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.

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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