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

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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

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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Received April 18, 2016; revised Oct. 2, 2016; accepted Oct. 11, 2016.

The authors report no conflict of interest.

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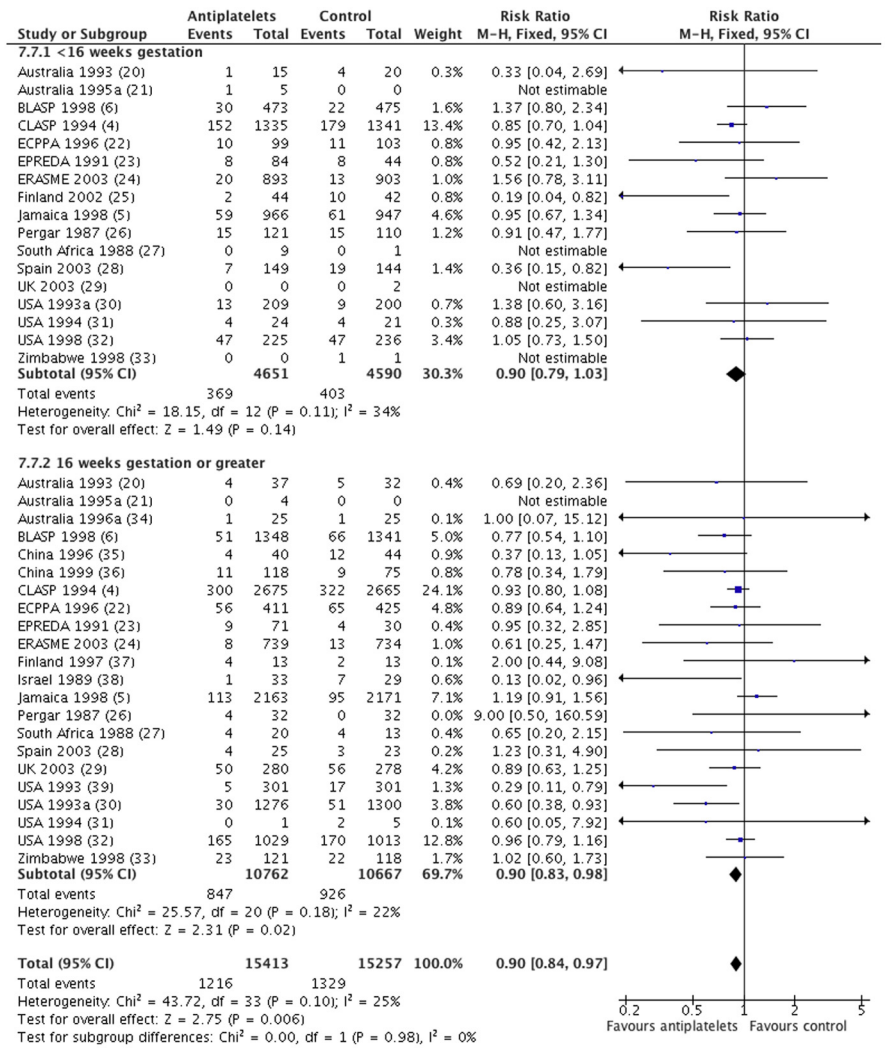
0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2016.10.016

Related editorial, page 95.

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



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.