–1.69)	
Pre-existing renal disease				
Yes	4/212	5/181	0.71 (0.19–2.70)	.22
No	248/10,331	269/10,293	0.91 (0.77–1.09)	
Pre-existing diabetes				
Yes	10/392	14/407	0.75 (0.32–1.67)	.93
No	330/44,407	376/11,308	0.87 (0.75–1.01)	
Pre-existing hypertensive disease				
Yes	21/1,266	27/1,252	0.76 (0.43–1.36)	.77
No	320/10,584	363/10,512	0.87 (0.74–1.02)	
Previous SGA neonate				
Yes	22/1,403	25/1,273	0.76 (0.42–1.35)	.36
No	232/10,388	251/10,387	0.92 (0.77–1.01)	
No previous neonate	205/7,968	224/7,873	0.90 (0.74–1.09)	
Current pregnancy				
Maternal age (y)				
Younger than 20	121/2,786	140/2,792	0.86 (0.67–1.10)	
20–35	169/5,199	200/2,146	0.84 (0.68–1.03)	.98
Older than 35	7/314	8/327	0.91 (0.33–2.54)	
Pregnancy type				
Singleton	274/12,985	310/12,848	0.87 (0.74–1.03)	.69
Multiple	86/839	103/835	0.85 (0.62–1.15)	
Fetal sex				
Male	137/6,624	154/6,542	0.88 (0.69–1.11)	.78
Female	131/6,195	147/6,117	0.88 (0.69–1.11)	
Preeclampsia				
Women with preeclampsia	20/1,039	20/1,126	1.09 (0.58–2.03)	.45
Women without preeclampsia	340/12,762	393/12,533	0.85 (0.73–0.98)	

Data are n/N unless otherwise specified.
RR, relative risk; CI, confidence interval; ASA, acetylsalicylic acid; SGA, small for gestational age.
* Aspirin-only trials.

(statistically significant results that are based on chance) should be considered. However, there is sound evidence underpinning our hypothesis within the published biomedical literature and because all outcomes in this project were in the direction of benefit for antiplatelets, we feel these new analyses are of clinical relevance. Second, studies published after 2005 were not included in the initial Perinatal Antiplatelet Review of International Studies Individual Participant Data meta-analysis (published in 2007) and no further individual participant data were collected as part of this new analysis. There have

Table 4. Effect in Prespecified Subgroups on Spontaneous Preterm Birth at Less Than 28 Weeks of Gestation

	Antiplatelets	Control	RR (95% CI)	Interaction *P*
Trial factors				
Gestational age at start of treatment (wk)				
Less than 16	20/3,374	24/3,348	0.82 (0.46–1.50)	.95
16 or greater	48/10,445	59/10,333	0.81 (0.55–1.18)	
Less than 20	41/7,748	51/7,706	0.80 (0.53–1.21)	.92
20 or greater	27/6,071	32/5,975	0.83 (0.50–1.38)	
Intended aspirin dose (mg)*				
ASA 75 or less	65/11,293	77/11,289	0.84 (0.61–1.17)	.26
ASA greater than 75	2/2,174	6/2,137	0.33 (0.07–1.63)	
Pregnancy and medical history				
Previous pregnancy				
Yes	33/5,819	42/5,777	0.78 (0.49–1.23)	.86
No	35/7,968	41/7,873	0.84 (0.54–1.33)	
1st pregnancy				
With high risk	11/1,052	10/1,044	1.09 (0.46–2.58)	.85
Without high risk	24/6,916	31/6,829	0.76 (0.45–1.30)	
2nd or subsequent pregnancy				
With high risk	22/4,442	35/4,351	0.61 (0.35–1.03)	.92
Without high risk	11/1,377	7/1,426	1.66 (0.64–4.29)	
Pre-existing renal disease				
Yes	0/212	1/181	—	.19
No	46/10,331	47/10,293	0.97 (0.65–1.46)	
Pre-existing diabetes				
Yes	1/392	0/407	—	.38
No	65/11,407	78/11,308	0.83 (0.59–1.15)	
Pre-existing hypertensive disease				
Yes	5/1,266	9/1,252	0.56 (0.19–1.68)	.31
No	61/10,584	69/10,512	0.88 (0.62–1.24)	
Previous SGA neonate				
Yes	4/1,403	2/1,273	1.71 (0.31–9.45)	.16
No	39/10,388	44/10,387	0.89 (0.58–1.36)	
No previous neonate	35/7,968	41/7,873	0.84 (0.54–1.33)	
Current pregnancy				
Maternal age (y)				
Younger than 20	20/2,786	33/2,792	0.60 (0.34–1.05)	
20–35	41/3,199	37/5,146	1.11 (0.71–1.73)	.23
Older than 35	2/314	3/327	1.30 (0.74–2.30)	
Pregnancy type				
Singleton	50/12,985	59/12,848	0.84 (0.57–1.22)	.75
Multiple	18/839	24/835	0.77 (0.41–1.44)	
Fetal sex†				
Male	23/6,624	35/6,542	0.65 (0.38–1.10)	.39
Female	6/6,195	21/6,117	1.22 (0.69–2.18)	
Preeclampsia				
Women with preeclampsia	0/1,039	2/1,126	—	—
Women without preeclampsia	68/12,762	81/12,533	0.83 (0.60–1.14)	

Data are n/N unless otherwise specified.
RR, relative risk; CI, confidence interval; ASA, acetylsalicylic acid; SGA, small for gestational age.
* Aspirin-only trials.
† Analysis including singleton pregnancies only (n=25,833).

been six relevant trials published since 2005, all with small sample sizes (n=49,[35] n=54,[36] n=152,[37] n=80,[38] n=164,[39] and n=70[40]). Although we could have requested and included aggregate data results from these additional 569 women, it is unlikely they would have substantially changed the findings from the 27,510 women in this analysis. Third, because the studies were not designed to evaluate spontaneous preterm birth, there was a possibility of inconsistency in definitions of this outcome between studies.

Table 5. Sensitivity Analyses

	RR	95% CI	*P*
Aspirin-only trials			
Spontaneous preterm birth (wk of gestation)			
37	0.92	0.849–0.998	.04
34	0.86	0.74–0.987	.03
28	0.80	0.582–1.110	.19
Placebo group–only trials			
Spontaneous preterm birth (wk of gestation)			
37	0.93	0.855–1.004	.06
34	0.86	0.746–0.995	.04
28	0.82	0.59–1.127	.22

RR, relative risk; CI, confidence interval.

However, because we used individual participant data and included only those studies that collected data on type of delivery (ie, birth after prelabor PROM, spontaneous labor with intact membranes, induced labor, nonlabor cesarean delivery), we minimized the potential bias resulting from inconsistency of outcome definition.

Finally, had the outcome of spontaneous preterm birth been part of an agreed core outcome data set for obstetric studies, it may have been part of the original Perinatal Antiplatelet Review of International Studies analysis, and thereby these important data would have been available earlier. Initiatives to standardize outcomes in obstetric research are now ongoing to improve this situation.[41]

In summary, administration of antiplatelet agents in pregnant women at risk for preeclampsia reduces the risk of spontaneous preterm birth by 7%. Moderate to very preterm birth at less than 34 weeks of gestation is reduced by 14%. Because antiplatelet agents in pregnancy are a low-cost and safe intervention, we suggest that antiplatelet agents may also be a promising intervention for women at high risk for a spontaneous preterm birth, especially in high-risk women with a previous pregnancy. The current study provides clinicians with the best available evidence to counsel women regarding who might benefit from this intervention.

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