Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis

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Research into the potential effects of low-dose aspirin and other antiplatelet agents for the prevention of preeclampsia and its complications has expanded exponentially, with data now available on more than 37,000 women recruited to more than 70 randomized trials.[1]

Whereas individually the large multicenter trials failed to confirm statistically significant benefits with the use of aspirin,[2-5] systematic reviews[6-8] including the Cochrane Review,[8] and an individual participant data (IPD) meta-analysis[9] have consistently shown a modest but clinically important reduction (10% to 15%)[6,9] in the risk of preeclampsia with the use of antiplatelet agents. Antiplatelet agents are also associated with reductions in the complications of preeclampsia such as perinatal death, preterm birth, and having a small-for-gestational-age baby.[8,9] Long-term follow-up provides reassurance about the safety of low-dose aspirin.[8,10,11]

Although the benefits associated with antiplatelet agents are modest, they have

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BACKGROUND: The optimum time for commencing antiplatelet therapy for the prevention of preeclampsia and its complications is unclear. Aggregate data meta-analyses suggest that aspirin is more effective if given prior to 16 weeks' gestation, but data are limited because of an inability to place women in the correct gestational age subgroup from relevant trials.

OBJECTIVE: The objective of the study was to use the large existing individual participant data set from the Perinatal Antiplatelet Review of International Studies Collaboration to assess whether the treatment effects of antiplatelet agents on preeclampsia and its complications vary based on whether treatment is started before or after 16 weeks' gestation.

STUDY DESIGN: A meta-analysis of individual participant data including 32,217 women and 32,819 babies recruited to 31 randomized trials comparing low-dose aspirin or other antiplatelet agents with placebo or no treatment for the prevention of preeclampsia has been published previously. Using this existing data set, we performed a prespecified subgroup analysis based on gestation at randomization to antiplatelet agents before 16 weeks, compared with at or after 16 weeks, for 4 of the main outcomes prespecified in the Perinatal Antiplatelet Review of International Studies protocol: preeclampsia, death of baby, preterm birth before 34 weeks, and small-for-gestational-age baby. Individual participant data for the subgroups were combined in a meta-analysis using RevMan software. Heterogeneity was assessed with the I^2 statistic. The χ^2 test for interaction was used to assess statistically significant ($P < .05$) differences in treatment effect between subgroups.
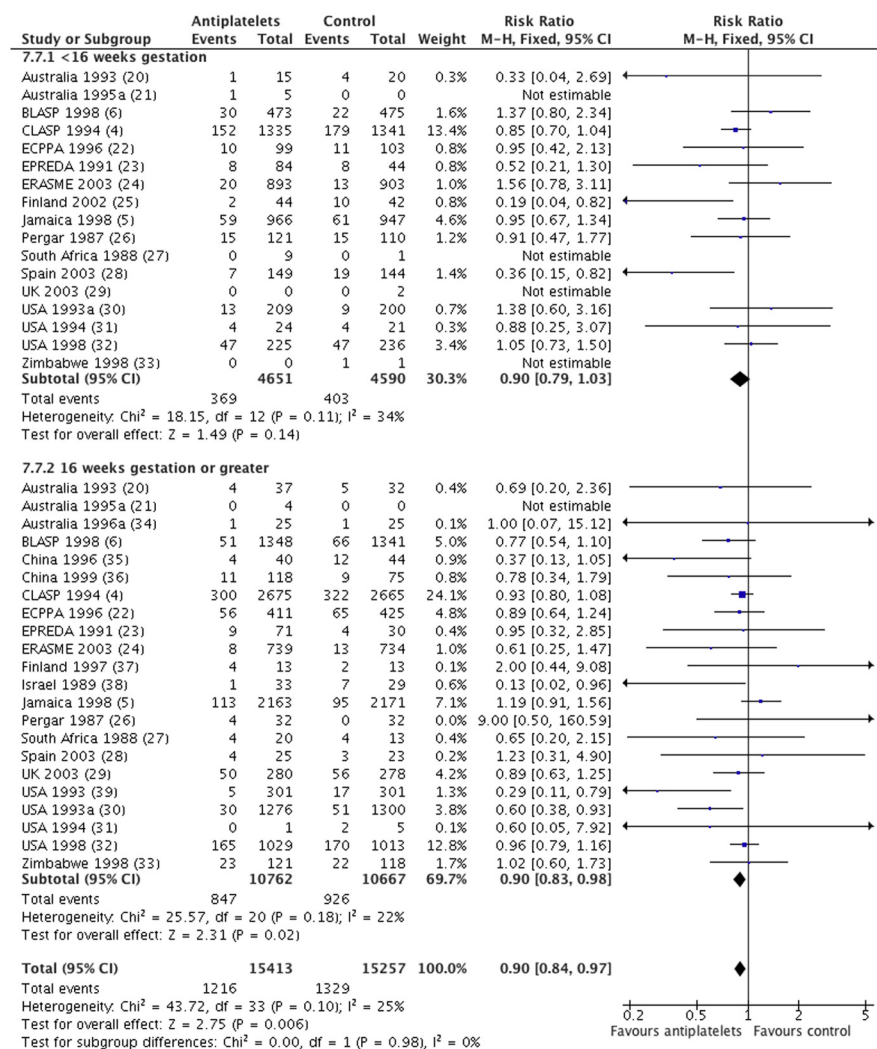
RESULTS: There was no significant difference in the effects of antiplatelet therapy for women randomized before 16 weeks' gestation compared with those randomized at or after 16 weeks for any of the 4 prespecified outcomes: preeclampsia, relative risk, 0.90, (95% confidence interval, 0.79−1.03; 17 trials, 9241 women) for <16 weeks and relative risk, 0.90 (95% confidence interval, 0.83−0.98; 22 trials, 21,429 women) for ≥16 weeks (interaction test, $P = .98$); death of baby, relative risk, 0.89 (95% confidence interval, 0.73−1.09; 15 trials, 8626 women) for <16 weeks and relative risk, 0.92 (95% confidence interval, 0.79−1.07; 21 trials, 22,336 women) for ≥16 weeks (interaction test, $P = .80$); preterm birth prior to 34 weeks, relative risk, 0.90 (95% confidence interval, 0.77−1.04; 19 trials, 9155 women) for <16 weeks and relative risk, 0.91 (95% confidence interval, 0.82−1.00; 25 trials, 22,117 women) for ≥16 weeks (interaction test, $P = .91$); and small-for-gestational-age baby, relative risk, 0.76 (95% confidence interval, 0.61−0.94; 13 trials, 6393 women) for <16 weeks and relative risk, 0.95 (95% confidence interval, 0.84−1.08; 18 trials, 14,996 women) for ≥16 weeks (interaction test, $P = .08$).

CONCLUSION: The effect of low-dose aspirin and other antiplatelet agents on preeclampsia and its complications is consistent, regardless of whether treatment is started before or after 16 weeks' gestation. Women at an increased risk of preeclampsia should be offered antiplatelet therapy, regardless of whether they are first seen before or after 16 weeks' gestation.

Key words: antiplatelets, aspirin, gestation, preeclampsia, prevention

FIGURE 1
Preeclampsia: subgroup by randomization at 16 weeks' gestational age

Study or Subgroup	Antiplatelets Events	Total	Control Events	Total	Weight	Risk Ratio M–H, Fixed, 95% CI
7.7.1 <16 weeks gestation						
Australia 1993 (20)	1	15	4	20	0.3%	0.33 [0.04, 2.69]
Australia 1995a (21)	1	5	0	0		Not estimable
BLASP 1998 (6)	30	473	22	475	1.6%	1.37 [0.80, 2.34]
CLASP 1994 (4)	152	1335	179	1341	13.4%	0.85 [0.70, 1.04]
ECPPA 1996 (22)	10	99	11	103	0.8%	0.95 [0.42, 2.13]
EPREDA 1991 (23)	8	84	8	44	0.8%	0.52 [0.21, 1.30]
ERASME 2003 (24)	20	893	13	903	1.0%	1.56 [0.78, 3.11]
Finland 2002 (25)	2	44	10	42	0.8%	0.19 [0.04, 0.82]
Jamaica 1998 (5)	59	966	61	947	4.6%	0.95 [0.67, 1.34]
Pergar 1987 (26)	15	121	15	110	1.2%	0.91 [0.47, 1.77]
South Africa 1988 (27)	0	9	0	1		Not estimable
Spain 2003 (28)	7	149	19	144	1.4%	0.36 [0.15, 0.82]
UK 2003 (29)	0	0	0	2		Not estimable
USA 1993a (30)	13	209	9	200	0.7%	1.38 [0.60, 3.16]
USA 1994 (31)	4	24	4	21	0.3%	0.88 [0.25, 3.07]
USA 1998 (32)	47	225	47	236	3.4%	1.05 [0.73, 1.50]
Zimbabwe 1998 (33)	0	0	1	1		Not estimable
Subtotal (95% CI)		4651		4590	30.3%	0.90 [0.79, 1.03]
Total events	369		403			
Heterogeneity: Chi² = 18.15, df = 12 (P = 0.11); I² = 34%						
Test for overall effect: Z = 1.49 (P = 0.14)						
7.7.2 16 weeks gestation or greater						
Australia 1993 (20)	4	37	5	32	0.4%	0.69 [0.20, 2.36]
Australia 1995a (21)	0	4	0	0		Not estimable
Australia 1996a (34)	1	25	1	25	0.1%	1.00 [0.07, 15.12]
BLASP 1998 (6)	51	1348	66	1341	5.0%	0.77 [0.54, 1.10]
China 1996 (35)	4	40	12	44	0.9%	0.37 [0.13, 1.05]
China 1999 (36)	11	118	9	75	0.8%	0.78 [0.34, 1.79]
CLASP 1994 (4)	300	2675	322	2665	24.1%	0.93 [0.80, 1.08]
ECPPA 1996 (22)	56	411	65	425	4.8%	0.89 [0.64, 1.24]
EPREDA 1991 (23)	9	71	4	30	0.4%	0.95 [0.32, 2.85]
ERASME 2003 (24)	8	739	13	734	1.0%	0.61 [0.25, 1.47]
Finland 1997 (37)	4	13	2	13	0.1%	2.00 [0.44, 9.08]
Israel 1989 (38)	1	33	7	29	0.6%	0.13 [0.02, 0.96]
Jamaica 1998 (5)	113	2163	95	2171	7.1%	1.19 [0.91, 1.56]
Pergar 1987 (26)	4	32	0	32	0.0%	9.00 [0.50, 160.59]
South Africa 1988 (27)	4	20	4	13	0.4%	0.65 [0.20, 2.15]
Spain 2003 (28)	4	25	3	23	0.2%	1.23 [0.31, 4.90]
UK 2003 (29)	50	280	56	278	4.2%	0.89 [0.63, 1.25]
USA 1993 (39)	5	301	17	301	1.3%	0.29 [0.11, 0.79]
USA 1993a (30)	30	1276	51	1300	3.8%	0.60 [0.38, 0.93]
USA 1994 (31)	0	1	2	5	0.1%	0.60 [0.05, 7.92]
USA 1998 (32)	165	1029	170	1013	12.8%	0.96 [0.79, 1.16]
Zimbabwe 1998 (33)	23	121	22	118	1.7%	1.02 [0.60, 1.73]
Subtotal (95% CI)		10762		10667	69.7%	0.90 [0.83, 0.98]
Total events	847		926			
Heterogeneity: Chi² = 25.57, df = 20 (P = 0.18); I² = 22%						
Test for overall effect: Z = 2.31 (P = 0.02)						
Total (95% CI)		15413		15257	100.0%	0.90 [0.84, 0.97]
Total events	1216		1329			
Heterogeneity: Chi² = 43.72, df = 33 (P = 0.10); I² = 25%						
Test for overall effect: Z = 2.75 (P = 0.006)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						

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Favours antiplatelets Favours control

A meta-analysis of randomized trials subgrouped by gestation at randomization before and after 16 weeks, for the outcome preeclampsia.

CI, confidence interval.

Meher. IPD subgroup meta-analysis of antiplatelets for preeclampsia. Am J Obstet Gynecol 2017.

public health importance, particularly because there is reassurance about safety, and aspirin is both easily available and of a low cost. International guidelines widely recommend that aspirin should be offered to women at an increased risk of preeclampsia.[12-16] However, recommendation about when to start treatment vary, ranging from before or at 12 weeks' gestation[12,15] to before 16[13] or 20 weeks.[16]

Controversy remains about whether commencing treatment earlier in pregnancy has greater benefits.[7] A recent meta-analysis of aggregate data suggests that starting antiplatelets prior to 16 weeks is associated with a greater reduction in the risk of preeclampsia compared with after 16 weeks, and significant reductions in perinatal death, severe preeclampsia, and fetal growth restriction are seen only if aspirin is commenced at ≤16 weeks.[17,18] However, because of the problems of placing women in the correct gestational age category when using aggregate data, this analysis was restricted to 1479 women recruited before 16 weeks.[17] Nevertheless, findings from aggregate data meta-analyses have led to

the belief that if aspirin is not started before 16 weeks, then it may no longer be beneficial and therefore is not prescribed.

Our Perinatal Antiplatelet Review of International Studies (PARIS) IPD meta-analysis of antiplatelet trials prespecified a subgroup analysis based on gestational age at randomization at a gestation of <16 weeks, 16–19 weeks, 20–23 weeks, 24–27 weeks, and ≥28 weeks.[19] The protocol stated that if numbers were insufficient for any category, categories would be combined.

In the original publication, we combined data on outcomes based on whether randomization was before and after 20 weeks, and this showed no clear difference in the risk of preeclampsia between these 2 subgroups (interaction test, P = .24).[9] However, in view of the current controversy, in this paper we present data on outcomes based on combining subgroups at randomization before and after 16 weeks. Individual participant data are available from the PARIS data set for more than 9000 women recruited before 16 weeks.[9]

The aim of this paper is to use this large existing data set to assess whether the effect of antiplatelet therapy on preeclampsia and its consequences varies based on whether gestation at which treatment is started is before or after 16 weeks. This will inform clinical decision making and guidelines as to whether women who are first seen in the clinic after 16 weeks should be offered a potentially effective intervention.

Materials and Methods
Detailed methods for the PARIS individual participant data systematic review and meta-analysis have been published previously.[9,19] A brief description of the methodology relevant to the analysis presented here is outlined in the following text.

Search strategy
The Cochrane Pregnancy and Childbirth Review Group's register of trials was searched up to December 2005 for relevant trials. This register is maintained by the regular searching of Medline, Embase, CENTRAL, and relevant journals by hand; PARIS trialists were also contacted for any further studies.

Eligibility criteria

Studies were included if they randomized women at risk of developing preeclampsia, gestational hypertension, or intrauterine growth restriction (based on previous or current obstetric factors or a preexisting medical disease) to receive 1 or more antiplatelet agents (eg, low-dose aspirin or dipyridamole) vs a placebo or no antiplatelet agent. Quasirandomized trials, and trials that included women who started treatment postpartum or had a diagnosis of preeclampsia at trial entry were excluded.

The analysis presented here includes women enrolled for primary prevention only (ie, women without gestational hypertension). Each potentially eligible study was assessed independently by at least 2 members of the IPD steering group, and any differences of opinion were resolved by discussion.

Four main outcomes were prespecified: preeclampsia (hypertension with new-onset proteinuria at or beyond 20 weeks' gestation); death in utero or death of the baby before discharge from the hospital; preterm birth at less than 34 weeks' gestation; and infant small for gestational age at birth (as defined by individual trialists).

Data extraction and analyses

Anonymized data for each of the prespecified variables were requested from trialists for each woman randomized. Data were supplied in a variety of formats, recoded as necessary, and checked for internal consistency, consistency with published reports, and missing items. Inconsistencies or missing data were discussed with relevant trialists and corrected when necessary.

Analyses included all women randomized and were based on an intention to treat. The analysis was restricted to trials with at least 80% of data available for that particular outcome. Outcomes were analyzed in their original trial and then these individual results combined in a meta-analysis to give an overall measure of effect.

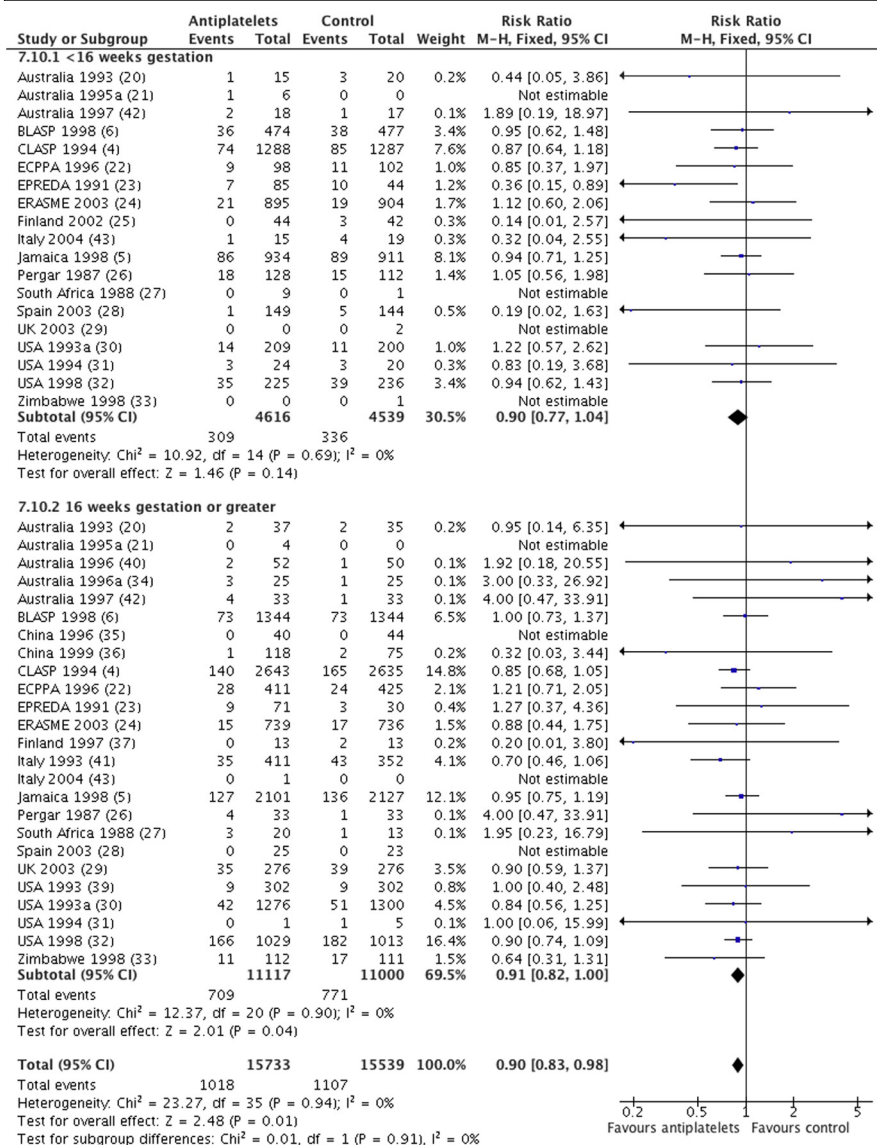A fixed-effect model was used, and the level of heterogeneity assessed with the I^2 statistic. Random-effects models were also run to test the robustness of results to the choice of model. We used a fixed-effect analysis in which the heterogeneity was low ($I^2 \leq 30\%$) and random-effects analysis in which the heterogeneity was high ($I^2 > 30\%$). Analyses were done using SCHARP software, version 4.0 (SAS Institute, Cary, NC), for the original IPD analyses and RevMan software (The Nordic Cochrane Centre, Copenhagen, Denmark) for the analysis presented here. χ^2 tests for interaction were performed to assess whether there were statistically significant differences ($P < .05$) in the treatment effect between subgroups.

The protocol prespecified subgroup analysis based on gestational age at randomization at a gestation of <16 weeks, 16−19 weeks, 20−23 weeks, 24−27 weeks, and ≥28 weeks and stated that if the numbers were insufficient for any category, categories would be combined.[19] For this analysis, a subgroup analysis based on gestation at randomization before 16 weeks, compared with

FIGURE 2
Death of baby: subgroup by randomization at 16 weeks
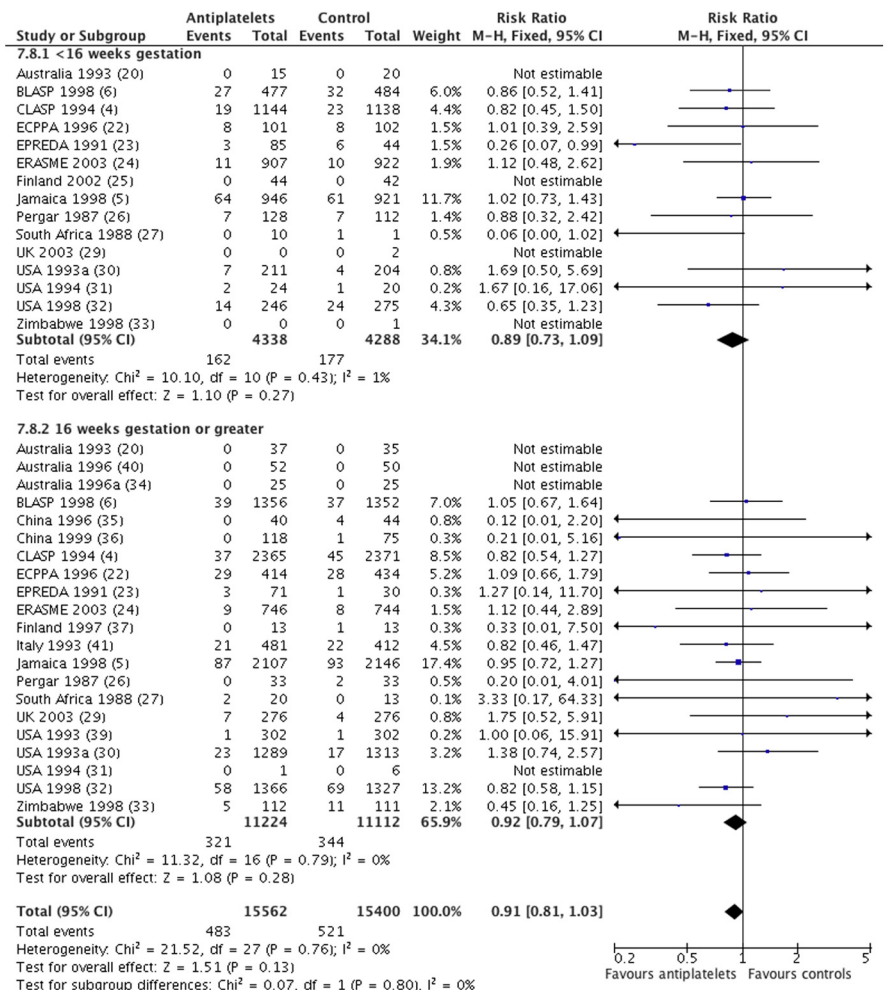
Death of baby in utero or up to discharge from hospital: subgroup by randomization at 16 weeks' gestational age. This shows a meta-analysis of randomized trials subgrouped by gestation at randomization before and after 16 weeks, for the outcome death of baby in utero or up to discharge from hospital.

CI, confidence interval.

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FIGURE 3
Preterm birth before 34 weeks' gestation: subgroup by randomization at 16 weeks

Study or Subgroup	Antiplatelets Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
7.10.1 <16 weeks gestation							
Australia 1993 (20)	1	15	3	20	0.2%	0.44 [0.05, 3.86]	
Australia 1995a (21)	1	6	0	0		Not estimable	
Australia 1997 (42)	2	18	1	17	0.1%	1.89 [0.19, 18.97]	
BLASP 1998 (6)	36	474	38	477	3.4%	0.95 [0.62, 1.48]	
CLASP 1994 (4)	74	1288	85	1287	7.6%	0.87 [0.64, 1.18]	
ECPPA 1996 (22)	9	98	11	102	1.0%	0.85 [0.37, 1.97]	
EPREDA 1991 (23)	7	85	10	44	1.2%	0.36 [0.15, 0.89]	
ERASME 2003 (24)	21	895	19	904	1.7%	1.12 [0.60, 2.06]	
Finland 2002 (25)	0	44	3	42	0.3%	0.14 [0.01, 2.57]	
Italy 2004 (43)	1	15	4	19	0.3%	0.32 [0.04, 2.55]	
Jamaica 1998 (5)	86	934	89	911	8.1%	0.94 [0.71, 1.25]	
Pergar 1987 (26)	18	128	15	112	1.4%	1.05 [0.56, 1.98]	
South Africa 1988 (27)	0	9	0	1		Not estimable	
Spain 2003 (28)	1	149	5	144	0.5%	0.19 [0.02, 1.63]	
UK 2003 (29)	0	0	0	2		Not estimable	
USA 1993a (30)	14	209	11	200	1.0%	1.22 [0.57, 2.62]	
USA 1994 (31)	3	24	3	20	0.3%	0.83 [0.19, 3.68]	
USA 1998 (32)	35	225	39	236	3.4%	0.94 [0.62, 1.43]	
Zimbabwe 1998 (33)	0	0	0	1		Not estimable	
Subtotal (95% CI)		4616		4539	30.5%	0.90 [0.77, 1.04]	
Total events	309		336				
Heterogeneity: Chi² = 10.92, df = 14 (P = 0.69); I² = 0%							
Test for overall effect: Z = 1.46 (P = 0.14)							
7.10.2 16 weeks gestation or greater							
Australia 1993 (20)	2	37	2	35	0.2%	0.95 [0.14, 6.35]	
Australia 1995a (21)	0	4	0	0		Not estimable	
Australia 1996 (40)	2	52	1	50	0.1%	1.92 [0.18, 20.55]	
Australia 1996a (34)	3	25	1	25	0.1%	3.00 [0.33, 26.92]	
Australia 1997 (42)	4	33	1	33	0.1%	4.00 [0.47, 33.91]	
BLASP 1998 (6)	73	1344	73	1344	6.5%	1.00 [0.73, 1.37]	
China 1996 (35)	0	40	0	44		Not estimable	
China 1999 (36)	1	118	2	75	0.2%	0.32 [0.03, 3.44]	
CLASP 1994 (4)	140	2643	165	2635	14.8%	0.85 [0.68, 1.05]	
ECPPA 1996 (22)	28	411	24	425	2.1%	1.21 [0.71, 2.05]	
EPREDA 1991 (23)	9	71	3	30	0.4%	1.27 [0.37, 4.36]	
ERASME 2003 (24)	15	739	17	736	1.5%	0.88 [0.44, 1.75]	
Finland 1997 (37)	0	13	2	13	0.2%	0.20 [0.01, 3.80]	
Italy 1993 (41)	35	411	43	352	4.1%	0.70 [0.46, 1.06]	
Italy 2004 (43)	0	1	0	0		Not estimable	
Jamaica 1998 (5)	127	2101	136	2127	12.1%	0.95 [0.75, 1.19]	
Pergar 1987 (26)	4	33	1	33	0.1%	4.00 [0.47, 33.91]	
South Africa 1988 (27)	3	20	1	13	0.1%	1.95 [0.22, 16.79]	
Spain 2003 (28)	0	25	0	23		Not estimable	
UK 2003 (29)	35	276	39	276	3.5%	0.90 [0.59, 1.37]	
USA 1993 (39)	9	302	9	302	0.8%	1.00 [0.40, 2.48]	
USA 1993a (30)	42	1276	51	1300	4.5%	0.84 [0.56, 1.25]	
USA 1994 (31)	0	1	1	5	0.1%	1.00 [0.06, 15.99]	
USA 1998 (32)	166	1029	182	1013	16.4%	0.90 [0.74, 1.09]	
Zimbabwe 1998 (33)	11	112	17	111	1.5%	0.64 [0.31, 1.31]	
Subtotal (95% CI)		11117		11000	69.5%	0.91 [0.82, 1.00]	
Total events	709		771				
Heterogeneity: Chi² = 12.37, df = 20 (P = 0.90); I² = 0%							
Test for overall effect: Z = 2.01 (P = 0.04)							
Total (95% CI)		15733		15539	100.0%	0.90 [0.83, 0.98]	
Total events	1018		1107				
Heterogeneity: Chi² = 23.27, df = 35 (P = 0.94); I² = 0%							
Test for overall effect: Z = 2.48 (P = 0.01)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%							

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Favours antiplatelets Favours control

Preterm birth before 34 weeks' gestation: subgroup by randomization at 16 weeks' gestational age. This shows a meta-analysis of randomized trials subgrouped by gestation at randomization before and after 16 weeks, for the outcome preterm birth before 34 weeks' gestation.

CI, confidence interval.

Meher. IPD subgroup meta-analysis of antiplatelets for preeclampsia. Am J Obstet Gynecol 2017.

at or after 16 weeks, was carried out for the 4 main outcomes prespecified in the PARIS protocol: preeclampsia, death of the baby, preterm birth before 34 weeks, and a small-for-gestational-age baby.[19]

Results
Information about the quality and characteristics of the included trials and main findings of the IPD meta-analysis can be found in the previous publication.[9] Results from the subgroup analysis based on gestational age at randomization before 16 weeks and at or after 16 weeks are presented in the following text.

For the outcome of preeclampsia, individual participant data were available from 23 trials (30,670 women) with an overall relative risk of 0.90 (95% confidence interval [CI], 0.84–0.97) (Figure 1). For women randomized before 16 weeks, the relative risk of preeclampsia was 0.90, with a 95% CI of 0.79–1.03 (17 trials, 9241 women). For those randomized at or after 16 weeks, the relative risk was also 0.90, with a 95% CI of 0.83–0.98 (22 trials, 21,429 women). There was no statistically significant difference in treatment effect between the 2 subgroups (interaction test, P = .98; heterogeneity I², 25%).

For the outcome death in utero or death of baby before discharge from the hospital, data were available from 22 trials (30,962 babies) with an overall relative risk of 0.91 (95% CI, 0.81–1.03) (Figure 2). For women randomized before 16 weeks, the relative risk of death of the baby was 0.89, with a 95% CI of 0.73–1.09 (15 trials, 8626 women), and for those randomized at or after 16 weeks, it was 0.92 with a 95% CI of 0.79–1.07 (21 trials, 22,336 women). There was no statistically significant difference in treatment effect between the 2 subgroups (interaction test, P = .80; heterogeneity I², 0%).

For preterm birth prior to 34 weeks' gestation, data were available from 26 trials (31,272 women) with an overall relative risk of 0.90 (95% CI, 0.83–0.98) (Figure 3). For women randomized before 16 weeks, the relative risk was 0.90, with a 95% of CI 0.77–1.04 (19 trials, 9155 women), and for those randomized at or after 16 weeks, it was 0.91, with a 95% CI of 0.82–1.00 (25 trials, 22,117 women). There was no statistically significant difference in treatment effect between the 2 subgroups (interaction test, P = .91; heterogeneity, I², 0%).

For the outcome of the baby being small for gestational age, data were available from 19 trials (21,389 women), with an overall relative risk of 0.90 (95% CI, 0.81–1.00) (Figure 4). For women randomized before 16 weeks, the relative risk was 0.76, with a 95% CI of 0.61–0.94 (13 trials, 6393 women). For women randomized at or after 16 weeks, the relative risk was 0.95, with a 95% CI of 0.84 to 1.08 (18 trials, 14,996 women). There was no statistically significant

difference in treatment effect between the 2 subgroups (interaction test, $P = .08$; heterogeneity I^2, 25%).

Sensitivity analyses based on variations in the definitions of preeclampsia, a low vs a higher dose of aspirin (aspirin-only trials), and use of placebo were carried out for the main analysis.[9] These factors did not have an impact on the overall results and therefore are unlikely to have an impact on the results of this subgroup meta-analysis (Appendix Table 1).

A sensitivity analysis that included IPD data from antiplatelet trials published up to 2005 as well as aggregate data from trials published between 2005 and 2015 was conducted. This did not show any significant differences between subgroups whether women were randomised to antiplatelets before or after 16 weeks' gestation for the 4 main outcomes (Appendix Table 2). Although the risk of having a small-for-gestational-age baby was borderline for statistical significance (relative risk, 0.68 [95% CI, 0.50−0.92] for <16 week subgroup; relative risk, 0.95 [95% CI, 0.84−1.07] for >16 week subgroup; $P = .05$), these data should be interpreted with caution because women randomized at 16 weeks in some aggregate data studies could not be accurately placed in the appropriate subgroup for analysis.

Comment

This systematic review and individual participant data meta-analysis using data from more than 30,000 women found no difference in the risk of preeclampsia and its consequences, regardless of whether antiplatelet treatment was started before or after 16 weeks' gestation, because the interaction tests for subgroup differences for all 4 outcomes were nonsignificant.

Strengths of our analysis are that each woman is correctly assigned to the appropriate subgroup, the data set is large, and potential for bias in selecting data for analysis is minimized. Because the outcome is rarely reported by gestation at randomization, the meta-analyses based on aggregate data may have assigned some participants to an incorrect subgroup.[17,18,44]

FIGURE 4
Small-for-gestational-age baby: subgroup by randomization at 16 weeks
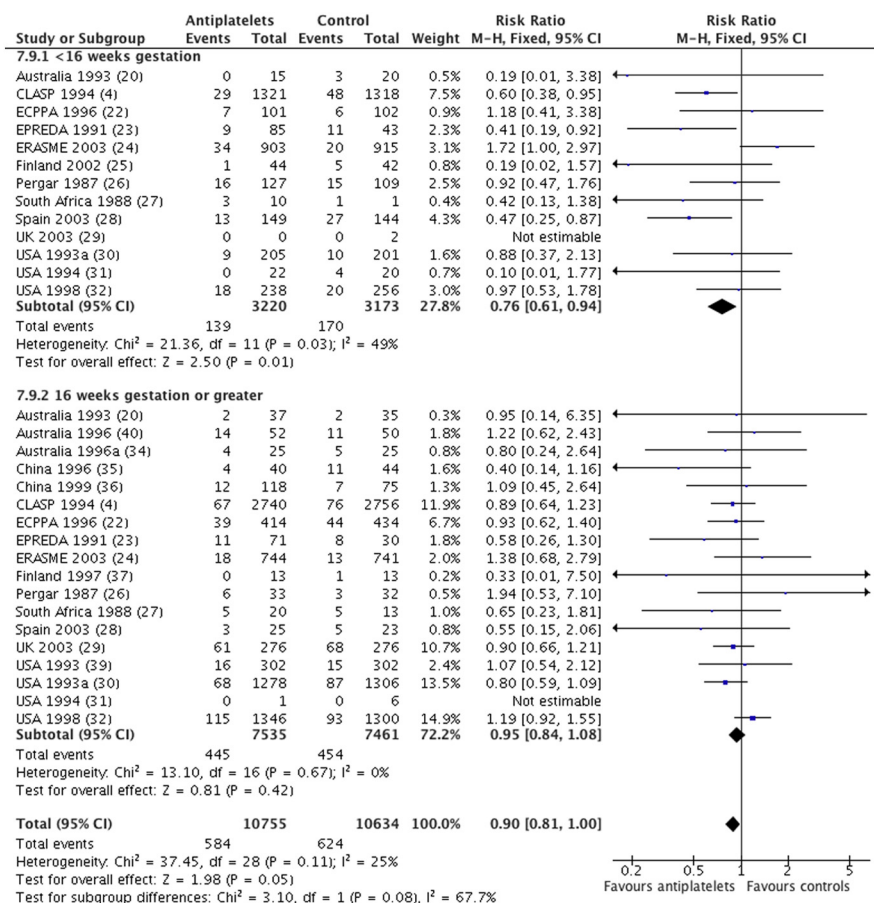
Small-for-gestational-age baby: subgroup by randomization at 16 weeks' gestational age. This shows a meta-analysis of randomized trials subgrouped by gestation at randomization before and after 16 weeks, for the outcome small-for-gestational-age baby.

CI, confidence interval.

Meher. IPD subgroup meta-analysis of antiplatelets for preeclampsia. Am J Obstet Gynecol 2017.

Although published aggregate data meta-analyses include many of the studies included in the IPD meta-analysis (21 of 32 IPD studies by Roberge et al,[17] 11 of 32 IPD studies by Xu et al[44]), in which women were recruited across a wide gestational age range, complete studies have been excluded from aggregate data subgroup analyses.[17,18,44]

Overcoming these limitations using the individual participant data from each trial means that a key strength of our analysis is that it includes data for 9241 women from the 17 trials that recruited women before 16 weeks' gestation and provided individual participant data for the original PARIS analysis, 6-fold more

participants than reported in the previously published aggregate data analysis (Table).[17]

Reducing missing data reduces potential for bias. The aggregate data analysis also has a marked imbalance in the control group between the proportion of women who developed preeclampsia and were randomized before 16 weeks rather than after 16 weeks (17.9% and 8.4%, respectively).[17] The incidence of preeclampsia in our individual participant data analysis also reflects that trial participants were women at an increased risk of preeclampsia; in the control group, there was no difference in the risk of preeclampsia for women recruited

TABLE
Systematic reviews with subgroup meta-analysis based on gestational age at randomization before or after 16 weeks for outcome preeclampsia

Review	Type of analysis	Number of trials	Number of women	Results for outcome preeclampsia RR (95% CI)	Subgroup interaction test
PARIS data set	Individual participant data meta-analysis	<16 wks: 17 ≥16 wks: 22	<16 wks: 9241 ≥16 wks: 21,429	<16 wks: RR, 0.90 (0.79–1.03) ≥16 wks: RR, 0.90 (0.83–0.98)[a]	No significant difference (P = .98)[a]
Xu et al, 2015[44]	Aggregate data meta-analysis	≤16 wks: 7 >16 wks: 14	≤16 wks: 1165 >16 wks: 3241	≤16 wks: OR, 0.37 (0.27–0.50) >16 wks: OR, 0.77 (0.62–0.97)	No significant difference (P = .05)[a]
Roberge et al, 2013[17b]	Aggregate data meta-analysis	≤16 wks: 13 >16 wks: 20	≤16 wks: 1479 >16 wks: 10,673	≤16 wks: RR, 0.47 (0.36–0.62) >16 wks: RR, 0.78 (0.61–0.99)	Significant difference (P < .01)

[a] Statistically significant result for individual subgroups but no statistically significant difference between subgroups; [b] Earlier version of this meta-analysis was published by the same authors,[18] but data from the most up-to-date meta-analysis is presented here.

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before 16 weeks rather than after 16 weeks (8.8% and 8.7%, respectively). Using individual participant data therefore reduced the potential to be misled either by the play of chance or by bias.

As for all subgroup analyses, this analysis by gestation at randomization is an indirect comparison and so should be interpreted with caution, as an observational analysis. Women were not randomized to early or late administration of antiplatelet treatment in these trials. The best test of whether findings of a subgroup analysis reflect a true difference or, as here, no difference is by confirmation in subsequent randomized trials.[45] Nevertheless, the data presented here suggest that for aspirin and other antiplatelet agents, a randomized trial comparing the effects of starting treatment before or after 16 weeks may not be justified.

Subgroup analyses may be important to explore differential effects if they can be carefully justified. It is well known that aspirin may suppress aspects of endothelial dysfunction, but whether it also has an impact on placentation remains poorly understood.[46-49] If the mechanism of action of aspirin in the prevention of preeclampsia is indeed related to placentation, it is not clear why a specific cutoff of 16 weeks should be used.

Placentation in early pregnancy is not completely understood, but it is believed that the first wave of trophoblast invasion is already complete around 10 weeks, the second wave does not start until 14–15 weeks, and active endovascular trophoblast has been seen up to 22 weeks.[50,51] If aspirin reduces preeclampsia by its impact on endothelial dysfunction, this may explain why it is beneficial, even if given at later gestations.

Preterm birth prior to 34 weeks' gestation was used as an indicator for early-onset or preterm preeclampsia in the PARIS Collaborative study, and there was no significant difference in this outcome between the subgroups. We have not reported the impact of gestation at randomization on severe preeclampsia because sufficient data are not available.

An aggregate data meta-analysis suggests that early aspirin is associated with a significant reduction in the risk of severe preeclampsia.[17] These findings should be interpreted with caution because only a small proportion of eligible trials have reported the outcome severe preeclampsia[17]; therefore, findings are susceptible to reporting bias, and conclusions could potentially change significantly if all eligible studies had reported this outcome.

Searches to identify studies for the IPD meta-analysis were last updated in 2005. For the updated Cochrane Review,[2] 7 new studies have been identified, which randomized women at or before 16 weeks' gestation.[52-58] These 7 studies were all small (totaling 705 women), and several had an unclear risk of bias and so are unlikely to change the overall conclusions of our analyses based on individual participant data for more than 9000 women randomized before 16 weeks.

A sensitivity analysis including IPD data and aggregate data from studies published between 2005 and 2015 showed no significant difference in overall results whether antiplatelets were given before or after 16 weeks' gestation. However, the data should be interpreted with caution because the women randomized at 16 weeks in some aggregate data studies could not be accurately placed in the appropriate subgroup for analysis. Without obtaining IPD data from these studies, adding them to the IPD meta-analysis, is problematic and the findings are inconclusive.

Implications for clinical practice and research
Our analysis suggests that women at risk of preeclampsia should be offered antiplatelet therapy, usually low-dose aspirin, regardless of whether they

are first seen before or after 16 weeks. It is unclear whether there is a gestational age beyond which commencing aspirin therapy may not be beneficial. Trials have recruited women after 28 weeks, and our prespecified IPD subgroup meta-analysis based on various gestational age cutoffs at randomization (<16 weeks, 16—19 weeks, 20—23 weeks, 24—27 weeks, and ≥28 weeks) found similar risk ratios across all subgroups (Appendix Figure 1). Use before 12 weeks requires further evidence about safety,[59] but aspirin can be commenced from 12 weeks with a reasonable reassurance of safety. Studies randomizing to aspirin therapy before 12 weeks may be indicated, particularly if earlier prediction of preeclampsia improves.[60] Such studies should collect data on short- and long-term safety.

Conclusions

The effect of low-dose aspirin and other antiplatelet agents on preeclampsia and its complications is consistent, regardless of whether treatment is started before or after 16 weeks' gestation. Women at an increased risk of preeclampsia should be offered antiplatelet therapy, even if health professionals first see them after 16 weeks' gestation. ∎

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APPENDIX TABLE 1
Sensitivity analysis for outcome preeclampsia based on trials characteristics

Characteristics	RR (95% CI)	Subgroup interaction test
Relative risk of preeclampsia in main analysis	0.90 (0.84—0.97)	
PARIS definition of preeclampsia (SBP ≥140 mm Hg or DBP ≥90 mm Hg and trialist-defined proteinuria)	0.90 (0.83—0.97)	Sensitivity analysis only
Trialists' own definition of preeclampsia	0.88 (0.81—0.96)	
Placebo-controlled studies	0.90 (0.84—0.97)	$P = .52$
No placebo	0.71 (0.41—1.25)	
Aspirin dose ≤75 mg	0.92 (0.85—0.99)	$P = .23$
Aspirin dose >75 mg	0.77 (0.61—0.97)	

CI, confidence interval; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure; *PARIS*, Perinatal Antiplatelet Review of International Studies; *RR*, relative risk.

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APPENDIX TABLE 2
Sensitivity analysis: IPD data meta-analysis combined with aggregate data from studies published between 2005 and 2015

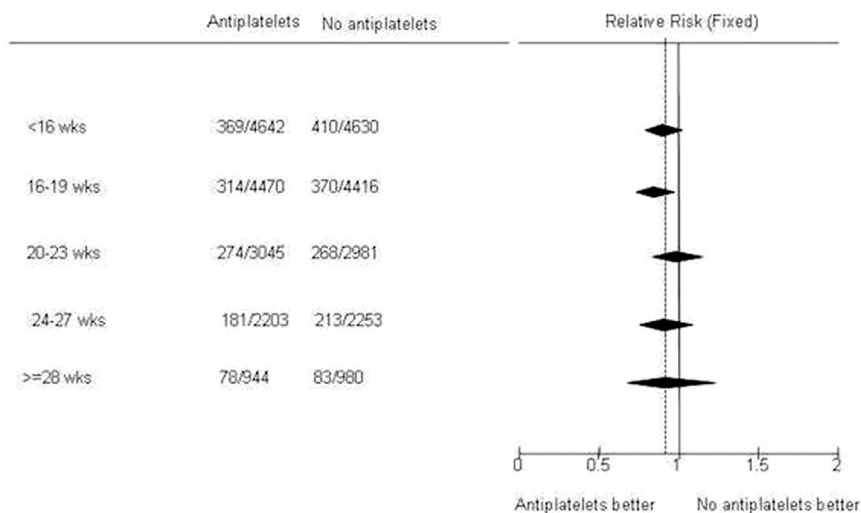| Outcome	Gestation at randomization <16 wks RR (95% CI)	Gestation at randomization >16 wks RR (95% CI)	Subgroup interaction test
Preeclampsia	RR 0.78 (0.63 to 0.97)	RR 0.88 (0.78 to 0.99)	$P = .36$
Death of baby	RR 0.81 (0.67 to 0.98)	RR 0.92 (0.79 to 1.07)	$P = .31$
Preterm birth <34 wks	RR 0.84 (0.73 to 0.97)	RR 0.91 (0.82 to 1.00)	$P = .39$
SGA baby	RR 0.68 (0.50 to 0.92)	RR 0.95 (0.84 to 1.07)	$P = .05$

CI, confidence interval; *RR*, relative risk; *SGA*, small for gestational age.

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Preeclampsia: subgroups by gestational age at randomization

Pre eclampsia by gestational age at randomisation (5 categories)

[no. events / no. entered]

	Antiplatelets	No antiplatelets	Relative Risk (Fixed)
<16 wks	369/4642	410/4630	
16-19 wks	314/4470	370/4416	
20-23 wks	274/3045	268/2981	
24-27 wks	181/2203	213/2253	
>=28 wks	78/944	83/980	

Antiplatelets better   No antiplatelets better

Interaction Test: chi-square=1.77, df=4, p=0.779

GestAgeRand <16 wks   RR=0.90 (0.79-1.03), p=0.113; Heterogeneity: chi-square=19.91, df=14, p=0.133, I2=29.68

GestAgeRand 16-19 wks   RR=0.85 (0.73-0.97), p=0.020; Heterogeneity: chi-square=10.56, df=15, p=0.783, I2=0.00

GestAgeRand 20-23 wks   RR=0.99 (0.84-1.15), p=0.858; Heterogeneity: chi-square=11.53, df=15, p=0.714, I2=0.00

GestAgeRand 24-27 wks   RR=0.88 (0.74-1.06), p=0.192; Heterogeneity: chi-square=12.11, df=13, p=0.518, I2=0.00

GestAgeRand >=28 wks   RR=0.95 (0.71-1.27), p=0.730; Heterogeneity: chi-square=9.97, df=8, p=0.267, I2=19.73

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