Annals of Internal Medicine | Review

Low-Dose Aspirin for Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Background: Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality.

Purpose: To systematically review benefits and harms of low-dose aspirin for preventing morbidity and mortality from preeclampsia.

Data Sources: MEDLINE, Database of Abstracts of Reviews of Effects, PubMed, and Cochrane Central Register of Controlled Trials (January 2006 to June 2013); previous systematic reviews, clinical trial registries, and surveillance searches for large studies (June 2013 to February 2014).

Study Selection: Randomized, controlled trials (RCTs) to assess benefits among women at high preeclampsia risk and RCTs or large cohort studies of harms among women at any risk level. English-language studies of fair or good quality were included.

Data Extraction: Dual quality assessment and abstraction of studies.

Data Synthesis: Two large, multisite RCTs and 13 smaller RCTs of high-risk women (8 good-quality) were included, in addition to 6 RCTs and 2 observational studies of average-risk women to assess harms (7 good-quality). Depending on baseline risk, aspirin use was associated with absolute risk reductions of 2% to 5% for preeclampsia (relative risk [RR], 0.76 [95% CI, 0.62 to 0.95]), 1% to 5% for intrauterine growth restriction (RR, 0.80 [CI, 0.65 to 0.99]), and 2% to 4% for preterm birth (RR, 0.86 [CI, 0.76 to 0.98]). No significant perinatal or maternal harms were identified, but rare harms could not be ruled out. Evidence on long-term outcomes was sparse, but 18-month follow-up from the largest trial found no developmental harms.

Limitations: Benefits may have been overestimated due to small-study effects. Predictive intervals were not statistically significant. Future studies could shift findings toward the null.

Conclusion: Daily low-dose aspirin beginning as early as the second trimester prevented clinically important health outcomes. No harms were identified, but long-term evidence was limited.

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Preeclampsia is a leading cause of maternal death, affecting 2% to 8% of pregnancies globally (1, 2). It affected 3.8% of U.S. deliveries in 2010, and the rate of severe preeclampsia has increased over the past 3 decades (3). Perinatal mortality is nearly 2 times higher in pregnancies affected by preeclampsia (4), with 12% of maternal deaths due to the condition (5). Serious illness is more common, with more than one third of serious maternal morbidity and 15% of preterm births related to preeclampsia (6, 7).

Preeclampsia is defined as hypertension (blood pressure ≥140/90 mm Hg) and proteinuria (presence of ≥0.3 g of protein in a 24-hour period) observed during the second half of pregnancy (>20 weeks of gestation) (8, 9). It is also classified as "having severe features" with any of the following: blood pressure above 160/110 mm Hg, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances (9). Preeclampsia with or without severe features can evolve rapidly into eclampsia or the hemolysis, elevated liver enzymes, and low platelets syndrome, sometimes leading to systemic complications and maternal death (10, 11). Poor perinatal health outcomes are associated with preeclampsia, primarily due to increased risk for intrauterine growth restriction (IUGR) or medically initiated preterm delivery. Once preeclampsia develops, the only effective treatment is delivery, with serious neonatal harms when remote from term (<34 weeks of gestation).

Current understanding of preeclampsia pathophysiology suggests that it may be a collection of syndromes with different precipitating factors and outcomes (12). Early in pregnancy, aberrations in placental development can result in placental ischemia and release of inflammatory and oxidative stress factors into the maternal bloodstream. In addition, even with normal placentation, preexisting hypertension, diabetes, and other inflammatory conditions (such as lupus) may activate systemic inflammatory and oxidative stress processes, as can twin or higher-order pregnancies. Accurate prediction of who will develop preeclampsia and have serious complications is not currently possible (13–15). The most consistent predictors of high risk are previous preeclampsia, certain medical conditions (diabetes, chronic hypertension, renal disease, autoimmune diseases, and the antiphospholipid syndrome), and multifetal preg-

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nancy (16). Moderately elevated risk for preeclampsia is associated with nulliparity (first birth), advanced maternal age (≥40 years), between-pregnancy interval of more than 10 years, high body mass index (≥35 kg/m^2), and family history of preeclampsia (mother or sister). Risk factors with less consistent evidence include changes in paternity between pregnancies, history of migraine headaches (17, 18), and asthma (17, 19–22). Predictive models combining various biomarkers, patient risk factors, and clinical readings hold promise but are not yet sufficiently validated for clinical use (10, 23–25).

Previous comprehensive systematic reviews have found antiplatelets (primarily low-dose aspirin) to be beneficial for the prevention of preeclampsia among women at heightened risk (26, 27). We conducted this systematic review to support the U.S. Preventive Services Task Force (USPSTF) in updating its 1996 recommendation, which is no longer active.

METHODS

Detailed methods are outlined in our full evidence report (28). This review addressed 3 key questions (**Appendix Figure 1**, available at www.annals.org). First, is low-dose aspirin effective for reducing adverse maternal and perinatal health outcomes among women at increased risk for preeclampsia? Second, is low-dose aspirin effective for preventing preeclampsia among women at increased risk for the condition? Third, are there harms to the woman and fetus associated with aspirin use during pregnancy?

Data Sources and Searches

In addition to considering all studies from the previous USPSTF review, we performed a comprehensive search of MEDLINE, PubMed, the Database of Abstracts of Reviews of Effects, and the Cochrane Central Register of Controlled Trials for studies published between January 2006 and 1 June 2013. We also examined the reference lists from existing systematic reviews to identify potentially eligible studies, including an individual-patient data (IPD) meta-analysis published by the Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration (27) and a 2007 Cochrane review (26). We searched ClinicalTrials.gov for ongoing trials (May 2013). Between the last search date and this publication, we actively monitored published literature for potentially important new trials or other large observational studies directly relevant to our key questions; none were identified.

Study Selection

Two investigators independently reviewed abstracts and full-text articles for inclusion according to predetermined criteria. We resolved discrepancies through consensus with a third investigator. To evaluate benefits of aspirin prophylaxis, we included any study that used a risk selection approach aimed at achieving a sample of women at high risk for preeclampsia. The trials could define risk on the basis of medical history, pregnancy characteristics, or clinical measurements known to be associated with risk for the condition. Although preeclampsia occurs more often in first births than in subsequent ones, prevalence rates are relatively low (approximately 4%) compared with other high-risk groups. Because aspirin treatment based only on this risk factor has not been supported, trials with nulliparity as the sole risk factor were not included for evaluation of benefits.

We used broader inclusion criteria to identify possible harms of aspirin exposure during pregnancy. The trials of women at high risk were combined with trials of women at low or average risk exposed to daily low-dose aspirin. Large prospective observational studies were also included to assess harms but were not included in pooled analyses.

We included interventions that compared patients receiving 50 to 150 mg of aspirin with a placebo or "no treatment" group and excluded studies of nonaspirin antiplatelet medications or aspirin combined with another active substance. We also excluded studies that we rated as poor-quality on the basis of the USPSTF quality rating standards (29) and studies not published in English.

Data Extraction and Quality Assessment

Two investigators critically appraised all included studies independently using the USPSTF's design-specific criteria (29), which we supplemented with the National Institute for Health and Care Excellence methodology checklists (30) and the Newcastle-Ottawa Scale (31). According to the USPSTF criteria, a good-quality study met all prespecified standards. A fair-quality study did not meet (or it was unclear whether it met) at least 1 criterion, but it also had no known limitation that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations that could seriously bias its results. Discrepancies were resolved through discussion of identified limitations and consultation with a third investigator, if necessary. One investigator extracted study details and results, and a second investigator reviewed the abstracted information.

Data Synthesis and Analysis

We used the metan procedure in Stata, version 11.2 (StataCorp, College Station, Texas), for all reported meta-analyses and the metaan procedure for sensitivity analyses (32). For dichotomous outcomes, we entered the number of events and nonevents and estimated pooled random-effects risk ratios by using the DerSimonian–Laird method for all outcomes, except those in which fewer than 10% of the participants had the event (33), for which we used a fixed-effects Mantel–Haenszel model (34). We also included prediction intervals in forest plots of random-effects models, which provided an estimate of where the effect size from 95% of newly conducted trials would fall, assuming that the between-study variability in the included trials held for new trials (35). The prediction intervals are shown on the forest plots by the horizontal lines that extend from

Table. **Pooled Effects for Perinatal Death and Placental Abruption in Studies of Women at High Preeclampsia Risk and at All Risk Levels Combined***

Outcome	High Preeclampsia Risk					All Preeclampsia Risk Levels Combined				
	RR (95% CI)	Trials, *n*	Participants, *n*	I^2, %	*P* Value	RR (95% CI)	Trials, *n*	Participants, *n*	I^2, %	*P* Value
Perinatal death†	0.81 (0.65–1.01)	10	12 240	0	0.78	0.92 (0.76–1.11)	14	22 848	0	0.65
Placental abruption‡	1.12 (0.86–1.46)	3	12 366	50.1	0.135	1.17 (0.93–1.48)	8	22 988	36.4	0.138

RR = relative risk.
* Estimated using fixed-effects models because of low event rates.
† In trials of women at high risk, the total number of events and event rate were 310 and 0.0248, respectively. In trials among women at all risk levels, the values were 412 and 0.0177, respectively.
‡ In trials of women at high risk, the total number of events and event rate were 214 and 0.0168, respectively. In trials among women at all risk levels, the values were 276 and 0.0118, respectively.

the diamond representing the 95% CI of the pooled estimate.

Potential sources of heterogeneity in effect size by aspirin timing, dosage, and preeclampsia risk determination were identified a priori and explored using meta regression and visual inspection of sorted forest plots. We used the I^2 and chi-square statistics to assess statistical heterogeneity. To evaluate small-study effects, we examined funnel plots and used the Begg or Peter test depending on the outcome distribution (36, 37). We used profile likelihood estimation to conduct sensitivity analyses for the pooled effects because the DerSimonian–Laird method can overestimate CI precision in meta-analysis, particularly when fewer than 10 studies or when smaller studies with few events are pooled (38).

Role of the Funding Source

This study was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Members of the USPSTF and the AHRQ medical officer assisted in the development of the review's scope. Approval from AHRQ was required before the manuscript could be submitted for publication, but the authors are solely responsible for its content and the decision to submit it for publication.

RESULTS

Our literature search yielded 544 unique citations. From these, we reviewed the full text of 75 articles. Twenty-three studies (27 articles) met our inclusion criteria (**Appendix Figure 2** and **Appendix Table 1**, available at www.annals.org).

We identified 15 randomized, controlled trials (RCTs) (8 good-quality) that met inclusion criteria for evaluation of maternal and perinatal health benefits from aspirin chemoprevention and 13 RCTs (8 good-quality) reporting preeclampsia incidence with and without low-dose aspirin among women at high risk. We identified 21 studies (14 good-quality) to evaluate maternal, perinatal, and developmental harms with antenatal aspirin use, including all 15 trials in women at high preeclampsia risk. Eighteen trials described adequate randomization, with 2 trials not clearly reporting appropriate allocation concealment (39, 40). All RCTs reported valid outcome measures, and all but 1 study reported using identical placebo formulations (41). Adherence to treatment was high, with 14 trials reporting adherence of approximately 80% or greater among participants. All but 11 studies reported attrition, which ranged from 3.3% to 20.4%. Eight studies reported no loss to follow-up.

Overall, women included in the trials were young (mean age ranged from 20 to 33 years) and predominantly white (assumed from trial country of origin and reported data), although 3 trials (42–44) reported majorities of black women in their samples. Only 9 of the 23 studies included in this review reported race or ethnicity (40, 42–49). **Appendix Table 2** (available at www.annals.org) provides study details.

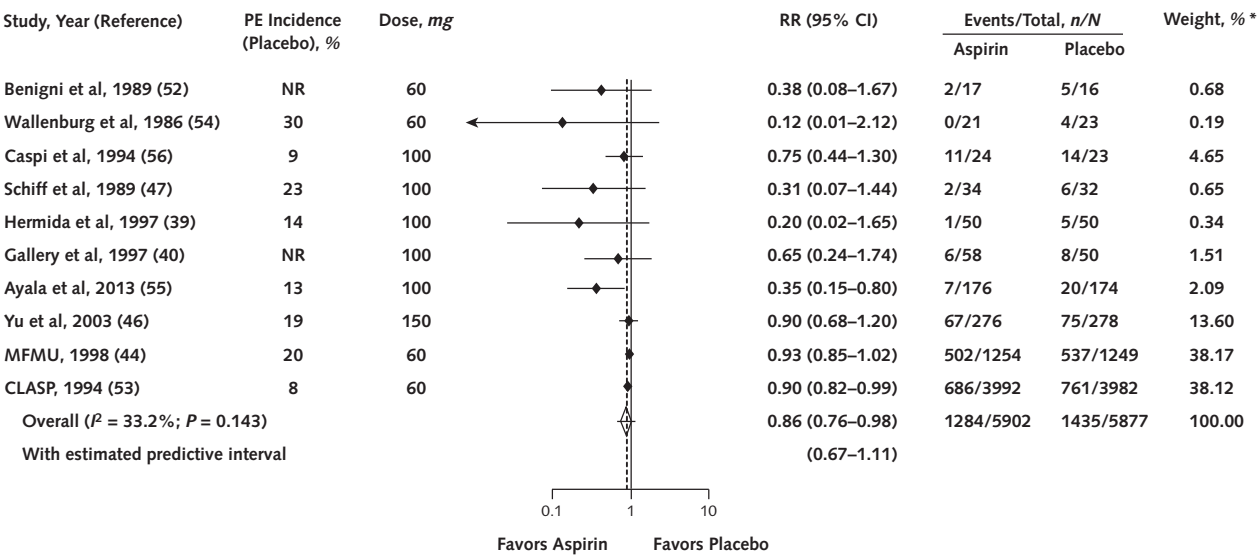
None of the trials initiated treatment before 12 weeks of gestation, and 9 trials initiated treatment before 16 weeks. Treatment was often continued until delivery, but 6 trials (40, 44, 46, 47, 50, 51) stopped treatment earlier. Daily aspirin doses ranged from 60 to 150 mg, with 1 trial reporting a dose of 0.5 mg/kg of body weight (41). Most trials used doses of 60 mg (6 trials [42–44, 52–54]) or 100 mg (9 trials [39, 40, 47, 50, 51, 55–57, 60]).

Benefits of Low-Dose Aspirin Treatment

For perinatal death, the fixed-effects pooled estimate from 10 trials in high-risk women (40, 44, 46, 49, 52–56, 58) (12 240 participants) suggested a possible reduced risk with low-dose aspirin use (relative risk [RR], 0.81 [95% CI, 0.65 to 1.01]; $I^2 = 0\%$), but the result was not statistically significant (**Table**). Three of the 4 trials with lower mortality in the placebo group had sample sizes of 100 or fewer per group (40, 54, 58). The fourth study was larger (554 participants), used a higher aspirin dose (150 mg), and enrolled women on the basis of abnormal readings on uterine artery ultrasonograms at 22 to 24 weeks of gestation (46); the total number of events was 11.

We found evidence of a risk reduction of 14% for preterm birth (<37 weeks of gestation) (RR, 0.86 [CI, 0.76 to 0.98]; $I^2 = 33.2\%$) in a meta-analysis of 10 trials with the outcome (11 779 participants) (**Figure 1**) (39, 40,

Figure 1. **Pooled analysis of preterm birth from trials of women at risk for preeclampsia, sorted by sample size.**



CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; MFMU = Maternal-Fetal Medicine Units; NR = not reported; PE = preeclampsia; RR = relative risk.
* From random-effects analysis.

44, 46, 47, 52–56, 58). There was evidence of a 20% reduction in IUGR (RR, 0.80 [CI, 0.65 to 0.99]; I^2 = 36.9%; 13 trials [39, 41, 44, 46, 47, 49, 50, 52–56, 58]; 12 504 participants) (**Figure 2**). Sensitivity analyses using the profile likelihood method did not change these estimates; however, the upper 95% confidence limits for both were close to the null and the predictive intervals suggested that future studies could shift pooled estimates toward nonsignificance. We also found evidence of small-study effects based on funnel plot asymmetry for preterm birth (Peter test P = 0.048) and IUGR (Peter test P = 0.018).

Consistent with reduced rates of preterm birth and IUGR, treatment was associated with an average birthweight increase of 130 g (CI, 36.22 to 223.33 g; I^2 = 60.0%; P = 0.010), with moderate heterogeneity among studies (data not shown). There also was a 24% reduction in preeclampsia (RR, 0.76 [CI, 0.62 to 0.95]) with aspirin treatment (13 trials; 12 184 participants) (**Figure 3**). Heterogeneity of preeclampsia incidence was moderate (I^2 = 40.5%; P = 0.064), and there was evidence of small-study effects (Peter test P = 0.028).

We did not find evidence in prespecified stratified comparisons that the timing of aspirin administration (<16 weeks) or the dosage had different effects. The estimated risk reduction was greater in studies using more than 75 mg of aspirin (RR, 0.58 [CI, 0.36 to 0.95]) than in those using less than 75 mg (RR, 0.85 [CI, 0.68 to 1.05]), but the difference in the effect size was not significant. Analysis of the effect of dosage also was confounded by unequal distribution of sample sizes in different dosage categories because both of the large studies used doses of 60 mg (44, 53).

Harms of Aspirin Treatment

We found no evidence of perinatal mortality harms from low-dose aspirin exposure during pregnancy, even with the addition of average-risk study populations to the fixed-effects model (RR, 0.92 [CI, 0.76 to 1.11]; I^2 = 0%; P = 0.65) (**Table** and **Appendix Figure 3**, available at www.annals.org). Eleven trials (23 332 participants) reported on placental abruption (6 in women at increased preeclampsia risk [39, 44, 46, 53, 56, 58] and 5 in women at low or average risk [42, 43, 48, 51, 59]) (**Appendix Figure 4**, available at www.annals.org). Results of fixed-effects meta-analysis suggested possible increases in abruption but were not statistically significant (RR, 1.17 [CI, 0.93 to 1.48]) (**Table**). Studies were somewhat heterogeneous (I^2 = 36.4%; P = 0.138). The pooled estimate of placental abruption from studies of women at elevated preeclampsia risk (RR, 1.12 [CI, 0.86 to 1.46]; I^2 = 50.1%; P = 0.135) was similar to the estimate among women at all risk levels. No significant harm of perinatal death or abruption was found, but low event rates and studies with no events could introduce bias when effects are pooled, thus increasing statistical uncertainty. For perinatal death, however, the nonsignificant estimates and direction of effect support no harm, and possibly a benefit, with low-dose aspirin prophylaxis.

Meta-analysis of 7 trials (outcome reported for 6 trials in women at high preeclampsia risk [39, 44, 46, 53–55] and 3 in women at low or average risk [43, 51, 59]; 22 616

total participants; 2 trials reported no events) indicated no treatment differences in rates of postpartum hemorrhage (RR, 1.02 [CI, 0.96 to 1.09]). We also found no evidence that low-dose aspirin affected mean blood loss; all 5 trials reporting the outcome (41, 43, 49, 52, 58) found either slightly lower mean blood loss or equivalent amounts between study groups. Of the 10 trials reporting on intracranial hemorrhage in neonates (39, 43, 44, 47, 49, 51–53, 59, 60), 4 reported no events in either study group (22 158 participants) (39, 47, 49, 52). All but 1 trial (44) reported more events in the placebo group. The fixed-effects pooled risk ratio was 0.84 (CI, 0.61 to 1.16), and heterogeneity was low ($I^2 = 27.1\%$; $P = 0.23$) (**Appendix Figure 5**, available at www.annals.org).

Two observational studies on aspirin use during pregnancy had null findings for the potentially harmful outcomes considered (miscarriage and cryptorchidism) (45, 61). Follow-up data from the large CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) trial reported no differences in developmental outcomes of the infants up to age 18 months and no treatment group differences in hospital visits, gross motor development, or height and weight (62). Seven trials reported adverse events during the trial (40, 41, 46, 47, 49, 50, 53). In most cases, single adverse events were concluded to be unrelated to treatment. Two studies reported women dropping out of treatment because of itching of the throat and epigastric pain (41, 46).

Sensitivity analyses using an alternate method for estimating the pooled random effects resulted in similar point estimates and CIs and did not change the statistical significance of our findings for any benefits or harms.

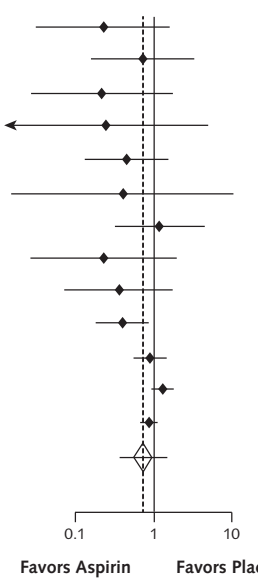
Discussion

Daily prophylaxis with low-dose aspirin beginning after the first trimester reduced risk for preterm birth by 14% and for IUGR by 20%. The risk reduction of 24% for preeclampsia among high-risk women supports the causal pathway for perinatal health benefits. Our confidence in the magnitude of the pooled result, however, is tempered by evidence of small-study effects and modest findings in the 2 largest trials. Risk reductions closer to 10% for preeclampsia, IUGR, and preterm birth represent a more conservative interpretation of the results.

Although aspirin use in pregnancy does not seem to increase perinatal mortality, whether it prevents this outcome is unclear. Given the rarity of the outcome and the limited number of high-risk women studied, available evidence cannot rule out the possibility of a 20% reduction in perinatal mortality.

Absolute risk reductions were calculated on the basis of event rates in the trial data at 25th- and 75th-percentile incidence levels for the outcome. These were 10% and 23% for preeclampsia, 7% and 24% for IUGR, and 11% and 31% for preterm birth. Treatment was associated with absolute risk reductions of 2% to 5% for preeclampsia, 1% to 5% for IUGR, and 2% to 4% for preterm birth. Although no short-term harms seem to be associated with

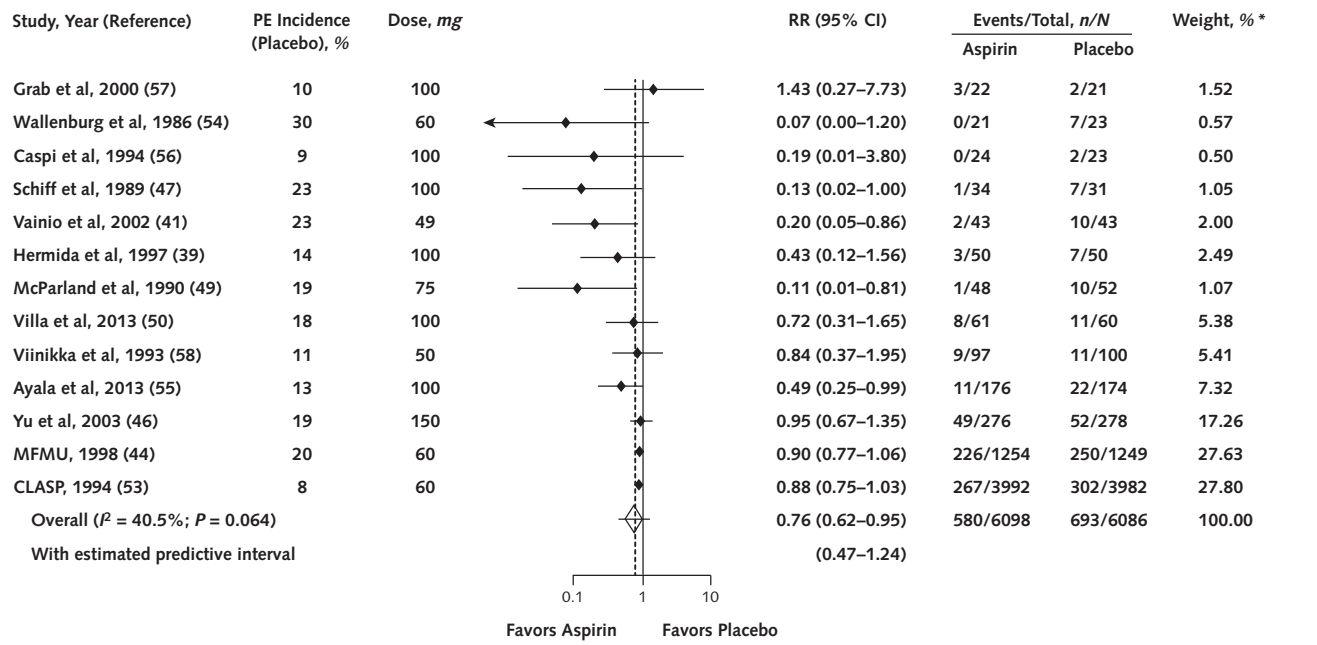
Figure 2. **Pooled analysis of intrauterine growth restriction from trials of women at risk for preeclampsia, sorted by sample size.**



Study, Year (Reference)	PE Incidence (Placebo), %	Dose, *mg*	RR (95% CI)	Events/Total, *n/N*		Weight, % *
				Aspirin	Placebo	
Benigni et al, 1989 (52)	NR	60	0.31 (0.07–1.33)	2/17	6/16	2.02
Wallenburg et al, 1986 (54)	30	60	0.73 (0.24–2.23)	4/21	6/23	3.24
Schiff et al, 1989 (47)	23	100	0.30 (0.07–1.40)	2/34	6/31	1.83
Vainio et al, 2002 (41)	23	49	0.33 (0.04–3.08)	1/43	3/43	0.89
Caspi et al, 1994 (56)	9	100	0.52 (0.21–1.30)	6/48	11/46	4.66
Hermida et al, 1997 (39)	14	100	0.50 (0.05–5.34)	1/50	2/50	0.79
McParland et al, 1990 (49)	19	75	1.08 (0.41–2.86)	7/48	7/52	4.15
Villa et al, 2013 (50)	18	100	0.33 (0.07–1.56)	2/61	6/60	1.75
Viinikka et al, 1993 (58)	11	50	0.46 (0.15–1.44)	4/97	9/100	3.11
Ayala et al, 2013 (55)	13	100	0.49 (0.28–0.87)	16/176	32/174	9.82
Yu et al, 2003 (46)	19	150	0.90 (0.67–1.22)	61/276	68/278	19.18
MFMU, 1998 (44)	20	60	1.19 (0.93–1.52)	129/1254	108/1249	22.26
CLASP, 1994 (53)	8	60	0.90 (0.76–1.06)	244/4123	272/4134	26.30
Overall ($I^2 = 36.9\%$; $P = 0.088$)			0.80 (0.65–0.99)	479/6248	536/6256	100.00
With estimated predictive interval			(0.49–1.31)			

CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; MFMU = Maternal-Fetal Medicine Units; NR = not reported; PE = preeclampsia; RR = relative risk.
* From random-effects analysis.

Figure 3. **Pooled analysis of preeclampsia from trials of women at risk for preeclampsia, sorted by sample size.**



CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; MFMU = Maternal-Fetal Medicine Units; PE = preeclampsia; RR = relative risk.
* From random-effects analysis.

low-dose aspirin use during pregnancy, the evidence on long-term outcomes for offspring with in utero aspirin exposure is limited. Follow-up data from 1 large RCT were reassuring (62), with no differences in physical or mental development at 18 months.

Our findings are generally consistent with the results of the most recent Cochrane review (26), which included 65 trials (1965 to 2007), and those from the PARIS Collaboration IPD meta-analysis (27), which included data from 31 RCTs (32 217 women and 32 819 infants). Our review found similar effect estimates for preeclampsia, IUGR, preterm birth, and perinatal mortality, particularly compared with the PARIS results, despite differences in study inclusion criteria and the fact that our literature search was more recent. The PARIS Collaboration was able to meta-analyze an outcome not consistently available in the published literature (27) and found that aspirin treatment reduced the need for assisted ventilation of infants after delivery by 21% ($P = 0.01$).

Timing and dosage of aspirin treatment had no consistent effect on outcomes. Comparisons of dosage effects when a cut point of 75 mg was used revealed only 1 outcome with a significant difference: The preterm birth benefit was greater in studies using doses of at least 75 mg. Results for these stratified analyses, however, were confounded by study size; both large studies used 60 mg of aspirin. Forest plots sorted by dose did not indicate a dose–response relationship. The absence of convincing evidence for a dosage effect on benefits or harms is consistent with the PARIS Collaboration IPD meta-analysis (27) and other recent systematic reviews (63, 64). The Cochrane review, however, found greater benefit in studies using more than 75 mg of aspirin (26).

Although included trials reported considerable variation in timing of treatment initiation, all started after the first trimester. In terms of cessation, only the large, U.S.-based MFMU (Maternal-Fetal Medicine Units) trial instructed women to stop treatment if preeclampsia developed; most trials instructed women to continue treatment until delivery. We found that initiating aspirin treatment at 12 to 16 weeks conferred no more benefit than starting later, consistent with the PARIS IPD meta-analysis (27). However, another recent systematic review reported that starting treatment at no later than 16 weeks was associated with reduced preeclampsia risk (64). Because some cases of preeclampsia may result from problems with the process of trophoblastic invasion completed around 16 weeks of gestation, the importance of initiating treatment before or during this process remains a salient research question (65).

Estimated effect sizes were modest, but the averted outcomes are considered critical. Preterm birth is the cause of 70% of neonatal mortality and 75% of neonatal morbidity in developed countries (66). Preterm neonates have higher rates of intraventricular hemorrhage, respiratory distress, infection, seizures, and rehospitalizations (66, 67). Neonates with IUGR, even when born at term, are more likely to have respiratory distress, seizures, sepsis, and long-term disability (66–69).

Although we did not find evidence of direct maternal health benefits, preventing preeclampsia could reduce medical intervention in pregnancy and delivery (70–73). Preventing poor perinatal health outcomes could also confer quality-of-life benefits. Preeclampsia is associated with poor psychosocial outcomes, the posttraumatic stress syndrome, and postpartum depression (74–77). Maternal health and paternal well-being should be considered in addition to perinatal health outcomes given the stress of caring for a preterm infant or a child with long-term health problems. Many studies also have found associations between preeclampsia and long-term cardiovascular health outcomes (78, 79). Current estimates suggest a possible doubling or tripling of cardiovascular disease risk among women who have had preeclampsia during any pregnancy (80, 81). It is unclear whether common risk factors or a causal relationship account for the association or whether there is a lifetime benefit from preeclampsia prevention.

Methods for determining high risk for preeclampsia varied considerably across trials, resulting in a wide range of preeclampsia incidence in the control groups (8% to 30%). Recent recommendations from the American Congress of Obstetricians and Gynecologists more narrowly defined the high-risk population for aspirin prophylaxis (women with preeclampsia during >1 previous pregnancy or with prior early preterm birth) (9). We found no consistent pattern in effect size by incidence of preeclampsia. Tools to assess individual risk for the condition and to identify subgroups most likely to benefit are needed.

Our study has several limitations. We included only fair- to good-quality studies published in English. Some smaller studies had no events for rare outcomes, such as perinatal death and placental abruption, limiting evidence and the ability to summarize effects. The rarity of maternal morbidity and mortality outcomes did not permit their analysis. Observational studies offer hypothesis-generating evidence on long-term effects of aspirin exposure during pregnancy but have limited applicability and serious threats to validity. Those reporting associations between aspirin exposure and fetal or longer-term outcomes commonly lack information on dosage, timing, or regularity of exposure and often ascertain exposure retrospectively. Data from RCTs on women taking low-dose aspirin during pregnancy are more applicable than observational data, but information on long-term harms is sparse. The CLASP trial conducted an 18-month follow-up, but only for a subset of its sample. It was the only good-quality study that provided evidence on longer-term effects (cognition and growth) of in utero, low-dose aspirin exposure.

Cut points for IUGR were not consistently defined. Included studies used definitions ranging from less than the third percentile to less than the tenth percentile of birthweight for gestational age, with the latter definition from the American Congress of Obstetricians and Gynecologists most commonly used (82).

Our review identified small-study effects (26, 27, 44), with larger studies reporting more modest results. Two large trials provided the bulk of the data for pooled estimates of potential benefit (44, 53). Three additional large studies were added for evaluation of harm (43, 51, 59). Most of the large trials were national multisite studies (43, 44) or international collaborations (51, 53). Smaller studies have important merits in terms of the ability to closely monitor study protocols, but small trials with null findings may be more difficult to publish, potentially leading to inflated estimates of a treatment benefit (69).

On the basis of the predictive intervals observed for pooled estimates from random-effects models, the distribution of future studies would include nonsignificant or negative trials. Thus, there is some uncertainty about the likely persistence of the observed effects with future research. If lessons from previous studies and the developing understanding of preeclampsia pathophysiology are incorporated, future trials may more accurately identify women at greatest risk and most likely to benefit.

In conclusion, our systematic review identified benefits of low-dose aspirin for prevention of preeclampsia and perinatal illness in women at high risk for preeclampsia. Potential rare or long-term harms could not be ruled out, but none were identified. Research is needed to address remaining uncertainties. More primary research is needed to illuminate how preeclampsia arising from different risk factors develops and responds to aspirin. More robust and consistent tools for preeclampsia risk stratification would support future research and clinical practice. Few trials have been conducted among African American women in the United States, who have the greatest disease burden; clinical research focused on this important subpopulation is urgently needed. For women at high risk for preeclampsia, available evidence indicates modest effects but important benefits of daily low-dose aspirin for prevention of the condition and consequent illness.

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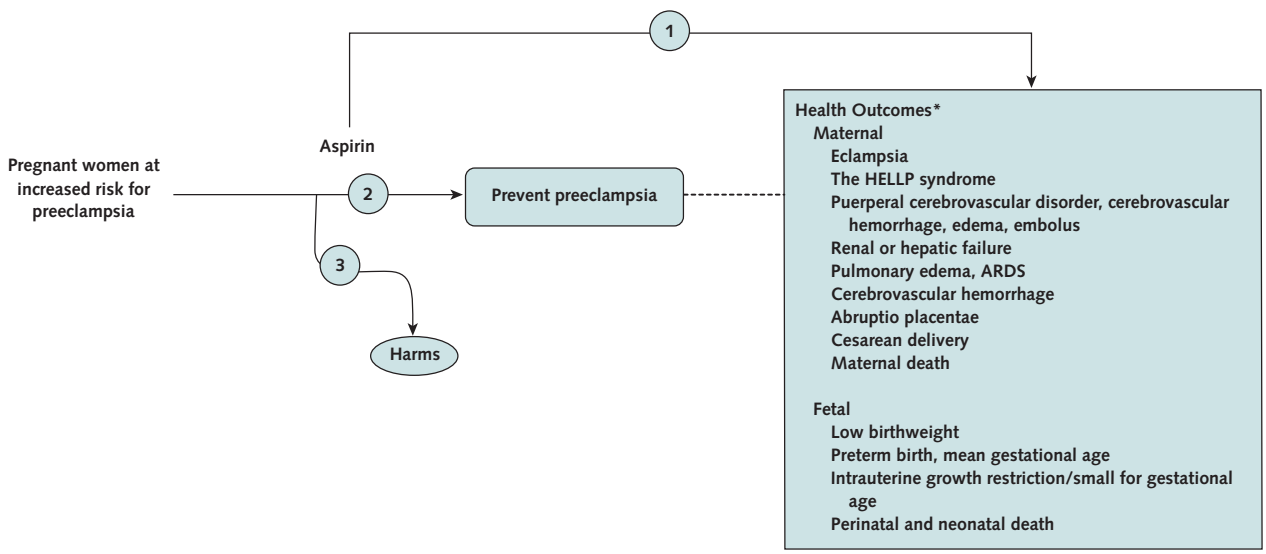
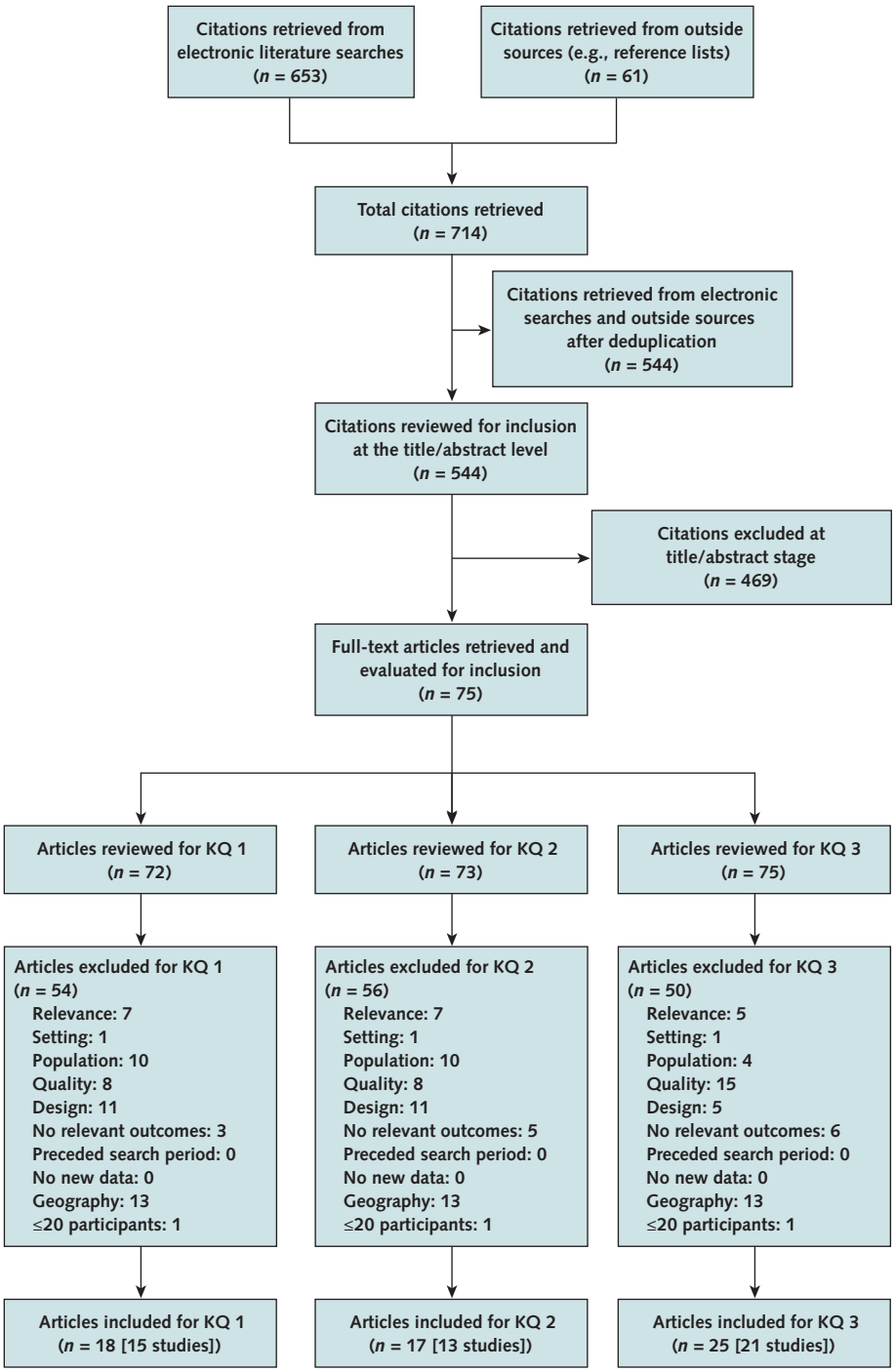
Appendix Figure 1. **Analytic framework and key questions.**



ARDS = acute respiratory distress syndrome; HELLP = hemolysis, elevated liver enzymes, and low platelets.
* Abbreviated list of health outcomes. See **Appendix Table 2** for a full list.

Appendix Figure 2. **Summary of evidence search and selection.**



The diagram excludes 51 RefMan (Thomson Reuters, Philadelphia, Pennsylvania) citations that were pulled for background or informational purposes only and were not systematically reviewed. KQ = key question.

Appendix Table 1. Excluded Studies*

Study Citation	KQ	Reason for Exclusion
Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. Italian study of aspirin in pregnancy. Lancet. 1993;341:396-400. [PMID: 8094168]	1–3	Study quality
Bakhti A, Vaiman D. Prevention of gravidic endothelial hypertension by aspirin treatment administered from the 8th week of gestation. Hypertens Res. 2011;34:1116-20. [PMID: 21881579]	1–3	Geography
Benigni A, Gregorini G, Frusca T, Chiabrando C, Ballerini S, Valcamonico A, et al. Effect of low-dose aspirin on fetal and maternal generation of thromboxane by platelets in women at risk for pregnancy-induced hypertension. N Engl J Med. 1989;321:357-62. [PMID: 2664523]	2	No relevant outcomes
Byaruhanga RN, Chipato T, Rusakaniko S. A randomized controlled trial of low-dose aspirin in women at risk from pre-eclampsia. Int J Gynaecol Obstet. 1998;60:129-35. [PMID: 9509950]	1–3	Geography
Chandiramani M, Seed P, Poston L, Shennan AH. Antiplatelet agents for prevention of pre-eclampsia [Letter]. Lancet. 2007;370:1685; author reply 1685-6. [PMID: 18022031]	1–3	Study design
Chiaffarino F, Parazzini F, Paladini D, Acaia B, Ossola W, Marozio L, et al. A small randomised trial of low-dose aspirin in women at high risk of pre-eclampsia. Eur J Obstet Gynecol Reprod Biol. 2004;112:142-4. [PMID: 14746947]	1–3	Study quality
Cowchock S, Reece EA. Do low-risk pregnant women with antiphospholipid antibodies need to be treated? Organizing Group of the Antiphospholipid Antibody Treatment Trial. Am J Obstet Gynecol. 1997;176:1099-100. [PMID: 9166175]	1–3	Population (KQs 1 and 2); no relevant outcomes (KQ 3)
Cruickshank DJ, Robertson AA, Campbell DM, Macgillivray I. Maternal obstetric outcome measures in a randomised controlled study of labetalol in the treatment of hypertension in pregnancy. Hypertens Pregnancy. 1991;b10:333-44.	1–3	Study relevance (other compound or co-treatment)
Dasari R, Narang A, Vasishta K, Garewal G. Effect of maternal low dose aspirin on neonatal platelet function. Indian Pediatr. 1998;35:507-11. [PMID: 10216644]	1–3	Geography
Davies NJ, Gazvani MR, Farquharson RG, Walkinshaw SA. Low-dose aspirin in the prevention of hypertensive disorders of pregnancy in relatively low-risk nulliparous women. Hypertens Pregnancy. 1995;14:49-55.	1, 2	Population (healthy nulliparous women)
Ebrashy A, Ibrahim M, Marzook A, Yousef D. Usefulness of aspirin therapy in high-risk pregnant women with abnormal uterine artery Doppler ultrasound at 14-16 weeks pregnancy: randomized controlled clinical trial. Croat Med J. 2005;46:826-31. [PMID: 16158479]	1–3	Geography
Elder MG, de Swiet M, Sullivan M. A randomised trial of low dose aspirin for primiparae in pregnancy (Golding)/Barbados low dose aspirin study in pregnancy (BLASP) (Rotchell et al.) [Letter]. Br J Obstet Gynaecol. 1999;106:180. [PMID: 10426687]	1–3	Study design
Gallery EDM, Ross MR, Hawkins M, Leslie G, Györy ÁZ. Low-dose aspirin in high-risk pregnancy? Hypertens Pregnancy. 1997;16:229-38.	2	No relevant outcomes
Goffinet F, Bréart G, Uzan S. ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women [Letter]. Br J Obstet Gynaecol. 1996;103:719-20. [PMID: 8688404]	1–3	Geography
Golding J. A randomised trial of low dose aspirin for primiparae in pregnancy. The Jamaica Low Dose Aspirin Study Group. Br J Obstet Gynaecol. 1998;105:293-9. [PMID: 9532989]	1–3	Geography
Gunawardana L, Zammit S, Lewis G, Gunnell D, Hollis C, Wolke D, et al. Examining the association between maternal analgesic use during pregnancy and risk of psychotic symptoms during adolescence. Schizophr Res. 2011;126:220-5. [PMID: 21146371]	1–3	Study relevance (KQs 1 and 2); study quality (KQ 3)
Hauth JC, Goldenberg RL, Parker CR Jr, Philips JB 3rd, Copper RL, DuBard MB, et al. Low-dose aspirin therapy to prevent preeclampsia. Am J Obstet Gynecol. 1993;168:1083-91; discussion 1091-3. [PMID: 8475955]	1, 2	Population (healthy nulliparous women)
Hermida RC, Ayala DE, Iglesias M, Mojón A, Silva I, Ucieda R, et al. Time-dependent effects of low-dose aspirin administration on blood pressure in pregnant women. Hypertension. 1997;30:589-95. [PMID: 9322987]	3	No relevant outcomes
Hermida RC, Ayala DE, Fernández JR, Mojón A, Alonso I, Silva I, et al. Administration time-dependent effects of aspirin in women at differing risk for preeclampsia. Hypertension. 1999;34:1016-23. [PMID: 10523401]	1–3	No relevant outcomes
Hermida RC, Ayala DE, Iglesias M. Administration time-dependent influence of aspirin on blood pressure in pregnant women. Hypertension. 2003;41:651-6. [PMID: 12623974]	1–3	No relevant outcomes
Hernandez RK, Werler MM, Romitti P, Sun L, Anderka M; National Birth Defects Prevention Study. Nonsteroidal antiinflammatory drug use among women and the risk of birth defects. Am J Obstet Gynecol. 2012;206:228.e1-8. [PMID: 22196851]	1–3	Study design (KQs 1 and 2); study quality (KQ 3)
Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP, et al. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiology. 2010;21:779-85. [PMID: 20805751]	1, 2	Study design
Jensen MS, Henriksen TB, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, et al. Analgesics during pregnancy and cryptorchidism: additional analyses [Letter]. Epidemiology. 2011;22:610-2. [PMID: 21642784]	1–3	Study design
Keim SA, Klebanoff MA. Aspirin use and miscarriage risk. Epidemiology. 2006;17:435-9. [PMID: 16755260]	1, 2	Study design
Kincaid-Smith P, North RA, Fairley KF, Kloss M, Ihle BU. Prevention of pre-eclampsia in high risk women with renal disease: A prospective randomized trial of heparin and dipyridamole. Nephrology. 1995;1:297-300.	1–3	Study relevance (other compound or co-treatment)
Louden KA, Broughton Pipkin F, Symonds EM, Tuohy P, O'Callaghan C, Heptinstall S, et al. A randomized placebo-controlled study of the effect of low dose aspirin on platelet reactivity and serum thromboxane B2 production in non-pregnant women, in normal pregnancy, and in gestational hypertension. Br J Obstet Gynaecol. 1992;99:371-6. [PMID: 1622907]	1, 2	<20 participants
Marret S, Marchand L, Kaminski M, Larroque B, Arnaud C, Truffert P, et al; EPIPAGE Study Group. Prenatal low-dose aspirin and neurobehavioral outcomes of children born very preterm. Pediatrics. 2010;125:e29-34. [PMID: 20026499]	1–3	Study design (KQs 1 and 2); population (KQ 3)
Michael CA, Walters BNJ. Low-dose aspirin in the prevention of pre-eclampsia: current evaluation. In: Teoh ERS, MacNaughton M, eds. Maternal Physiology and Pathology. Carnforth, United Kingdom: Parthenon; 1992:183-9.	1–3	Study quality

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Appendix Table 1—**Continued**

Study Citation	KQ	Reason for Exclusion
Miller EA, Rasmussen SA, Siega-Riz AM, Frías JL, Honein MA; National Birth Defects Prevention Study. Risk factors for non-syndromic holoprosencephaly in the National Birth Defects Prevention Study. Am J Med Genet C Semin Med Genet. 2010;154C:62-72. [PMID: 20104597]	1–3	Study design (KQs 1 and 2); study quality (KQ 3)
Newnham JP, Godfrey M, Walters BJ, Phillips J, Evans SF. Low dose aspirin for the treatment of fetal growth restriction: a randomized controlled trial. Aust N Z J Obstet Gynaecol. 1995;35:370-4. [PMID: 8717556]	1, 2	Population
Ognjanovic S, Blair C, Spector LG, Robison LL, Roesler M, Ross JA. Analgesic use during pregnancy and risk of infant leukaemia: a Children's Oncology Group study. Br J Cancer. 2011;104:532-6. [PMID: 21157452]	1–3	Study quality
Porreco RP, Hickok DE, Williams MA, Krenning C. Low-dose aspirin and hypertension in pregnancy [Letter]. Lancet. 1993;341:312. [PMID: 8093955]	1–3	Study quality
Prakalapakorn SG, Rasmussen SA, Lambert SR, Honein MA; National Birth Defects Prevention Study. Assessment of risk factors for infantile cataracts using a case-control study: National Birth Defects Prevention Study, 2000-2004. Ophthalmology. 2010;117:1500-5. [PMID: 20363508]	1–3	Study design (KQs 1 and 2); study quality (KQ 3)
Rai U, Chakravorty M, Juneja Y. Role of low dose aspirin in PIH. J Obstet Gynaecol India. 1993:883-6.	1–3	Geography
Ramaiya C, Mgaya HN. Low dose aspirin in prevention of pregnancy-induced hypertension in primigravidae at the Muhimbili Medical Center, Dar es Salaam. East Afr Med J. 1995;72:690-3. [PMID: 8904056]	1–3	Geography
Rivas-Echeverria CA, Echeverria Y, Molina L, Novoa D. Synergic use of aspirin, fish oil and vitamins C and E for the prevention of preeclampsia. Hypertens Pregnancy. 2000;19(Suppl 1):30.	1–3	Geography
Roberts JM, Catov JM. Aspirin for pre-eclampsia: compelling data on benefit and risk. Lancet. 2007;369:1765-6. [PMID: 17512047]	1–3	Study design
Rogers MS, Fung HY, Hung CY. Calcium and low-dose aspirin prophylaxis in women at high risk of pregnancy-induced hypertension. Hypertens Pregnancy. 1999;18:165-72. [PMID: 10476618]	1–3	Study quality
Rotchell YE, Cruickshank JK, Gay MP, Griffiths J, Stewart A, Farrell B, et al. Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications. Br J Obstet Gynaecol. 1998;105:286-92. [PMID: 9532988]	1, 2	Population
Roy UK, Pan S. A study of use of low dose aspirin in prevention of pregnancy induced hypertension. J Indian Med Assoc. 1994;92:188-91. [PMID: 7930659]	1–3	Geography
Schiff E, Barkai G, Ben-Baruch G, Mashiach S. Low-dose aspirin does not influence the clinical course of women with mild pregnancy-induced hypertension. Obstet Gynecol. 1990;76:742-4.	1–3	Population
Schröcksnadel H, Sitte B, Alge A, Steckel-Berger G, Schwegel P, Pastner E, et al. Low-dose aspirin in primigravidae with positive roll-over test. Gynecol Obstet Invest. 1992;34:146-50. [PMID: 1427414]	1–3	Study quality
Seki H, Kuromaki K, Takeda S, Kinoshita K, Satoh K. Trial of prophylactic administration of TXA2 synthetase inhibitor, ozagrel hydrochloride, for preeclampsia. Hypertens Pregnancy. 1999;18:157-64. [PMID: 10476617]	1–3	Study relevance (other compound or co-treatment)
Shenoy S, Chandrika D, Pisharody R. RCT of low dose aspirin to prevent the progression of pregnancy induced hypertension grade A to B. J Clin Epidemiol. 1999;52(Suppl 1):28S.	1–3	Geography
Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rocco L, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med. 1993;329:1213-8. [PMID: 8413387]	1, 2	Population (healthy nulliparous women)
de Souza EV, Sass N, Atallah AN, Kular Jr L. Aspirin and calcium to prevent pre eclampsia in chronic hypertension women with abnormal uterine artery Doppler ultrasound [Abstract]. Hypertens Pregnancy. 2006;25(Suppl 1):152.	1–3	Study relevance
Subtil D, Goeusse P, Puech F, Lequien P, Biausque S, Breart G, et al; Essai Régional Aspirine Mère-Enfant (ERASME) Collaborative Group. Aspirin (100 mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Régional Aspirine Mère-Enfant study (Part 1). BJOG. 2003;110:475-84. [PMID: 12742332]	1, 2	Population (healthy nulliparous women)
Tewari S, Kaushish R, Sharma S, Gulati N. Role of low dose aspirin in prevention of pregnancy induced hypertension. J Indian Med Assoc. 1997;95:43-4, 47. [PMID: 9357241]	1–3	Geography
Tulppala M, Marttunen M, Söderstrom-Anttila V, Foudila T, Ailus K, Palosuo T, et al. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. Hum Reprod. 1997;12:1567-72. [PMID: 9262298]	1–3	Population
Tyler CP, Paneth N, Allred EN, Hirtz D, Kuban K, McElrath T, et al; ELGAN Study Investigators. Brain damage in preterm newborns and maternal medication: the ELGAN Study. Am J Obstet Gynecol. 2012;207:192.e1-9. [PMID: 22939723]	1–3	Population
Uzan S, Beaufils M, Breart G, Bazin B, Capitant C, Paris J. Prevention of fetal growth retardation with low-dose aspirin: findings of the EPREDA trial. Lancet. 1991;337:1427-31. [PMID: 1675315]	1–3	Study relevance (other compound or co-treatment)
Vaseie M. The effect of low-dose acetylsalicylic acid (ASA) on control of hypertension in pregnancy [Abstract]. Hypertens Pregnancy. 2006;25:148.	1–3	Setting
Villa PM, Kajantie E, Räikkönen K, Pesonen AK, Hämäläinen E, Vainio M, et al; PREDO Study group. Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. BJOG. 2013;120:64-74. [PMID: 23126307]	3	No relevant outcomes
Wallenburg HC, Dekker GA, Makovitz JW, Rotmans N. Effect of low-dose aspirin on vascular refractoriness in angiotensin-sensitive primigravid women. Am J Obstet Gynecol. 1991;164:1169-73. [PMID: 2035557]	1–3	No relevant outcomes
Wang Z, Li W. A prospective randomized placebo-controlled trial of low-dose aspirin for prevention of intra-uterine growth retardation. Chin Med J (Engl). 1996;109:238-42. [PMID: 8758317]	1–3	Geography
Werler MM, Mitchell AA, Moore CA, Honein MA; National Birth Defects Prevention Study. Is there epidemiologic evidence to support vascular disruption as a pathogenesis of gastroschisis? Am J Med Genet A. 2009;149A:1399-406. [PMID: 19533769]	1–3	Study design (KQs 1 and 2); study quality (KQ 3)
Werler MM, Bosco JL, Shapira SK; National Birth Defects Prevention Study. Maternal vasoactive exposures, amniotic bands, and terminal transverse limb defects. Birth Defects Res A Clin Mol Teratol. 2009;85:52-7. [PMID: 19067400]	3	Study quality

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Appendix Table 1—**Continued**

Study Citation	KQ	Reason for Exclusion
Wyatt-Ashmead J. Antenatal closure of the ductus arteriosus and hydrops fetalis. Pediatr Dev Pathol. 2011;14:469-74. [PMID: 21985268]	1–3	Study relevance (KQs 1 and 2); study design (KQ 3)
Zimmermann P, Eiriö V, Koskinen J, Niemi K, Nyman R, Kujansuu E, et al. Effect of low-dose aspirin treatment on vascular resistance in the uterine, uteroplacental, renal and umbilical arteries—A prospective longitudinal study on a high risk population with persistent notch in the uterine arteries. Eur J Ultrasound. 1997;5:17-30.	1–3	Study quality

KQ = key question.
* Includes studies that were included for a different KQ from the one listed.

Appendix Table 2. Details of Studies Included for Effects of Low-Dose Aspirin on Preeclampsia and Other Maternal and Fetal Outcomes

Study, Year (Reference)	Study Quality	Country	Study Design	Participants, *n*	PE Risk Criteria	Daily Aspirin Dose, *mg*	Time of Starting and Stopping Treatment	Mean (SD) Age, *y*	Non-Hispanic White, %	Nulliparous, %	PE Incidence Reported
Ayala et al, 2013 (55)	Good	Spain	RCT	350	Receiving medical care at a high-risk unit Criteria for high risk include family or personal history of PE; chronic HTN; CVD; endocrine, metabolic, or bleeding disease; spontaneous abortion; multiple pregnancy; obesity; and age	100	12–16 wk; delivery	IG: 30.3 (5.3) CG: 31.1 (5.2)	NR	IG: 49.4 CG: 55.1	Yes
Benigni et al, 1989 (52)	Fair	Italy	RCT	33	HTN or obstetric history (fetal death due to placental insufficiency, severe IUGR, or early-onset PE [<32 wk])	60	12 wk; delivery	IG: 31.0 (5) CG: 32.0 (6)	NR	NR	No
Caspi et al, 1994 (56)	Good	Israel	RCT	47	Twin pregnancy	100	15–23 wk (mean, 17.7 wk); delivery	IG: 28.8 (4.4) CG: 27.8 (4.5)	NR	IG: 41.7* CG: 30.4*	Yes
CLASP, 1994 (53)	Good	Argentina, Australia, Belgium, Canada, Germany, Hong Kong, Israel, Malaysia, New Zealand, Russia, Spain, Sweden, the Netherlands, United Arab Emirates, United Kingdom, United States	RCT	9364	Population at risk for PE or IUGR as determined by a clinician; women were considered for prophylactic entry or therapeutic entry Prophylactic entry: pregnant women with PE or IUGR in previous pregnancy; chronic HTN; renal disease; or such other risk factors as maternal age, family history, or multiple pregnancy Therapeutic entry: pregnant women with signs or symptoms of PE or IUGR in current pregnancy	60	12–32 wk; delivery	IG: 28.5 (5.4) CG: 28.5 (5.5)	NR	IG: 28.0 CG: 28.0	Yes
Davies et al, 1995 (48)†	Fair	United Kingdom	RCT	122	Population not at elevated risk (healthy nulliparous women); study included for KQ 3 only	75	18 wk; delivery	IG: 25.4 (5.5) CG: 25.4 (4.2)	IG: 96.6 CG: 95.0	IG: 100 CG: 100	Yes
Gallery et al, 1997 (40)	Fair	Australia	RCT	108	Preexisting chronic HTN, renal disease, or history of PE as determined by patient interview at 16 wk of gestation	100	17–19 wk; 2 wk before planned delivery	IG: 29 (23–28)‡ CG: 28 (22–38)‡	IG: 96.0 CG: 95.0	IG: 42.0 CG: 43.0	No
Grab et al, 2000 (57)	Fair	Germany	RCT	43	Current IUGR; impaired uteroplacental blood flow; chronic HTN; or history of PE, stillbirth, or growth restriction	100	18 wk; 38 wk	NR	NR	NR	Yes
Hauth et al, 1993 (42)†	Good	United States	RCT	606	Population not at elevated risk (healthy nulliparous women); study included for KQ 3 only	60	23 wk; delivery	IG: 20.3 (2.6) CG: 20.4 (2.7)	IG: 30.0 CG: 27.0	100	Yes
Hermida et al, 1997 (39)	Good	Spain	RCT	100	Treatment at high-risk unit of hospital (reasons included family or personal history of gestational HTN, PE, or chronic HTN; cardiovascular, endocrine, bleeding, or metabolic disease; and personal history of spontaneous abortion, multiple pregnancy, obesity, or adolescent or middle-aged nulliparous pregnancy [<18 y or >35 y])	100	12–16 wk; delivery	IG: 30.3 (0.9) CG: 30.1 (0.8)	NR	Primiparous: 70.0	Yes
Jensen et al, 2010 (61)†	Good	Denmark	Cohort	47 400	Population not at elevated risk (all children born to women who were pregnant between 1996 and 2002 were enrolled); study included for KQ 3 only	NR	Anytime during pregnancy	All children were aged 18 mo at follow-up	NR	Primiparous: Unexposed: 48.2 Exposed: 44.5	No
Keim and Klebanoff, 2006 (45)†	Good	United States	Case–control	3129	Population not at elevated risk (early fetal loss in previous pregnancy); study included for KQ 3 only	NR	Anytime during pregnancy	Case patients: 26.9 (6.5) Control participants: 25.2 (5.7)	Case patients: 62.0 Control participants: 66.0	NR	No
McParland et al, 1990 (49)	Fair	United Kingdom	RCT	106	Persistent abnormal Doppler flow velocity waveforms at 24 wk of gestation (measured twice)	75	24 wk; delivery	IG: 25.6 (4.2) CG: 26.5 (5.1)	IG: 73.0 CG: 65.0	IG: 79.2* CG: 75.0*	Yes

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Appendix Table 2 —Continued

Study, Year (Reference)	Study Quality	Country	Study Design	Participants, *n*	PE Risk Criteria	Daily Aspirin Dose, *mg*	Time of Starting and Stopping Treatment	Mean (SD) Age, *y*	Non-Hispanic White, *%*	Nulliparous, *%*	PE Incidence Reported
MFMU, 1998 (44)	Good	United States	RCT	2539	Medical history that placed women in 1 of 4 high-risk groups: women with DM, those with chronic HTN, those with MGs, and those with previous PE Women with DM could also have HTN (but were analyzed with the DM group), but those with MGs were excluded if they also had DM or HTN	60	13–26 wk; delivery or development of PE	DM: 26.0 (6) HTN: 30.0 (6) MG: 25.0 (6) PE: 25.0 (5)	DM: 53.0 HTN: 27.0 MG: 32.0 PE: 25.0	Total n = 668	Yes
Newnham et al, 1995 (60)†	Good	Australia	RCT	51	Population not at risk for PE (at risk for IUGR); study included for KQ 3 only	100	28–36 wk; delivery	IG: 26.8 (7.2) CG: 28.6 (6.2)	NR	IG: 48 CG: 65	No
Rotchell et al, 1998 (59)†	Good	Barbados	RCT	3647	Population not at elevated risk (healthy women without contraindication for aspirin therapy); study included for KQ 3 only	75	12–32 wk; delivery	NR§	NR	Primigravid: IG: 44.0 CG: 44.0	Yes
Schiff et al, 1989 (47)	Good	Israel	RCT	65	≥1 of the following: nulliparity, twin gestation, history of PE, or positive rollover test result	100	28 or 29 wk; 38 wk	IG: 27.1 (6.1) CG: 27.6 (5.7)	100	NR	Yes
Sibai et al, 1993 (43)†	Good	United States	RCT	3135	Population not at elevated risk (healthy nulliparous women); study included for KQ 3 only	60	13–25 wk; delivery	IG: 20 (4.0) CG: 21 (5.0)	IG: 17.5 CG: 18.5	100	Yes
Subtil et al, 2003 (51)†	Good	France, Belgium	RCT	3294	Population not at elevated risk (healthy nulliparous women); study included for KQ 3 only	100	14–20 wk; 34 wk	IG: 24.7 (4.4) CG: 24.6 (4.4)	NR	IG: 100 CG: 100	Yes
Vainio et al, 2002 (41)	Fair	Finland	RCT	90	Bilateral diastolic notch identified by transvaginal Doppler ultrasonography and risk for PE or IUGR as determined by medical history	0.5 per kg of body weight	12–14 wk; not clearly specified	IG: 30.6 (6.3) CG: 30.0 (5.9)	NR	IG: 34.9 CG: 23.3	Yes
Viinikka et al, 1993 (58)	Fair	Finland	RCT	208	Diagnosis of arterial HTN (BP >140/90 mm Hg without treatment before pregnancy) or history of severe PE	50	15–16 wk; delivery	IG: 33.2 (4.9) CG: 32.7 (5.4)	NR	IG: 25.2 CG: 23.8	Yes
Villa et al, 2013 (50)	Fair	Finland	RCT	152	Age, BMI >30 kg/m^2, chronic HTN, the Sjögren syndrome or lupus, history of gestational diabetes, PE, small for gestational age, fetus mortus, and second-degree diastolic notch present at $12^{0/7}$ through $13^{6/7}$ wk of gestation	100	12–13 wk; 35 wk or delivery	IG: 30.8 (5.3) CG: 31.0 (5.1)	NR	NR	Yes
Wallenburg et al, 1986 (54)	Good	The Netherlands	RCT	46	Angiotensin II sensitivity determined by blood test	60	26 wk; delivery	IG: 23.0 (17–38)‖ CG: 25.0 (19–36)‖	NR	IG: 100 CG: 100	Yes
Yu et al, 2003 (46)	Good	Brazil, Chile, South Africa, United Kingdom	RCT	560	Women with mean PI >1.6 and early diastolic notching of uterine arteries identified by transvaginal color Doppler ultrasonography	150	22–24 wk; 35 wk¶	IG: 29 (23–33)** CG: 29 (24–33)**	IG: 66.3 CG: 58.3	IG: 26.8 CG: 23.4	Yes

BMI = body mass index; BP = blood pressure; CG = control group; CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; CVD = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension; IG = intervention group; IUGR = intrauterine growth restriction; KQ = key question; MFMU = Maternal-Fetal Medicine Units; MG = multifetal gestation; NR = not reported; PE = preeclampsia; PI = pulsatility index; RCT = randomized, controlled trial.

* Calculated.

† Included for analysis of KQ 3 (harms only) and not in a high-risk population.

‡ Mean (range).

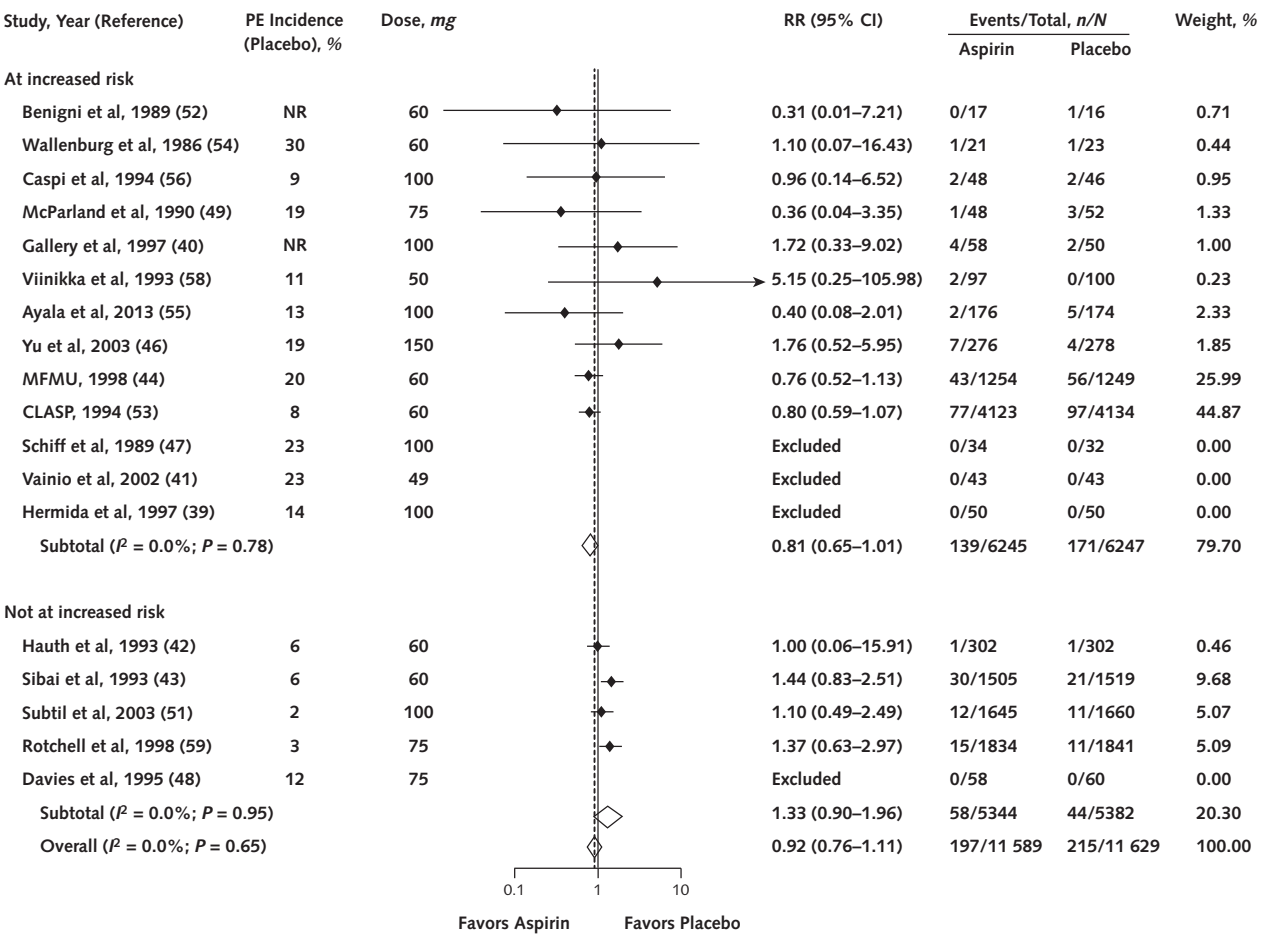
§ Authors reported that 24% of patients in each group were aged <20 y, 55% in each group were aged 20 to 29 y, 20% in each group were aged 30 to 39 y, and 1% in each group were aged >40 y.

‖ Median (range).

¶ Estimated.

** Median (interquartile range).

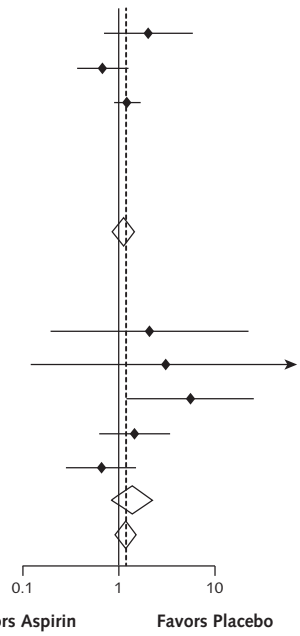
Appendix Figure 3. **Pooled analysis of perinatal mortality from all trials, sorted by sample size.**



CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; MFMU = Maternal-Fetal Medicine Units; NR = not reported; PE = preeclampsia; RR = relative risk.

Appendix Figure 4. **Pooled analysis of placental abruption from all trials, sorted by sample size.**

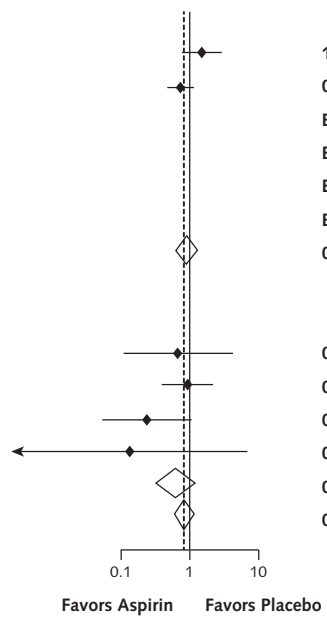
Study, Year (Reference)	PE Incidence (Placebo), %	Dose, *mg*	RR (95% CI)	Events/Total, *n/N*		Weight, %
				Aspirin	Placebo	
At increased risk						
Yu et al, 2003 (46)	19	150	2.01 (0.70–5.82)	10/276	5/278	3.91
MFMU, 1998 (44)	20	60	0.68 (0.37–1.25)	17/1254	25/1249	19.64
CLASP, 1994 (53)	8	60	1.21 (0.89–1.65)	86/4659	71/4650	55.72
Caspi et al, 1994 (56)	9	100	Excluded	0/24	0/23	0.00
Hermida et al, 1997 (39)	14	100	Excluded	0/50	0/50	0.00
Viinikka et al, 1993 (58)	11	50	Excluded	0/97	0/100	0.00
Subtotal (I^2 = 50.1%; P = 0.135)			1.12 (0.86–1.46)	113/6360	101/6350	79.27
Not at increased risk						
Davies et al, 1995 (48)	12	75	2.07 (0.19–22.20)	2/58	1/60	0.77
Hauth et al, 1993 (42)	6	60	3.00 (0.12–73.35)	1/302	0/302	0.39
Sibai et al, 1993 (43)	6	60	5.56 (1.23–25.02)	11/1485	2/1500	1.56
Subtil et al, 2003 (51)	2	100	1.45 (0.62–3.38)	13/1634	9/1640	7.04
Rotchell et al, 1998 (59)	3	75	0.64 (0.28–1.48)	9/1819	14/1822	10.97
Subtotal (I^2 = 41.6%; P = 0.144)			1.38 (0.84–2.28)	36/5298	26/5324	20.73
Overall (I^2 = 36.4%; P = 0.138)			1.17 (0.93–1.48)	149/11 658	127/11 674	100.00



CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; MFMU = Maternal-Fetal Medicine Units; PE = preeclampsia; RR = relative risk.

Appendix Figure 5. **Pooled analysis of intracranial fetal bleeding from all trials, sorted by sample size.**

Study, Year (Reference)	PE Incidence (Placebo), %	Dose, *mg*	RR (95% CI)	Events/Total, *n/N*		Weight, %
				Aspirin	Placebo	
At increased risk						
MFMU, 1998 (44)	20	60	1.49 (0.77–2.91)	21/1254	14/1249	23.74
CLASP, 1994 (53)	8	60	0.74 (0.47–1.15)	33/4810	45/4821	53.22
Benigni et al, 1989 (52)	NR	60	Excluded	0/17	0/16	0.00
Schiff et al, 1989 (47)	23	100	Excluded	0/34	0/32	0.00
Hermida et al, 1997 (39)	14	100	Excluded	0/50	0/50	0.00
McParland et al, 1990 (49)	19	75	Excluded	0/48	0/52	0.00
Subtotal (I^2 = 66.7%; P = 0.083)			0.91 (0.63–1.33)	54/6213	59/6220	76.96
Not at increased risk						
Newnham et al, 1995 (60)	NR	100	0.67 (0.11–4.15)	2/29	3/30	3.20
Sibai et al, 1993 (43)	6	60	0.92 (0.39–2.18)	10/1480	11/1505	14.35
Subtil et al, 2003 (51)	2	100	0.24 (0.05–1.06)	1/1645	6/1660	4.81
Rotchell et al, 1998 (59)	3	75	0.14 (0.00–6.85)	0/1834	1/1841	0.69
Subtotal (I^2 = 0.0%; P = 0.40)			0.63 (0.32–1.24)	13/4988	21/5036	23.04
Overall (I^2 = 27.1%; P = 0.23)			0.84 (0.61–1.16)	67/11 201	80/11 256	100.00



CLASP = Collaborative Low-dose Aspirin Study in Pregnancy; MFMU = Maternal-Fetal Medicine Units; NR = not reported; PE = preeclampsia; RR = relative risk.