Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis

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OBJECTIVE DATA: Metaanalyses of randomized controlled trials have reported contradictory results about the effect of aspirin in the prevention of preeclampsia, both in terms of the gestational age at the onset of treatment and the dose of the drug. The controversy may be resolved by a metaanalysis that includes several recently published trials and particularly the large Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-based Preeclampsia Prevention trial and by examination of whether there is a difference of the effect of aspirin on preterm vs term preeclampsia.

STUDY: We performed a systematic review and metaanalysis that evaluated the prophylactic effect of aspirin during pregnancy.

STUDY APPRAISAL AND SYNTHESIS METHODS: We completed a literature search through PubMed, Cinhal, Embase, Web of Science, and Cochrane library from 1985 to June 2017. Relative risks with random effect were calculated with their 95% confidence intervals.

RESULTS: Sixteen trials that included 18,907 participants provided data for preterm and term preeclampsia. Eight of the included studies were evaluated as being of good quality, and the other 8 studies were deemed to be of poor or uncertain quality. There was high heterogeneity within studies (I^2 >50%) for preterm and term preeclampsia, but no heterogeneity was found in the subgroup of preterm preeclampsia when the onset of treatment was ≤16 weeks of gestation and the daily dose of aspirin was ≥100 mg (I^2=0%). Administration of aspirin was associated with reduction in the risk of preterm preeclampsia (relative risk, 0.62; 95% confidence interval, 0.45–0.87), but there was no significant effect on term preeclampsia (relative risk, 0.92; 95% confidence interval, 0.70–1.21). The reduction in preterm preeclampsia was confined to the subgroup in which aspirin was initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg (relative risk, 0.33; 95% confidence interval, 0.19–0.57). This effect was also observed in the high-quality studies. The reduction in preterm preeclampsia that was observed in the largest trial (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-based Preeclampsia Prevention; n=1620; relative risk, 0.38; 95% confidence interval, 0.20–0.72) was similar to that in the 5 smaller trials in which aspirin was initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg (n=639; relative risk, 0.22; 95% confidence interval, 0.07–0.66).

CONCLUSION: Aspirin reduces the risk of preterm preeclampsia, but not term preeclampsia, and only when it is initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg.

Key words: aspirin, metaanalysis, preeclampsia

Preeclampsia is a major cause of maternal and fetal morbidity and death.[1] The adverse consequences of preeclampsia are particularly evident if it is associated with preterm birth. Several randomized studies investigated the possibility of preventing preeclampsia by the prophylactic use of aspirin, with contradictory results.[2,3]

A metaanalysis of individual-participant data reported that the effect of aspirin in the reduction of preeclampsia was 10%; this was not affected by the gestational age at the onset of therapy or the dose of aspirin.[3] In contrast, other metaanalyses reported that aspirin may confer greater benefit if it is started at ≤16 weeks of gestation rather than >16 weeks of gestation, the daily dose is ≥100 mg rather than <100 mg, and prevention is confined to preterm preeclampsia rather than total preeclampsia.[4-6] However, these metaanalyses included a small number of studies with important heterogeneity between them.[4-6] Some of these issues have now been overcome by the recent publication of a larger number of trials and particularly the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial with 1620 participants.[7]

The objective of this systematic review and metaanalysis was to examine the effect of aspirin in the prevention of preterm and term preeclampsia in relation to gestational age at onset of treatment and the dose of aspirin.

Methods

This is a systematic review and metaanalysis of randomized controlled trials that evaluated the prophylactic use of aspirin for the prevention of preeclampsia. The inclusion criteria were trials in which (1) 1 group received any

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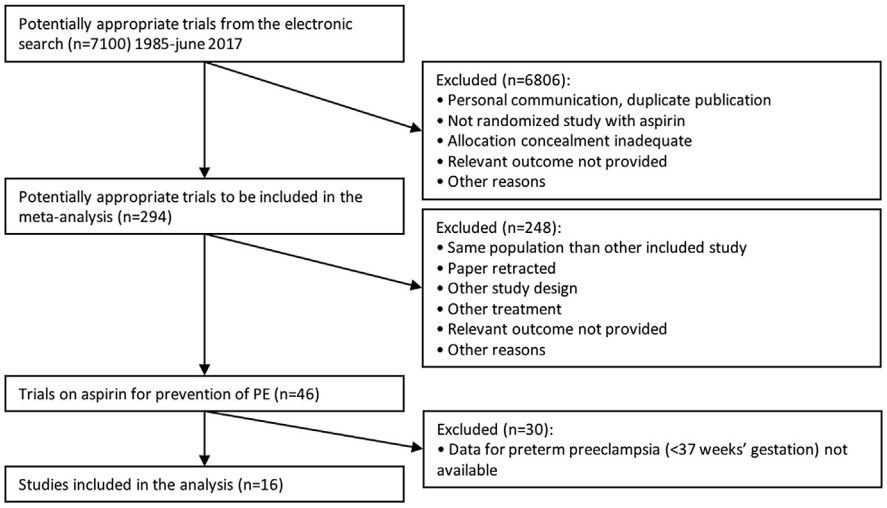
FIGURE 1
Selection of the articles



Selection tree for the selection of included articles.

PE, preeclampsia.

Roberge. Aspirin for prevention of preterm preeclampsia. Am J Obstet Gynecol 2018.

dose of aspirin either alone or in combination with dipyridamole and the other group received placebo or no treatment and (2) data on the prevalence of both preterm and term preeclampsia were provided in the publication or were provided by the authors. Protocol was registered in PROSPERO (#71275).

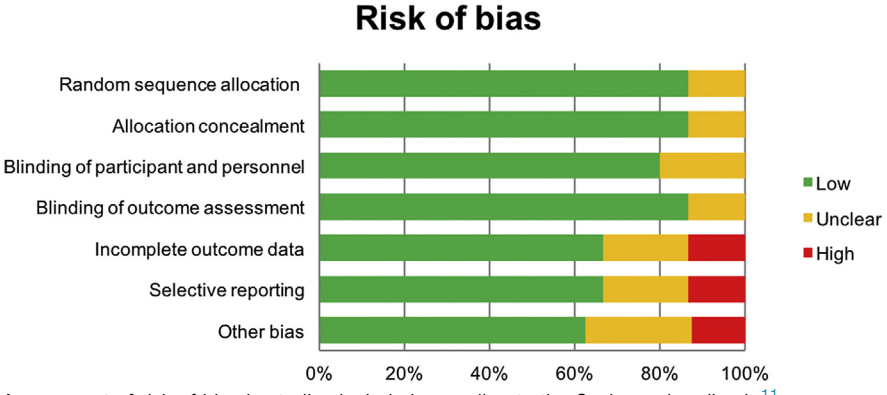
Research strategy

MeSH terms and keywords related to aspirin and preeclampsia were searched through PubMed, Embase, Cinahl, Web of science, and the Cochrane CENTRAL library from 1985, when the first trial was published,[8] to June 2017 and from references of other systematic reviews. No language restrictions applied.

Selection of the articles

All citations were examined to identify potentially relevant studies; the abstracts of these studies were then revised by 2 independent reviewers (S.R. and E.B.) who selected eligible studies for full assessment of the complete article. Any disagreements were resolved by discussion and the opinion of a third party (K.N.). For articles with incomplete data, the corresponding author was contacted for additional information.

FIGURE 2
Quality of the studies



Assessment of risk of bias in studies included according to the Cochrane handbook.[11]

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Outcome measures

The primary outcome measure for this analysis was preterm preeclampsia with delivery at <37 weeks of gestation; the secondary outcome was term preeclampsia with delivery at ≥37 weeks of gestation. Preplanned subgroup analyses were examination of the effect of aspirin on preeclampsia, depending on gestational age at onset of therapy (≤16 and >16 weeks of gestation) and daily dose of the drug (<100 and ≥100 mg), both in the whole population and in the subgroup of trials considered to be of high quality. The diagnosis of preeclampsia was based on the development of hypertension (blood pressure, ≥140/90 mm Hg) after 20 weeks of gestation in combination of proteinuria (urinary excretion, ≥300 mg protein in a 24-hour urine specimen or ≥1+ protein on dipstick) or the equivalent of this.[9]

Quality evaluation

The preferred reporting items for systematic review and meta-analysis (PRISMA) tool was used to assess the quality of the included trials; the Cochrane Handbook criteria were used to assess the risk of bias.[10,11]

Analyses

Relative risks (RR) were calculated with their 95% confidence intervals (CI) with the use of random effects.[12] As standard practice, to maximize the number of studies, trials with zero total events were included when we calculated pooled estimates.[13]

Assessment for publication bias was by funnel plots and heterogeneity with Higgins's I^2; the latter was high if ≥50%.[14,15] Analyses were carried out with Review Manager software (version 5.3; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark).

Results

The literature search identified 7100 citations, 294 of which were selected for

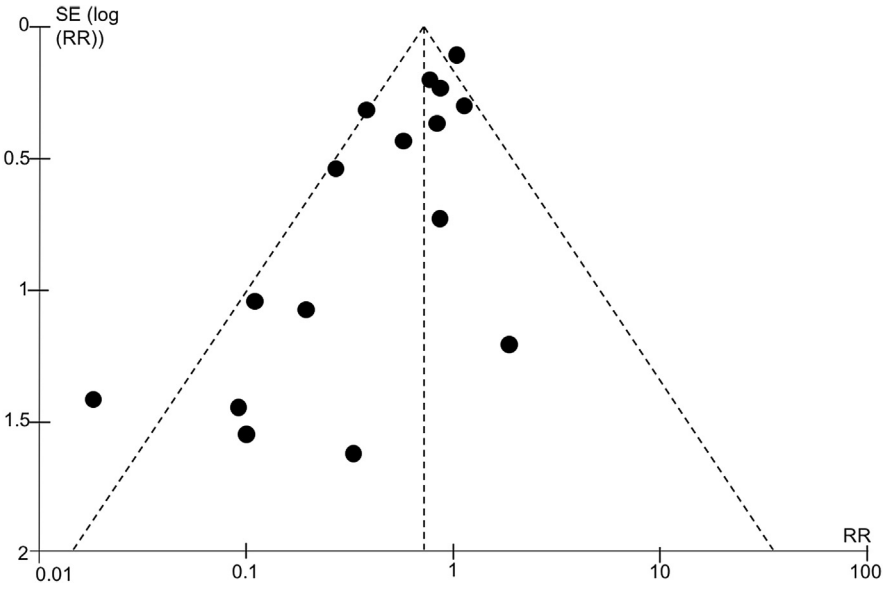
further evaluation (Figure 1). There were 46 trials that investigated the effect of aspirin on preeclampsia. The inclusion criteria were met in 16 studies for a total of 18,907 participants.[7,16-30] Thirty of the studies were excluded because data for preterm preeclampsia were not provided by the authors. Details of individual studies are given in the Appendix. The quality of the included studies is shown in Figure 2; 8 studies were evaluated as being of good quality,[7,17-23] and the other 8 studies were considered to be of poor or uncertain quality.[16,24-30] There was high heterogeneity within studies (I^2 >50%) for preterm and term preeclampsia, but no heterogeneity was found in the subgroup of preterm preeclampsia when the onset of treatment was ≤16 weeks of gestation and the daily dose of aspirin was ≥100 mg (I^2=0%). Publication bias cannot be excluded based on the analysis of the funnel plot (Figure 3).

Administration of aspirin was associated with reduction in the risk of preterm preeclampsia (RR, 0.62; 95% CI, 0.45−0.87), but there was no significant effect on term preeclampsia (RR, 0.92; 95% CI, 0.70−1.21; Table 1, Figure 4). The reduction in preterm preeclampsia was confined to the subgroup in which aspirin was initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg (Table 2, Figure 4). There was no significant reduction in risk of preterm preeclampsia in the subgroup in which aspirin was initiated at ≤16 weeks of gestation and at a daily dose of <100 mg (RR, 0.59; 95% CI, 0.29−1.19) or in the subgroup in which aspirin was initiated at >16 weeks of gestation, irrespective of whether the dose was ≥100 mg (RR, 0.88; 95% CI, 0.54−1.43) or <100 mg (RR, 1.00; 95% CI, 0.80−1.25).

Subgroup analysis of good-quality studies showed that the overall results were similar to those obtained from all studies: the risk of preterm preeclampsia was reduced only when aspirin was started at ≤16 weeks of gestation at a daily dose of ≥100 mg (RR, 0.38; 95% CI, 0.20−0.72; *P*=.003; Table 2).

The reduction in preterm preeclampsia that was observed in the largest trial (ASPRE; n=1620; RR, 0.38; 95% CI, 0.20−0.72) was similar to that in the 5 smaller trials in which aspirin was initiated at ≤16 weeks of gestation and at a daily dose of ≥100 mg (n=639; RR, 0.22; 95% CI, 0.07−0.66).

FIGURE 3
Funnel plot on aspirin for the prevention of preterm preeclampsia



Funnel plot of distribution of relative risk for preterm preeclampsia associated with aspirin treatment for studies included in our analysis.

RR, risk ratio; *SE*, standard error.

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Comment

Principal findings of this study

The results of this metaanalysis demonstrate that the administration of aspirin in women who are at high-risk of the development of preeclampsia is associated with a significant reduction in the risk of preterm preeclampsia, but not term preeclampsia. This beneficial effect of aspirin in reducing the risk of preterm preeclampsia is observed only if the onset of aspirin is at ≤16 weeks of gestation at the daily dose is ≥100 mg.

The finding of the differential effect of aspirin on preterm preeclampsia compared with term preeclampsia is consistent with our previous metaanalysis that included only 5 trials.[5] In the current metaanalysis, there are >3 times as many studies, including 5 large trials.[7,17,18,21,22]

There are 2 possibilities for the apparent effect of aspirin in the reduction of the risk of preterm preeclampsia, but not term preeclampsia. First, the pathophysiologic effect of

TABLE 1
Risk of preterm and term preeclampsia

Preeclampsia	Trials, n	Participants, n	Random effect, relative risk (95% confidence interval)	*P* value	I^2, %
Preterm (<37 wk)	16	18,907	0.62 (0.45-0.87)	.006	57
Term (≥37 wk)	16	18,907	0.92 (0.70-1.21)	.57	68

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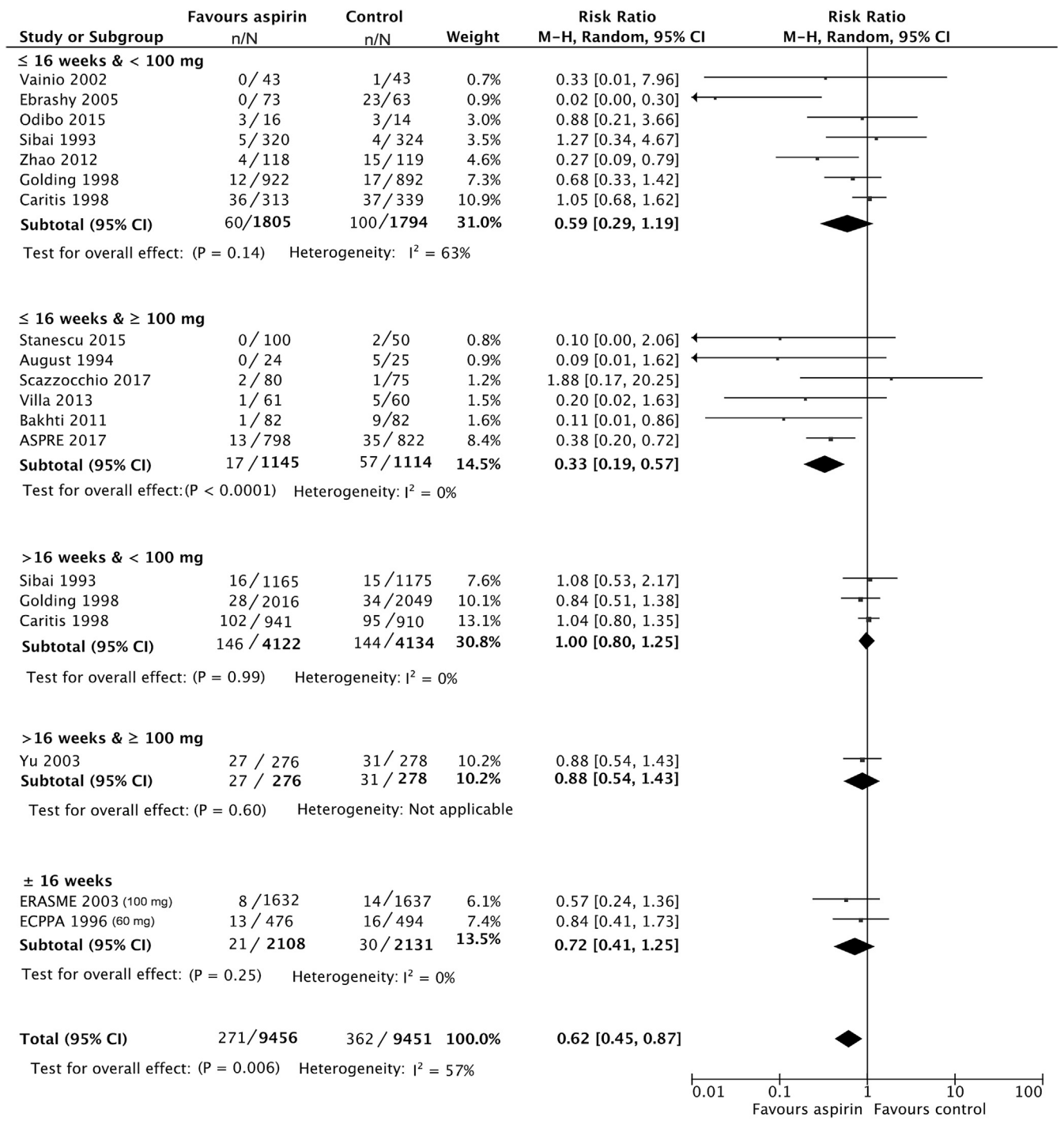
FIGURE 4
Forest plot on aspirin for the prevention of preterm preeclampsia



Forest plot of effect of low-dose aspirin on risk of preterm preeclampsia, subgrouped by gestational age at initiation of treatment and dose of treatment.

CI, confidence interval; *M-H*, Mantel-Haenszel.

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the 2 conditions is different, and aspirin affects only the cases of preterm preeclampsia. Second, aspirin reduces the risk of both preterm preeclampsia and term preeclampsia, and its effect is to shift the gestational age at delivery with preeclampsia to the right so that the cases of term preeclampsia that are prevented are replaced by cases of preterm preeclampsia.

Limitations of the study

Our metaanalysis included only 16 of the 46 trials that examined the effect of aspirin on preeclampsia because most of the studies did no report separately the risk of preterm and term preeclampsia and because most authors either did not respond to our request for additional data or did not have the data anymore. Therefore, we were not able to exclude the possibility of publication bias. However, our results are strengthened by the high homogeneity between studies after stratification according to gestational age at onset of therapy and dosage of aspirin. Moreover, our findings on the effectiveness of aspirin in reducing the risk of preterm preeclampsia if the onset of treatment is at ≤16 weeks of gestation and the daily dose is ≥100 mg were similar in high-quality trials to the overall results.

Subgroup metaanalyses have been criticized because (1) these were often not prespecified in the original trials and (2) the trials did not have sufficient power for such analyses.[31] Despite these criticisms, subgroup analyses are necessary to explain the heterogeneity between studies and to compare the results of different studies more appropriately.[32] One of the major limitations of previous metaanalyses on the use of aspirin for the prevention of preeclampsia was the lack of large trials in which treatment was initiated at ≤16 weeks of gestation and at a dose of ≥100 mg/day. This problem has now been overcome by the publication of the ASPRE trial, which randomly assigned 1620 participants to receive aspirin (150 mg/d) vs placebo from 11−14 until 36 weeks of gestation.[7] Our finding of complete homogeneity between the trials (I^2=0%) and the consistency of results in the ASPRE trial to that in the smaller trials are reassuring.[7]

In the ASPRE trial,[7] the beneficial effect of aspirin in the prevention of preterm preeclampsia was related to compliance.[33] In our metaanalysis, we could not properly evaluate the effect of compliance, because this was reported in only one-half of the included studies (Appendix).

Comparison with previous metaanalyses on the use of aspirin for prevention of preeclampsia

In 2007, Askie et al[34] published the results of an individual patient data metaanalysis of 31 trials and reported that aspirin use was associated with a 10% reduction in risk of total preeclampsia. A recent metaanalysis of the same data reported that the effect of aspirin was not related to either the gestational age at the onset of therapy (<16 vs ≥16 weeks of gestation) or dose of the drug (≤75 vs >75 mg daily).[3] However, in contrast to our study, these metaanalyses[3,34] (1) did not include several new studies that recruited patients at <16 weeks of gestation with a daily dose of aspirin >75 mg,[7,19,25,28-30,35] (2) reported that the daily dose of aspirin at <16 weeks of gestation was only 60 mg in the majority of their included studies, and (3) did not report results separately for preterm and term preeclampsia.

TABLE 2
Risk of preterm preeclampsia detailed by onset of treatment and dose of aspirin in all studies and in the high-quality studies

Onset/dose	Trials	Participants	Random effect, relative risk (95% confidence interval)	*P* value	I^2, %
All studies					
≤16 Wk	13	5858	0.45 (0.26−0.79)	.005[a]	58
<100 mg	7	3599	0.59 (0.29−1.19)	.14	63
≥100 mg	6	2259	0.33 (0.19−0.57)	.0001[a]	0
>16 Wk	4	8810	0.98 (0.80−1.19)	.82	0
<100 mg	3	8256	1.00 (0.80−1.25)	.99	0
≥100 mg	1	554	0.88 (0.54−1.43)	.60	—
High-quality studies					
≤16 Wk	5	3239	0.53 (0.26−1.08)	.08	64
<100 mg	4	1619	0.71 (0.32−1.57)	.40	51
≥100 mg	1	1620	0.38 (0.20−0.72)	.003[a]	—
>16 Wk	3	4745	1.01 (0.81−1.26)	.95	0
<100 mg	2	4191	1.04 (0.81−1.34)	.74	0
≥100 mg	1	554	0.88 (0.54−1.43)	.60	—

[a] Significant at a probability value of <.05.

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Clinical implications of the study

Professional bodies recommend the use of aspirin at a dose of 75−80 mg/day for the prevention of preeclampsia.[36,37] The results of our metaanalysis suggest that the recommendation should be updated to emphasize that the onset of treatment should be at ≤16 weeks of gestation, that the dose of aspirin should be ≥100 mg/day, and that the outcome measure should be preterm preeclampsia.

Prophylactic aspirin should be given to women who are identified by screening as being at high risk of the development of preeclampsia, rather than to the whole population.[38] The current study did not address the issue of how to select the

women who would benefit from the prophylactic use of aspirin. The traditional approach has been to define the high-risk group based on factors in maternal characteristics and medical history.[36,37] However, recent evidence suggests that the most effective way of to identify the high-risk group is by a combination of maternal factors with biophysical and biochemical markers,[39,40] as was used in the ASPRE trial.[7] Large screening studies demonstrated that the use of the approaches advocated by the National Institute for Health and Clinical Excellence[36] and American College of Obstetricians and Gynecologists[37] would identify only approximately 40% and 5%, respectively, of women who would experience preterm preeclampsia, compared with 75% by the method of combined screening at 11−13 weeks of gestation.[40,41]

Conclusion

The administration of aspirin starting at ≤16 weeks of gestation and at a dose of ≥100 mg/day reduces the risk of preterm preeclampsia by approximately 70%. ■

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APPENDIX
Characteristics of included studies

Study	N	Inclusion criteria	Compliance[a]	Intervention		
				Aspirin	Controls	Onset, wk
Vainio et al, 2002	86	Abnormal uterine artery Doppler scan and history risk factors[b]	N/A	0.5 mg/kg	Placebo	12–14
Caritis et al, 1998[c]	652	History risk factor[b]	79%>80%	60 mg	Placebo	13–26
Sibai et al, 1993[c]	644	Nulliparity	73%>80%	60 mg	Placebo	13–25
Golding[c]	5875	Nulliparity	66% Known compliers	60 mg	Placebo	12–32
Ebrashy et al, 2005[c]	136	Abnormal uterine artery Doppler scan plus history risk factors[b]	N/A	75 mg	No treatment	14–16
Zhao et al, 2012	237	History risk factor[b]	N/A	75 mg	Placebo	13–16
Odibo et al, 2015	30	History risk factor[b]	N/A	80 mg	Placebo	11–13
August et al, 1994	54	History risk factors[b]	N/A	100 mg	Placebo	13–15
Bakhti and Vaiman, 2011	84	Nulliparity	N/A	100 mg	No treatment	8–10
Villa et al, 2013[c]	121	Abnormal uterine artery Doppler scan and history risk factors[b]	9% Excluded for noncompliance	100 mg	Placebo	13–14
Scazzocchio et al, 2017[c]	155	Abnormal uterine artery Doppler scan	100%>90%	150 mg	Placebo	11–14
ASPRE 2017	1620	High risk based on FMF screening	80%>90%	150 mg	Placebo	11–14
ECPPA 1996	606	History risk factors[b]	88% took 75%	60 mg	Placebo	12–32
ERASME 2003	3269	Nulliparity	Compliance level of 80%	100 mg	Placebo	13–23
Stanescu et al, 2015[c]	150	High risk based on FMF screening	N/A	150 mg	Placebo	11–14
Yu et al, 2003[c]	554	Abnormal uterine artery Doppler scan	N/A	150 mg	Placebo	22–24

FMF, Fetal Medicine Foundation; *N/A*, not available.

[a] Reported as percentage of women who taken percentage of pills; [b] Includes history of chronic hypertension, cardiovascular or endocrine disease, previous pregnancy hypertension, or fetal growth restriction; [c] Studies in which the authors provided additional information that was not included in the publication.

Roberge. Aspirin for prevention of preterm preeclampsia. Am J Obstet Gynecol 2018.