# The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis

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**BACKGROUND:** Preeclampsia and fetal growth restriction are major causes of perinatal death and handicap in survivors. Randomized clinical trials have reported that the risk of preeclampsia, severe preeclampsia, and fetal growth restriction can be reduced by the prophylactic use of aspirin in high-risk women, but the appropriate dose of the drug to achieve this objective is not certain.

**OBJECTIVE:** We sought to estimate the impact of aspirin dosage on the prevention of preeclampsia, severe preeclampsia, and fetal growth restriction.

**STUDY DESIGN:** We performed a systematic review and meta-analysis of randomized controlled trials comparing the effect of daily aspirin or placebo (or no treatment) during pregnancy. We searched MEDLINE, Embase, Web of Science, and Cochrane Central Register of Controlled Trials up to December 2015, and study bibliographies were reviewed. Authors were contacted to obtain additional data when needed. Relative risks for preeclampsia, severe preeclampsia, and fetal growth restriction were calculated with 95% confidence intervals using random-effect models. Dose-response effect was evaluated using meta-regression and reported as adjusted $R^2$. Analyses were stratified according to gestational age at initiation of aspirin ($\leq$16 and $>$16 weeks) and repeated after exclusion of studies at high risk of biases.

**RESULTS:** In all, 45 randomized controlled trials included a total of 20,909 pregnant women randomized to between 50-150 mg of aspirin daily. When aspirin was initiated at $\leq$16 weeks, there was a significant reduction and a dose-response effect for the prevention of preeclampsia (relative risk, 0.57; 95% confidence interval, 0.43—0.75; $P < .001$; $R^2$, 44%; $P = .036$), severe preeclampsia (relative risk, 0.47; 95% confidence interval, 0.26—0.83; $P = .009$; $R^2$, 100%; $P = .008$), and fetal growth restriction (relative risk, 0.56; 95% confidence interval, 0.44—0.70; $P < .001$; $R^2$, 100%; $P = .044$) with higher dosages of aspirin being associated with greater reduction of the 3 outcomes. Similar results were observed after the exclusion of studies at high risk of biases. When aspirin was initiated at $>$16 weeks, there was a smaller reduction of preeclampsia (relative risk, 0.81; 95% confidence interval, 0.66—0.99; $P = .04$) without relationship with aspirin dosage ($R^2$, 0%; $P = .941$). Aspirin initiated at $>$16 weeks was not associated with a risk reduction or a dose-response effect for severe preeclampsia (relative risk, 0.85; 95% confidence interval, 0.64—1.14; $P = .28$; $R^2$, 0%; $P = .838$) and fetal growth restriction (relative risk, 0.95; 95% confidence interval, 0.86—1.05; $P = .34$; $R^2$, not available; $P = .563$).

**CONCLUSION:** Prevention of preeclampsia and fetal growth restriction using aspirin in early pregnancy is associated with a dose-response effect. Low-dose aspirin initiated at $>$16 weeks' gestation has a modest or no impact on the risk of preeclampsia, severe preeclampsia, and fetal growth restriction. Women at high risk for those outcomes should be identified in early pregnancy.

**Key words:** aspirin, fetal growth restriction, meta-analysis, meta-regression, preeclampsia, pregnancy, systematic review

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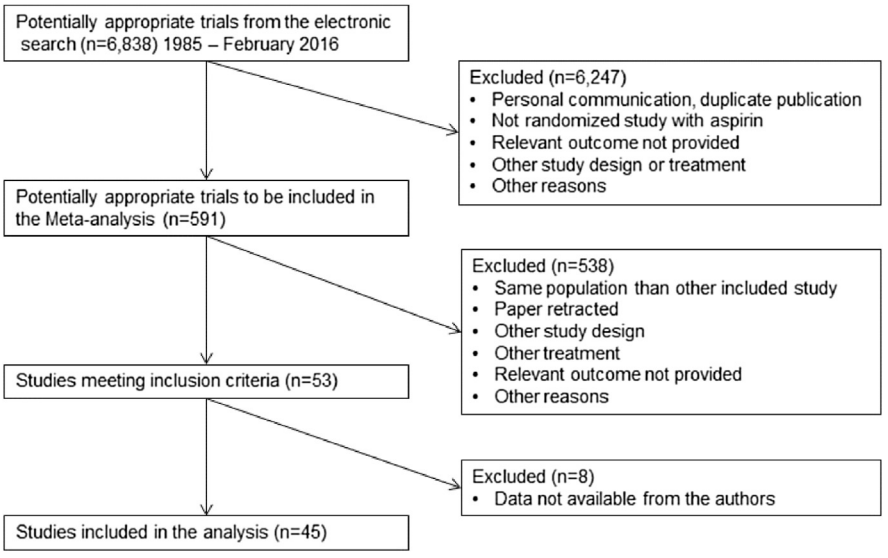
## Introduction

Preeclampsia (PE) and fetal growth restriction (FGR) are important causes of perinatal death and handicap in survivors. PE is responsible for >70,000 maternal deaths each year around the world.[1] Additionally, PE is associated with increased long-term risk for development of cardiovascular disease in both the mother and her infant.[2-4]

Several studies examined the possibility that prophylactic use of low-dose aspirin in women at high risk of developing PE could reduce the prevalence of the disease. Meta-analyses of randomized controlled trials (RCTs) of aspirin vs placebo or no treatment showed that the prevalence of PE and FGR can be reduced by aspirin started at ≤16 weeks' gestation and the effect is most marked for severe PE leading to delivery at <34 weeks' gestation; aspirin started at >16 weeks had no significant effect on the prevalence of severe PE or FGR.[5,6]

**FIGURE 1**
**Study selection process**




Selection tree for selection of included articles.

*Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.*

**TABLE 1**
**Characteristics of included studies according to gestational age at initiation of intervention**

| Study | N | Inclusion criteria | Intervention | | |
|---|---|---|---|---|---|
| ≤16 wk | | | Aspirin | Controls | Onset, wk |
| Tulppala et al,[63] 1997 | 66 | Previous consecutive miscarriage | 50 mg | Placebo | <7 |
| Benigni et al,[32] 1989 | 33 | History risk factors[a] | 60 mg | Placebo | 12 |
| [b]Caritis et al,[34] 1998 | 652 | History risk factor[a] | 60 mg | Placebo | 13–16 |
| [b]Sibai et al,[60] 1993 | 644 | Nulliparity | 60 mg | Placebo | 13–16 |
| [b]Golding,[41] 1998 | 1997 | Nulliparity | 60 mg | Placebo | 12–16 |
| [b]Ebrashy et al,[38] 2005 | 136 | Abnormal uterine artery Doppler plus history risk factors[a] | 75 mg | No treatment | 14–16 |
| Zhao et al,[69] 2012 | 237 | History risk factor[a] | 75 mg | Placebo | 13–16 |
| Odibo et al,[54] 2015 | 30 | History risk factor[a] | 80 mg | Placebo | 11–13 |
| Porreco et al,[56] 1993 | 90 | Nulliparity + multiple gestation | 80 mg | Placebo | <16 |
| Jamal et al,[46] 2012 | 70 | Diagnose PCOS before pregnancy, 18–40 y, singleton, no history of diabetes or HTN | 80 mg | No treatment | 6–12 |
| Mesdaghinia et al,[50] 2011 | 80 | Abnormal uterine artery Doppler | 80 mg | No treatment | 12–16 |
| August et al,[26] 1994 | 54 | History risk factors[a] | 100 mg | Placebo | 13–15 |
| Azar and Turpin,[28] 1990 | 91 | History risk factors[a] | 100 mg[c] | No treatment | 16 |
| Bakhti and Vaiman,[29] 2011 | 84 | Nulliparity | 100 mg | No treatment | 8–10 |
| Chiaffarino et al,[35] 2004 | 35 | Chronic HTN with or without history risk factors[a] | 100 mg | No treatment | <14 |
| Dasari et al,[36] 1998 | 50 | Nulliparity | 100 mg | Placebo | 12 |
| Hermida et al,[45] 1997 | 107 | History risk factors[a] | 100 mg | Placebo | 12–16 |

*Roberge. Aspirin's dose for prevention of preeclampsia. Am J Obstet Gynecol 2017.* *(continued)*