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

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Condensation

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

Short version of article title: Aspirin use and placental abruption.

ABSTRACT

Background: 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 examining the effect of aspirin in relation to gestational age at onset of therapy and dose 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 dose of the drug is ≥ 100 mg.

Objective: 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.

Study design: We performed a systematic review and meta-analysis of randomized controlled trials that evaluated the prophylactic effect of aspirin during pregnancy using PubMed, Cinhal, Embase, Web of Science and Cochrane library from 1985 to September 2017. Relative risks (RR) of placental abruption or antepartum hemorrhage with their 95% confidence intervals (95% CI) were calculated using 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) and compared using 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' gestation (RR 1.11, 95% CI 0.52 to 2.36) or at >16 weeks (RR 1.32, 95% CI 0.73 to 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 (RR 0.62, 95% CI 0.31 to 1.26), or at >16 weeks (RR 2.08 95% CI 0.86 to 5.06), but the difference between the subgroups was significant ($p=0.04$).

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

Keywords: Pregnancy, aspirin, placental abruption, preeclampsia

Introduction

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.¹⁻⁶ Numerous randomized controlled trials have investigated the potential value of prophylactic use of low-dose aspirin in prevention of preeclampsia and an early meta-analysis reported that the risk of preeclampsia and small for gestational age is reduced by about 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) or daily dose of aspirin (≤75 vs. >75 mg).⁸ In contrast, other meta-analyses reported that use of aspirin has a major effect on both preeclampsia and small for gestational age with a greater than 50% reduction in risk, provided 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 multicentre randomized trial (ASPREE) which demonstrated that aspirin (150 mg per day) from 11-14 weeks of gestation to 36 weeks was associated with a greater than 60% reduction in risk of preterm preeclampsia.¹²

Placental abruption is a major cause of perinatal mortality and maternal 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 is 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 including studies that recruited women for the prevention of preeclampsia using aspirin. Treatment includes aspirin or dipyridamole compared to placebo or no treatment. Studies will be 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 using 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 revised by two independent reviewers (SR, EB). All eligible studies were then fully evaluated by the same reviewers, and disagreements were resolved by the opinion of a third party (KN). Studies reporting placental abruption or antepartum hemorrhage were included in the final analysis.

Quality evaluation

The quality of this meta-analysis was assessed by PRISMA tool and the quality of each included trial was assessed by the Cochrane Handbook.^{17,18}

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) and compared using mixed regression weighted by the size of each study.^{10,19} Because there are only two 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-analysis reported that aspirin is effective in prevention of preeclampsia only if the onset of therapy is ≤ 16 weeks of gestation and 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), using random effects (DerSimonian and Laird).²⁰ Sensitivity analyses were performed to evaluate the effect of aspirin alone.

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

Results

The literature search identified 7,143 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 kindly provided by 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 antepartum hemorrhage.^{24,29-31,36}

All but one of the included studies were considered to be of good or unclear quality; one study was considered at high risk of bias⁴⁰ because in 20% of cases there was loss to follow-up (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 there was no significant difference between the subgroup with onset at ≤ 16 weeks and those with onset at >16 weeks ($p=0.72$).

In the case of aspirin at a daily dose of ≥ 100 mg (Table 2, Figure 5), onset of therapy at ≤ 16 weeks' gestation was associated with a non-significant reduction in the risk of placental abruption or antepartum hemorrhage (RR 0.62, 95% CI 0.31 to 1.26), whereas onset at >16 weeks was associated with a non-significant increase in the risk of placental abruption or antepartum hemorrhage (RR 2.08 95% CI 0.86 to 5.06) and the subgroup difference was significant ($p=0.04$). After excluding 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 to 1.47; vs aspirin ≥ 100 mg per day; >16 weeks: RR 2.08 95% CI 0.86 to 5.06), but the difference between subgroups was not significant ($p=0.07$).

Discussion

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 starting the treatment at ≤ 16 weeks of gestation and those starting at >16 weeks, with a non-significant 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 examining the effect of aspirin on 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 (1.5%) of the 11,585 participants 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 adequately powered for such 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 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 eight of the 20 trials compliance was not reported and 10 of the remaining 12 trials did not report results separately according to compliance.

Clinical implications of the study

National guidelines recommend that women, 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 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 emphasise that while such therapy is beneficial if treatment is initiated before 16 weeks, it may increase the risk of abruption or antepartum hemorrhage without reducing the risk of preeclampsia if treatment is initiated after 16 weeks.

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 may actually 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. Placentation is mostly completed 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 initiated after 16 weeks is not beneficial. In cases of persistent abnormal placentation, use of aspirin at ≥ 100 mg per day could through its antiplatelet properties 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

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, rather than > 16 weeks, the risk is decreased.

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Table 1. Characteristics of trials included in the meta-analysis.

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

* Includes history of chronic hypertension, cardiovascular or endocrine disease, previous pregnancy hypertension or fetal growth restriction.

** Combination of maternal risk factors, serum placental growth factor and pregnancy associated plasma protein-A, mean arterial pressure and uterine artery pulsatility index.

† Reported as % of women taking a certain % of the total number of prescribed pills.

§ With dipyridamole 300 mg.

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

Onset / dose	Trials	Participants	Relative risk (95% CI) (Random effect)	P value	I ²	Difference between subgroups (p value)
<100mg	11	9461	1.20 (0.79, 1.81)	0.39	9%	
≤16 weeks	4	1673	1.11 (0.52, 2.36)	0.79	0%	0.72
>16 weeks	9	7788	1.32 (0.73, 2.39)	0.35	29%	
≥100mg	10	3147	0.99 (0.57, 1.73)	0.98	0%	
≤16 weeks	6	2318	0.62 (0.31, 1.26)	0.19	0%	0.04*
>16 weeks	4	829	2.08 (0.86, 5.06)	0.11	0%	

CI = Confidence Interval, *significant $p < 0.05$

Figure legends

Figure 1: Selection of the included articles.

Figure 2: Assessment of risk of bias in studies included following Cochrane handbook.

Figure 3: Funnel plot on the effect of aspirin on placental abruption or antepartum hemorrhage.

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

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

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