# 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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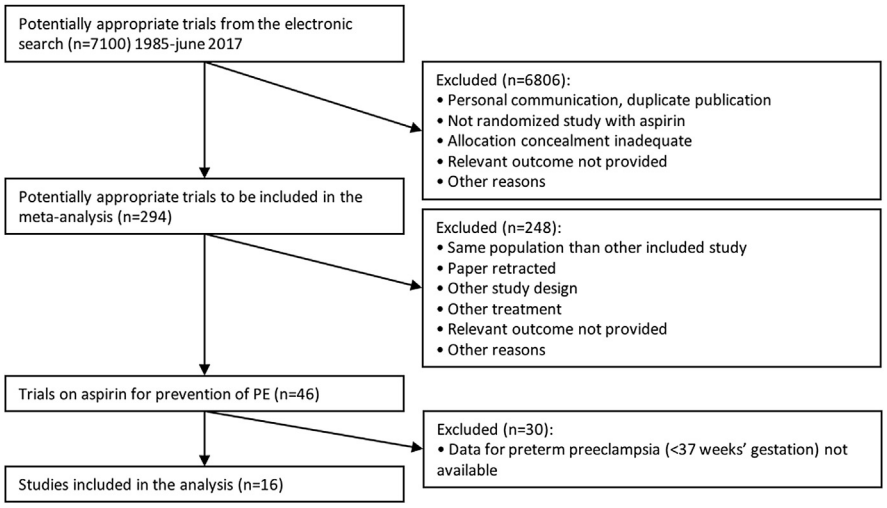
**FIGURE 1**
**Selection of the articles**




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).

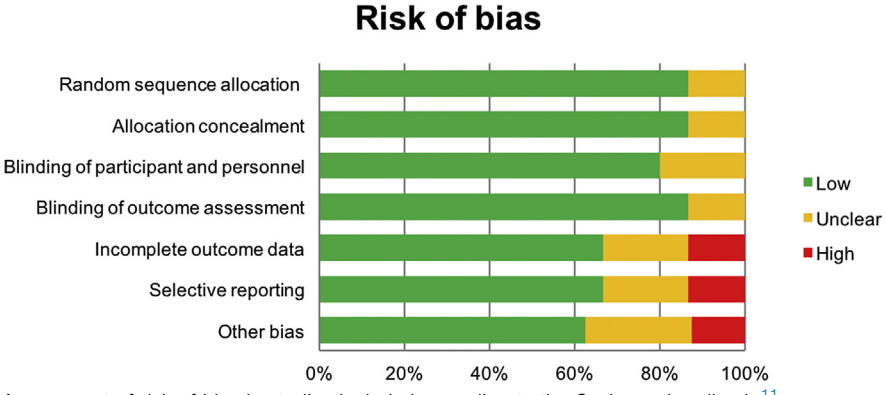
### Research strategy

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