Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage

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OBJECTIVE DATA: Impaired placentation in the first 16 weeks of pregnancy is associated with increased risk of subsequent development of preeclampsia, birth of small-for-gestational-age neonates, and placental abruption. Previous studies reported that prophylactic use of aspirin reduces the risk of preeclampsia and small-for-gestational-age neonates with no significant effect on placental abruption. However, meta-analyses of randomized controlled trials that examined the effect of aspirin in relation to gestational age at onset of therapy and dosage of the drug reported that significant reduction in the risk of preeclampsia and small-for-gestational-age neonates is achieved only if the onset of treatment is at ≤16 weeks of gestation and the daily dosage of the drug is ≥100 mg.

STUDY: We aimed to estimate the effect of aspirin on the risk of placental abruption or antepartum hemorrhage in relation to gestational age at onset of therapy and the dosage of the drug.

STUDY APPRAISAL AND SYNTHESIS METHODS: To perform a systematic review and meta-analysis of randomized controlled trials that evaluated the prophylactic effect of aspirin during pregnancy, we used PubMed, Cinhal, Embase, Web of Science and Cochrane library from 1985 to September 2017. Relative risks of placental abruption or antepartum hemorrhage with their 95% confidence intervals were calculated with the use of random effect models. Analyses were stratified according to daily dose of aspirin (<100 and ≥100 mg) and the gestational age at the onset of therapy (≤16 and >16 weeks of gestation) and compared with the use of subgroup difference analysis.

RESULTS: The entry criteria were fulfilled by 20 studies on a combined total of 12,585 participants. Aspirin at a dose of <100 mg per day had no impact on the risk of placental abruption or antepartum hemorrhage, irrespective of whether it was initiated at ≤16 weeks of gestation (relative risk, 1.11; 95% confidence interval, 0.52−2.36) or at >16 weeks of gestation (relative risk, 1.32; 95% confidence interval, 0.73−2.39). At ≥100 mg per day, aspirin was not associated with a significant change on the risk of placental abruption or antepartum hemorrhage, whether the treatment was initiated at ≤16 weeks of gestation (relative risk, 0.62, 95% confidence interval, 0.31−1.26), or at >16 weeks of gestation (relative risk, 2.08; 95% confidence interval, 0.86−5.06), but the difference between the subgroups was significant (P=.04).

CONCLUSION: Aspirin at a daily dose of ≥100 mg for prevention of preeclampsia that is initiated at ≤16 weeks of gestation, rather than >16 weeks, may decrease the risk of placental abruption or antepartum hemorrhage.

Key words: aspirin, placental abruption, preeclampsia, pregnancy

Impaired placentation in the first 16 weeks of pregnancy is associated with increased risk of the subsequent development of preeclampsia, birth of small-for-gestational-age neonates, and placental abruption.[1-6] Numerous randomized controlled trials have investigated the potential value of prophylactic use of low-dose aspirin in prevention of preeclampsia; an early meta-analysis reported that the risk of preeclampsia and small for gestational age is reduced by approximately 10%.[7] A recent individual patient meta-analysis by the same group reported that this modest reduction in risk was unrelated to the gestational age at onset of therapy (<16 vs ≥16 weeks of gestation) or a daily dose of aspirin (≤75 vs >75 mg).[8] In contrast, other meta-analyses reported that the use of aspirin has a major effect on both preeclampsia and small for gestational age with a greater than 50% reduction in risk, provided that the onset of therapy is ≤16 weeks of gestation and the daily dose of the drug is ≥100 mg; onset of therapy at >16 weeks or daily dose of <100 mg has no significant effect.[9-11] These results were confirmed by the findings of a recent large multicenter randomized trial (ASPRE) that demonstrated that aspirin (150 mg per day) from 11−14 weeks to 36 weeks of gestation was associated with a >60% reduction in risk of preterm preeclampsia.[12]

Placental abruption is a major cause of perinatal death and maternal

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TABLE 1
Characteristics of trials included in the meta-analysis

Study	N	Inclusion criteria	Compliance[a]	Intervention		
				Aspirin	Control	Onset (wk)
Zimmermann et al, 1997[41]	26	Abnormal uterine artery Doppler results	Not reported	50 mg	No treatment	22–24
Caritis et al, 1998[27]	2503	History risk factor[b]	79% of women took >80% of pills	60 mg	Placebo	13–26
Hauth et al, 1993[32,33]	604	Nulliparity	80% of aspirin group compliant	60 mg	Placebo	24
Sibai et al, 1993[15]	2911	Nulliparity	73% of women took >80% of pills	60 mg	Placebo	13–25
Golding 1998[30]	2547	Nulliparity	66% of women were compliant	60 mg	Placebo	12–32
Schiff et al, 1989[37]	65	History risk factor[b] with positive roll-over test	Not reported	100 mg	Placebo	28–29
Wallenburg et al, 1986[38]	44	Positive angiotensin II sensitivity test	Not reported	60 mg	Placebo	28
Byaruhanga et al, 1998[26]	230	History risk factor[b]	86% of women took >80% of pills	75 mg	Placebo	20–28
McParland et al, 1990[35]	100	Nulliparity with abnormal uterine artery Doppler result	26% of women took 100%, median number of tablets missing=2	75 mg	Placebo	24
Zhao et al, 2012[40]	237	History risk factor[b]	Not reported	75 mg	Placebo	13–16
Liu et al, 2017[34]	224	History risk factor[b]	100% of women were compliant	50, 75, 100 mg	No treatment	9–16
August et al, 1994[23]	49	History risk factor[b]	Not reported	100 mg	Placebo	13–15
Ayala et al, 2013[24]	350	History risk factor[b]	100% of women took >95% of pills	100 mg	Placebo	12–16
Morris et al, 1996[36]	102	Nulliparity with abnormal umbilical artery Doppler result	Not reported	100 mg	Placebo	17–19
Davies et al, 1995[28]	118	Nulliparity	Compliance was excellent	75 mg	Placebo	18
Gallery et al, 1997[29]	108	History risk factor[b]	≥80% of women were compliant	100 mg	Placebo	17–19
Hermida et al, 1997[31]	100	History risk factor[b]	100% of women were compliant	100 mg	Placebo	12–16
Rolnik et al, 2017[12]	1620	High risk based on combined screening[c]	80% of women took >90% of pills	150 mg	Placebo	11–14
Beaufils et al, 1985[25]	93	History risk factor[b]	Not reported	150 mg[d]	Placebo	14
Yu et al, 2003[39]	554	Abnormal uterine artery Doppler result	Not reported	150 mg	Placebo	22–24

[a] Reported as percentage of women who took a certain percentage of the total number of prescribed pills; [b] Includes history of chronic hypertension, cardiovascular or endocrine disease, previous pregnancy hypertension, or fetal growth restriction; [c] Combination of maternal risk factors, serum placental growth factor and pregnancy associated plasma protein-A, mean arterial pressure, and uterine artery pulsatility index; [d] With dipyridamole 300 mg.

Roberge. Aspirin use and placental abruption. Am J Obstet Gynecol 2018.

morbidity.[13,14] An early randomized trial on the use of aspirin (60 mg per day) for the prevention of preeclampsia reported that aspirin use was associated with a significant increase in risk of placental abruption, which was attributed to the antiplatelet effect of the drug.[15] Subsequent meta-analyses have reported that aspirin use for prevention of preeclampsia was not associated with increased risk of placental abruption; however, in these meta-analyses the effect of aspirin was not examined in relation to gestational age at onset of therapy or the daily dose of the drug.[7,16]

The objective of this systematic review and meta-analysis was to estimate the effect of aspirin on the risk of placental abruption or antepartum hemorrhage, in relation to gestational age at onset of therapy and the dose of the drug.

Method

This is a systematic review and meta-analysis of randomized controlled trials that includes studies that recruited women for the prevention of preeclampsia with the use of aspirin. Treatment includes aspirin or dipyridamole compared with placebo or no treatment. Studies were excluded if pregnant women started treatment before pregnancy or had preeclampsia or fetal growth restriction at randomization.

Research strategy

Keywords and MeSH terms related with aspirin for preeclampsia were

searched in Embase, PubMed, Cinahl, Web of science, Cochrane CENTRAL library from 1985 to September 2017. No language restrictions were applied.

Selection of the articles

Titles were selected for first screening, and abstracts were then reviewed by 2 independent reviewers (S.R., E.B.). All eligible studies were then fully evaluated by the same reviewers; disagreements were resolved by the opinion of a third party (K.N.). Studies that reported placental abruption or antepartum hemorrhage were included in the final analysis.

Quality evaluation

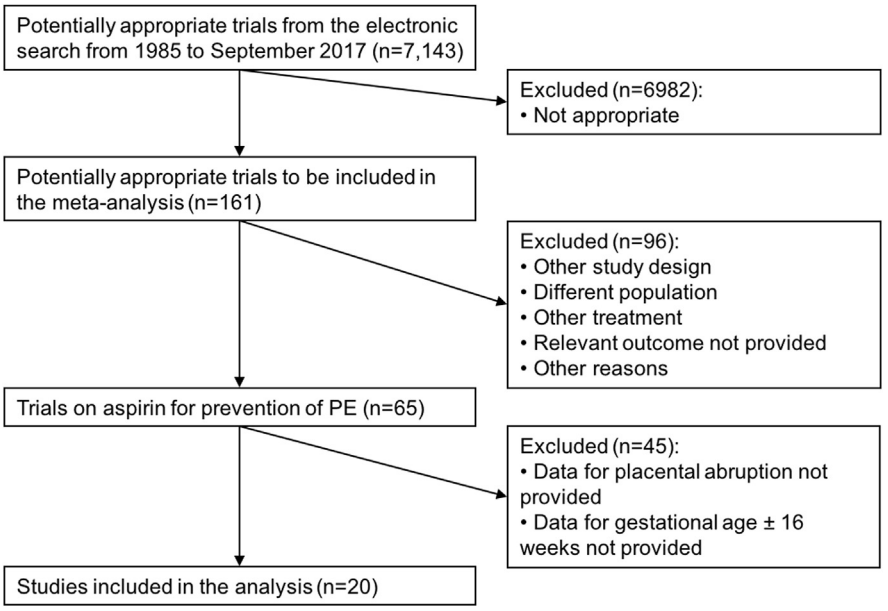
The quality of this meta-analysis was assessed with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) tool,[17] and the quality of each included trial was assessed by the Cochrane Handbook.[18]

Analysis

Subgroup analyses were performed in regards to the dose of aspirin (<100 and ≥100 mg) and the gestational age at onset of treatment (≤16 and >16 weeks).[10,19] Because there are only 2 groups of comparison, subgroup analysis with random effects will be performed.[20] The cut-offs of 16 weeks of gestation and 100 mg of the drug were selected because previous meta-analyses reported that aspirin is effective in the prevention of preeclampsia only if the onset of therapy is ≤16 weeks of gestation and if the daily dose of the drug is ≥100 mg.[9-11] Results was reported by relative risks (RR), calculated with their 95% confidence intervals (CI), with the use of random effects.[20] Sensitivity analyses were performed to evaluate the effect of aspirin alone.

Publication bias was assessed with funnel plots. Higgins I^2 was calculated for heterogeneity and was considered to be high if the score was ≥50%.[21,22] Analyses were carried out with Review Manager software (version 5.3; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark).

FIGURE 1
Selection of the included articles



Selection tree for selection of included articles.

PE, preeclampsia.

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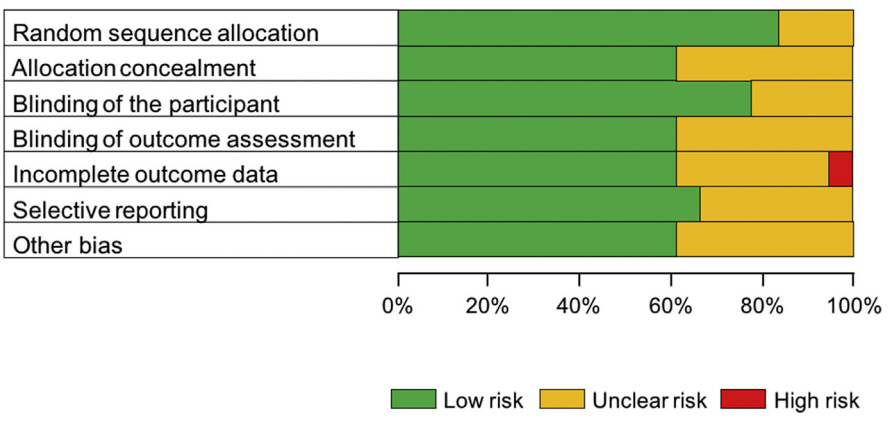
Results

The literature search identified 7143 citations: 161 were reviewed, and 20 trials on a combined total of 12,585 participants met the inclusion criteria (Table 1; Figure 1).[12,15,23-41] In 2 of the included trials, the data on onset of therapy (≤16 and >16 weeks of gestation) were not included in the original publications, but they were provided by

FIGURE 2
Risk of bias graph



Assessment of risk of bias in studies that were included according to the Cochrane handbook.

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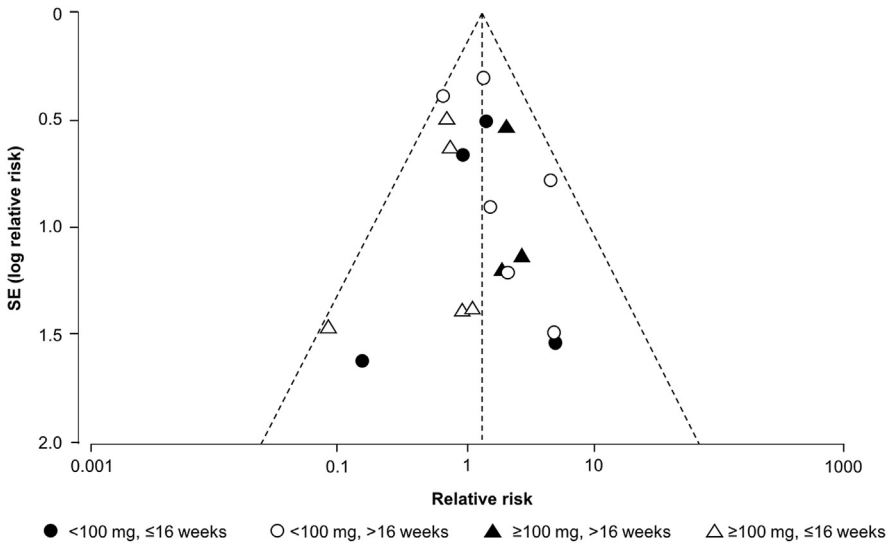
FIGURE 3
Funnel plot on the effect of aspirin on placental abruption or antepartum hemorrhage



Funnel plot to evaluate the presence of publication bias.

SE, standard error.

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the authors.[15,27] In 15 of the 20 studies, the reported outcome was placental abruption,[12,15,23,25-28,32,34,35,37-41] and in 5 studies, the outcome was antepartum hemorrhage.[24,29-31,36]

All but 1 of the included studies were considered to be of good or unclear quality; 1 study was considered at high risk of bias[40] because, in 20% of cases, there was loss to follow-up evaluation (Figure 2). The heterogeneity between the studies was low (I^2=0−29%). Although the distribution of studies in the funnel plots appears to be good, the small number of studies cannot exclude the possibility of publication bias (Figure 3).

In the case of aspirin at a daily dose of <100 mg (Table 2; Figure 4), there was no significant effect on risk of placental abruption or antepartum hemorrhage, irrespective of the gestational age at onset of treatment, and no significant difference between the subgroup with onset at ≤16 weeks and those with onset at >16 weeks (*P*=.72).

In the case of aspirin at a daily dose of ≥100 mg (Table 2; Figure 5), onset of therapy at ≤16 weeks of gestation was associated with a nonsignificant reduction in the risk of placental abruption or antepartum hemorrhage (RR, 0.62; 95% CI, 0.31−1.26), whereas onset at >16 weeks of gestation was associated with a nonsignificant increase in the risk of placental abruption or antepartum hemorrhage (RR, 2.08; 95% CI, 0.86−5.06); the subgroup difference was significant (*P*=.04). After we excluded the study in which dipyridamole was used,[25] the same trends were observed (aspirin ≥100 mg per day; ≤16 weeks: RR, 0.71; 95% CI, 0.34−1.47; vs aspirin ≥100 mg per day; >16 weeks: RR, 2.08; 95% CI, 0.86−5.06), but the difference between subgroups was not significant (*P*=.07).

Comment

Principal findings of this study

The findings of this study suggest that aspirin at <100 mg per day does not influence the risk of placental abruption or antepartum hemorrhage, irrespective of the gestational age at onset of therapy. However, in the case of aspirin at ≥100 mg per day, we observed a significant difference in the risk of placental abruption or antepartum hemorrhage between women who started the treatment at ≤16 weeks of gestation and those who started at >16 weeks, with a nonsignificant

TABLE 2
Risk of placental abruption or antepartum hemorrhage according to dose of aspirin and gestational age at onset of treatment

Dosage/onset	Trials	Participants	Random effect, relative risk (95% confidence interval)	*P* value	I^2, %	*P* value (difference between subgroups)
<100 Mg	11	9461	1.20 (0.79−1.81)	.39	9	.72
≤16 Wk	4	1673	1.11 (0.52−2.36)	.79	0	
>16 Wk	9	7788	1.32 (0.73−2.39)	.35	29	
≥100 Mg	10	3147	0.99 (0.57−1.73)	.98	0	.04[a]
≤16 Wk	6	2318	0.62 (0.31−1.26)	.19	0	
>16 Wk	4	829	2.08 (0.86−5.06)	.11	0	

[a] Significant at <.05.

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tendency of benefit for the former and harm for the latter.

Limitations of the study

Data for placental abruption or antepartum hemorrhage in relation to dosage and timing of aspirin were reported in only 20 of the 65 trials that examined the effect of aspirin on the prevention of preeclampsia; consequently, in our meta-analysis, there is a potential risk of selection bias. Results are also limited by the low prevalence of placental abruption or antepartum hemorrhage, which was reported in only 173 of the 11,585 participants (1.5%) in the included trials.

Placental abruption or antepartum hemorrhage was a secondary outcome in all the included trials, and, although aspirin did not have a significant effect on the risk of placental abruption or antepartum hemorrhage, none of the trials was powered adequately for such an outcome. Our approach for further subdivision of the study population according to dose and timing of onset of therapy could have resulted in even greater reduction of power to demonstrate significant effects. However, in the context of aspirin use for the prevention of preeclampsia, our previous subgroup analyses had demonstrated the importance of subdividing the population according to both the dose and timing of onset of therapy.[10,11]

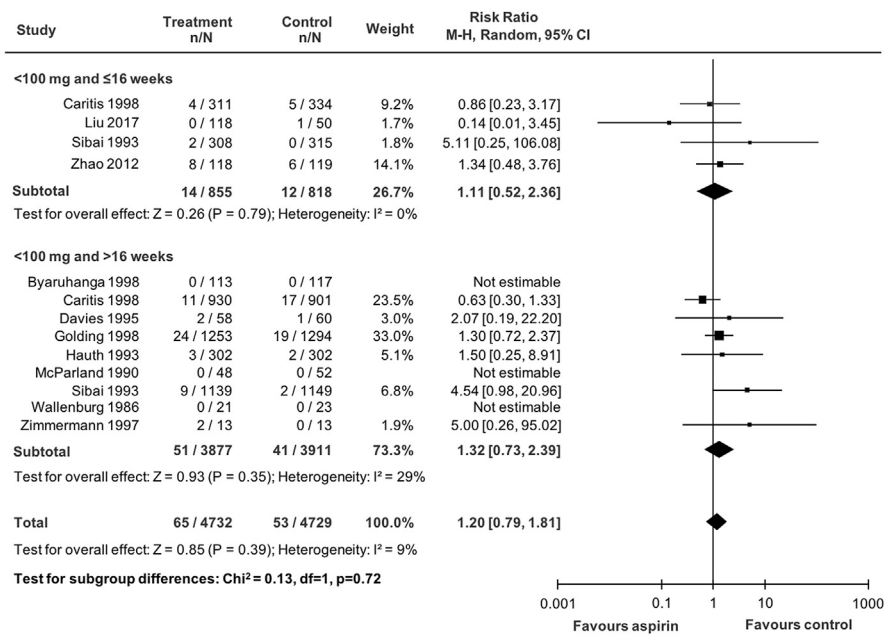
In the ASPRE trial, the beneficial effect of aspirin in the prevention of preterm preeclampsia appeared to depend on compliance.[42] In our meta-analysis, it was not possible to evaluate the effect of compliance on the risk of placental abruption or antepartum hemorrhage because, in 8 of the 20 trials, compliance was not reported and because 10 of the remaining 12 trials did not report results separately according to compliance.

Clinical implications of the study

National guidelines recommend that women who were identified by their demographic characteristics and medical history as being at high-risk for development of preeclampsia should be advised to take aspirin at a daily dose that varies between 75 and 80 mg, depending on the country.[16,43,44] However, on the basis of the results of our meta-analyses that aspirin is effective in reducing the risk of preeclampsia only if the daily dose is ≥100 mg and with the results of the ASPRE trial,[9,10,12] it is likely that the recommended daily dose of aspirin will become 150 mg. It would then be important to emphasize that, although such therapy is beneficial if treatment is initiated before 16 weeks of gestation, it may increase the risk of abruption or antepartum hemorrhage without reducing the risk of preeclampsia if treatment is initiated after 16 weeks of gestation.

Placental abruption has been considered, together with preeclampsia, to be the consequence of impaired placentation.[45,46] In this respect, aspirin administration in women at increased risk of impaired placentation actually may lead to a reduction in the risk of abruption, as it does for preeclampsia, provided the dose is ≥100 mg and the gestational age at onset of the treatment is ≤16 weeks of gestation. Placentation is completed mostly by 18 weeks of gestation;[19] if the mechanism whereby aspirin reduces the risk of preeclampsia is mediated by improving placentation, it should not be surprising that aspirin therapy that is initiated at >16 weeks of gestation is not beneficial. In cases of persistent abnormal placentation, the use of aspirin at ≥100 mg per day, through its antiplatelet proprieties, could increase the risk of hemorrhage and abruption. It is therefore doubtful that universal use of aspirin is beneficial, and it may actually be harmful.[47]

FIGURE 4
Forest plot on the effect of aspirin at a daily dose of <100 mg on placental abruption or antepartum hemorrhage

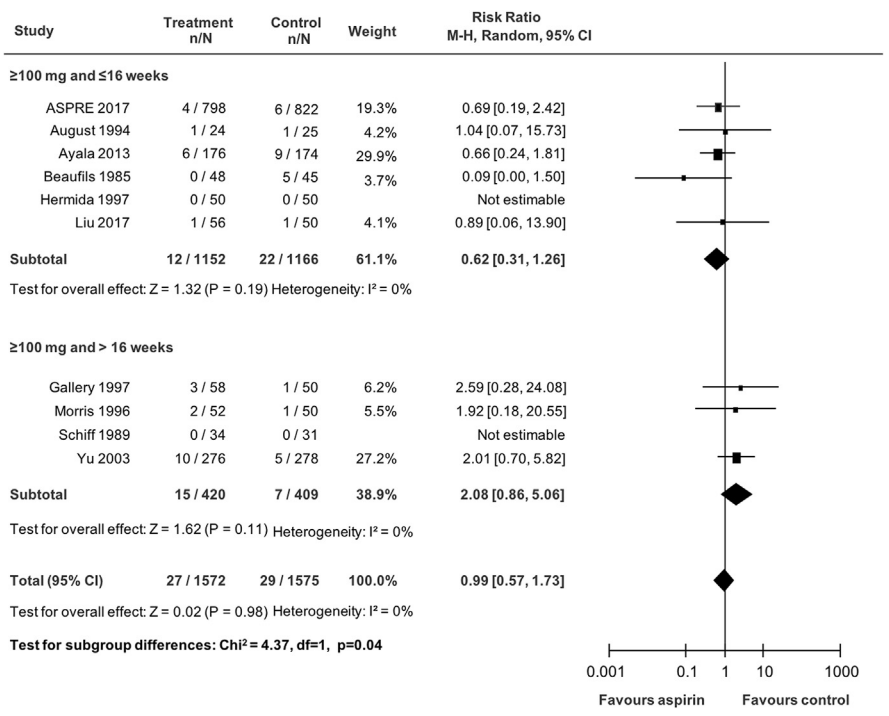


Forest plot of effect of low-dose aspirin at a daily dose of <100 mg on risk of placental abruption or antepartum hemorrhage, subgrouped by gestational age at initiation of treatment. Only the first author of each study is given. Cochrane forest plots are commonly used in meta-analyses and details about diamond, size of square, etc. are not typically reported, including in *AJOG*.

CI, confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel.

Roberge. Aspirin use and placental abruption. Am J Obstet Gynecol 2018.

FIGURE 5
Forest plot on the effect of aspirin at a daily dose of ≥100 mg on placental abruption or antepartum hemorrhage.



Forest plot of effect of low-dose aspirin at a daily dose of ≥100 mg on risk of placental abruption or antepartum hemorrhage, subgrouped by gestational age at initiation of treatment. Only the first author of each study is given. Cochrane forest plot are commonly used in meta-analyses and details about diamond, size of square, etc. are not typically reported, including in *AJOG*.

CI, confidence interval; *df*, degrees of freedom; *M-H*, Mantel-Haenszel.

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Conclusion

This study demonstrated that the prophylactic use of aspirin at a daily dose of ≥100 mg may have different effects on the risk of placental abruption or antepartum hemorrhage, depending on the gestational age at onset of treatment; if the onset of treatment is at ≤16 weeks of gestation, rather than >16 weeks, the risk is decreased. ■

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