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REVIEW

Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation

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ABSTRACT

Meta-analysis of randomized studies on the use of low-dose aspirin in women at high risk of preeclampsia (PE) has demonstrated that if treatment is initiated at ≤16 weeks' gestation, there is significant reduction in the risk of PE [relative risk (RR) 0.47, 95% confidence interval (CI) 0.36–0.62], fetal growth restriction (RR 0.46, 95% CI 0.33–0.64), preterm birth (RR 0.35, 95% CI 0.22–0.57) and perinatal death (RR 0.41, 95% CI 0.19–0.92), whereas the effect of treatment after 16 weeks is substantially less (RR 0.78, 95% CI 0.61–0.99; RR 0.98, 95% CI 0.88–1.08; RR 0.90, 95% CI 0.83–0.97; and RR 0.93, 95% CI 0.73–1.19, respectively). Moreover, the decrease in the risk of PE from early onset treatment seems to be related to the dose of aspirin, and a dose of >80 mg daily should be considered for optimal benefits. © 2014 John Wiley & Sons, Ltd.

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INTRODUCTION

The use of low-dose aspirin for prevention of preeclampsia (PE) has been an important research question for several decades. Now, several national professional bodies recommend that high-risk pregnancies should be treated with low-dose aspirin starting from around 12 weeks' gestation.[1–3] This review examines the evidence on the effect of prophylactic use of aspirin for the prevention of PE and reports on the timing of onset of treatment, the optimal dose of aspirin and the possible pathophysiological mechanism of action.

PREVENTION OF COMPLICATIONS OF IMPAIRED PLACENTATION BY LOW-DOSE ASPIRIN

Preeclampsia

In 1978, Goodlin reported the case of a woman with previous gestational hypertension, thrombocytopenia and preterm birth who benefit from aspirin and heparin treatment started at 15 weeks' gestation in the next pregnancy.[4] In 1979, Crandon and Isherwood observed that nulliparous women who had taken aspirin regularly during pregnancy were less likely to have PE than women who did not.[5] In 1985, Beaufils *et al.* published the first randomized trial in pregnant women where 150 mg of aspirin and 300 mg of dipyridamole were given daily from 3 months' gestation onwards to women with a history of risk factors for PE.[6] They observed a significant reduction in the risk of PE, fetal growth restriction (FGR) and stillbirth.

Subsequently, more than 50 trials have been carried out throughout the world.[7] However, most of these trials, including the six largest ones, randomized the participants mainly in the second trimester of pregnancy and used much lower doses of aspirin than the study of Beaufils.[6] None of the trials reported that use of aspirin was associated with a significant reduction in PE. In 2007, Askie *et al.* published an individual patients meta-analysis showing that the administration of low-dose aspirin in high-risk pregnancies was associated with a decrease in the risk of PE by approximately 10%.[8] In 2014, Henderson *et al.* published a meta-analysis showing a decrease in the risk of PE by approximately 25%.[9]

The most likely explanation for late onset of treatment with aspirin is the traditional approach to pregnancy care, where the first hospital visit was delayed until 16 weeks' gestation or later.[10,11] However, examination of the randomized trials of low-dose aspirin in women at high-risk for PE suggests that the effectiveness is strongly related to the gestational age at the onset of treatment.[12] Meta-analysis of randomized trials on the use of low-dose aspirin in women at high-risk for PE demonstrated that when treatment was initiated at ≤16 weeks' gestation, the risk of PE was reduced by about 50% [relative risk (RR) 0.47, 95% confidence interval (CI) 0.36–0.62]; whereas with treatment after 16 weeks, there was only a 20% reduction in the risk of PE (RR 0.78, 95% CI 0.61–0.99).[13] Table 1 summarizes the randomized trials that evaluated the use of low-dose aspirin started at ≤16 weeks in the prevention of PE and the global effect of the meta-analysis is shown in Figure 1.[6,14–25]

Table 1 **Characteristics of randomized trials that evaluated the impact of low-dose aspirin initiated at ≤16 weeks' gestation on the risk of preeclampsia**

Authors, year			Intervention		
≤16 weeks	*N*	Inclusion criteria	Aspirin	Controls	Onset (week)
August 1994	54	History risk factors[a]	100 mg	Placebo	13–15
Azar 1990	91	History risk factors[a]	100 mg[b]	No treatment	16
Bakhti 2011	84	Nulliparity	100 mg	No treatment	8–10
Beaufils 1985	102	History risk factors[a]	150 mg[b]	No treatment	14
Benigni 1989	33	History risk factors[a]	60 mg	Placebo	12
Ebrashy 2005	139	Abnormal uterine artery Doppler plus history risk factors[a]	75 mg	No treatment	14–16
Hermida 1997	107	History risk factors[a]	100 mg	Placebo	12–16
Hermida 1999	350	History risk factors[a]	100 mg	Placebo	12–16
Mesdaghinia 2011	80	Abnormal uterine artery Doppler	80 mg	No treatment	12–16
Michael 1992	110	Hypertension with history risk factors[a]	100 mg	Placebo	16
Tulppala 1997	66	Previous consecutive miscarriage	50 mg	Placebo	~7
Vainio 2002	90	Abnormal uterine artery Doppler & history risk factors[a]	0.5 mg/kg	Placebo	12–14
Villa 2010	121	Abnormal uterine artery Doppler & history risk factors[a]	100 mg	Placebo	12–14

[a]Includes history of chronic hypertension, cardiovascular or endocrine disease, previous pregnancy hypertension or fetal growth restriction.
[b]with Dipyridamole 300 mg daily.

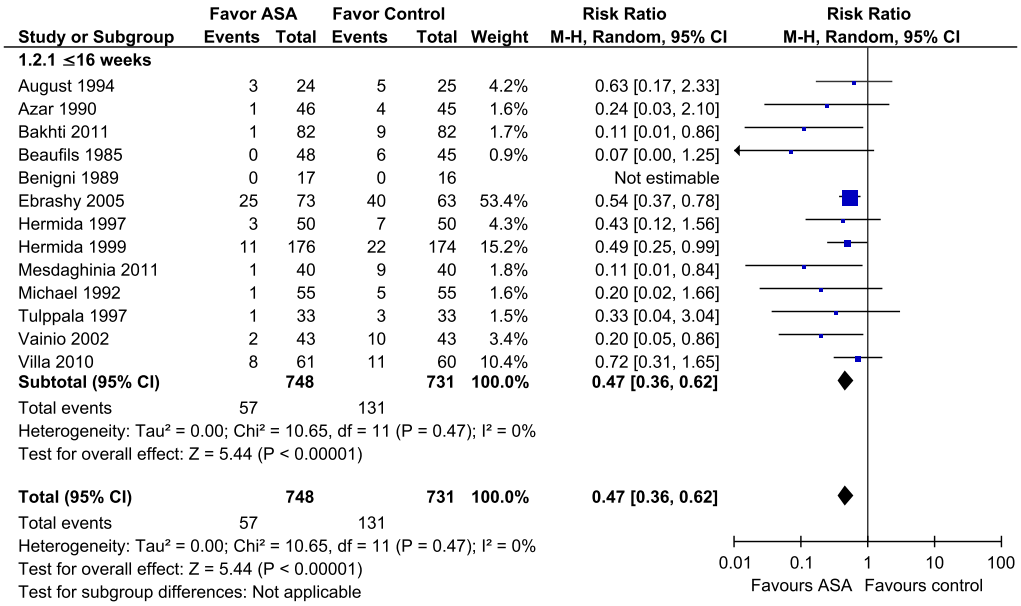

Figure 1 **Forest plot of randomized trials that evaluated the impact of low-dose aspirin initiated at <16 weeks' gestation on the risk of preeclampsia**

Preterm and severe preeclampsia compared with term and mild preeclampsia

Subgroup analysis of the data on the effect of low-dose aspirin started at or before 16 weeks' gestation in PE demonstrated that the treatment was particularly effective in preventing early disease requiring delivery before term, rather than at term (RR 0.11, 95% CI 0.04–0.33 vs RR 0.98, 95% CI 0.42–2.33) and in severe, rather than mild PE (RR 0.22, 95% CI 0.08–0.57 vs RR 0.81, 95% CI 0.33–1.96).[26,27]

These findings are in agreement with the results of the CLASP trial in which 9364 high-risk women were randomized to receive low-dose aspirin started between 12 and 32 weeks of gestation until delivery.[28] They found that the magnitude of reduction in the prevalence of PE was inversely related to the gestational age at delivery for PE. However, the data were not stratified according to gestational age at entry.

The greater effectiveness of low-dose aspirin in the prevention of the preterm and severe forms of PE, compared with the term and mild ones, can be explained by the fact that the prevalence of deep placental lesions in women with PE is inversely related to the gestational age at delivery.[29,30]

Perinatal death

A high proportion of stillbirths can be attributed to impaired placentation. In a study of 65 819 singleton pregnancies, in which the uterine artery PI was measured at 20–24 weeks' gestation, there were 306 (0.46%) stillbirths. In 52% of stillbirths, there were PE, placental abruption and/or birthweight below the tenth percentile [small for gestational age (SGA)], and these are likely to have been the consequence of impaired placentation. In the stillbirths, the uterine artery PI was significantly higher than in live births and was inversely associated with gestational age at delivery. The uterine artery PI was above the 90th percentile in 81% of stillbirths with PE, abruption and/or SGA delivering at <32 weeks' gestation, in 42% at 33–36 weeks and in 34% at ≥37 weeks.[31]

Meta-analysis of randomized trials on the use of low-dose aspirin in women at high-risk for PE demonstrated that when treatment was initiated at ≤16 weeks' gestation, the risk of perinatal death was reduced by about 60% (RR 0.41, 95% CI 0.19–0.92); whereas with treatment after 16 weeks, there was no significant effect (RR 0.93, 95% CI 0.73–1.19).[13] This finding is compatible with the hypothesis that aspirin improves the transformation of uterine spiral arteries and decreases disorders of deep placentation, which is a major cause of perinatal death.

Fetal growth restriction

Birth of SGA neonates is a heterogeneous condition that includes constitutionally small fetuses, at no or minimally increased risk of perinatal death and handicap, and growth-restricted fetuses (FGR) due to impaired placentation, genetic disease or environmental damage.

Meta-analysis of randomized trials on the use of low-dose aspirin in women at high-risk for PE demonstrated that when treatment was initiated at ≤16 weeks' gestation, the risk of FGR was reduced by about 50% (RR 0.46, 95% CI 0.33–0.64); whereas with treatment after 16 weeks, there was no significant effect (RR 0.98, 95% CI 0.88–1.08).[13]

Preterm birth

Meta-analysis of randomized trials on the use of low-dose aspirin in women at high-risk for PE demonstrated that when treatment was initiated at ≤16 weeks' gestation, the risk of preterm birth at <37 weeks was reduced by more than 60% (RR 0.35, 95% CI 0.22–0.57); whereas with treatment after 16 weeks, there was only a small effect (RR 0.90, 95% CI 0.83–0.97).[13]

The beneficial effects of low-dose aspirin on preterm birth may be partly due to the reduction of clinically indicated preterm delivery because of severe PE and/or FGR. However, the effect may also be the consequence of better placental implantation, because defective placentation plays a role in the genesis of spontaneous preterm birth and premature rupture of membranes as well.[31,33] Unfortunately, most randomized trials that evaluated the impact of low-dose aspirin did not report specifically on the risk of spontaneous preterm birth or premature rupture of membranes. However, the very low overall preterm birth risk reported in women who were taking low-dose aspirin (4.8% compared with 13.4% in the controls) in these trials indicates that the risk of spontaneous preterm birth was low as well.[13,34] Because intra-amniotic and systemic inflammation has been strongly linked with spontaneous preterm birth, it is possible that the beneficial effect of low-dose aspirin on preterm birth could be due to inhibition of prostaglandin synthesis and its anti-inflammatory properties.[34,35]

Placental abruption

It is uncertain whether low-dose aspirin started at ≤16 weeks' gestation affects the risk of placental abruption. Although our meta-analysis did not demonstrate a significant effect of aspirin (RR 0.55, 95% CI 0.21–1.47), this is likely to be due to the small number of cases examined.[13]

Preliminary results that suggested a potential increased risk of placental abruption with low-dose aspirin are likely to be incidental or related to the fact that aspirin was started late in gestation.[36] The relative risk of placental abruption with low-dose aspirin started after 16 weeks is 1.56 (95% CI 0.96–2.55).[12,13]

Summary

In women at high-risk of PE, the prophylactic use of low-dose aspirin started at 8–16 weeks' gestation is associated with a 50% reduction in the overall risk of PE and about 80% reduction in preterm and severe PE, 50% reduction in FGR, 60% reduction in preterm birth and 60% reduction in perinatal death. There are insufficient data concerning the possible association between aspirin use and placental abruption.

MECHANISM OF ACTION OF ASPIRIN IN IMPROVING PLACENTATION

In normal pregnancies, trophoblastic invasion of the myometrium and transformation of uterine spiral arteries from narrow muscular vessels to wide non-muscular channels usually start at around 8 weeks' gestation and are typically completed by 16–20 weeks.[37] This physiologic process of placentation is impaired in PE, particularly in preterm PE, FGR and to a lesser extent in spontaneous preterm birth. Studies of placental bed biopsies reported that in women with PE, only 0–40% of uterine spiral arteries are completely transformed, compared with 80–100% in women with normal pregnancies.[38]

There is indirect evidence that low-dose aspirin could lead to improvement in trophoblastic invasion of the uterine spiral arteries. An *in vitro* study evaluated the effect of low-dose aspirin on trophoblast cell line and demonstrated increase in production of placental growth factor (PlGF), decrease in apoptosis and improvement of the cytokines profile.[39] A randomized trial and a large observational study reported that the prophylactic use of low-dose aspirin started in the first trimester was associated with an improvement in uterine artery pulsatility index (PI) when evaluated at 20–22 weeks of gestation.[40,41]

OPTIMAL DOSE OF ASPIRIN

Aspirin is considered at low dose when taken at less than 300 mg/day. In 1979, Masotti *et al.* demonstrated that aspirin, at a dose corresponding to 175 mg for a woman weighing 50 kg, was associated with inhibition of platelet aggregation with only a slight inhibition of prostacyclin production.[42] The

authors concluded that inhibition of platelet cyclooxygenase occurs with smaller doses of aspirin and lasts longer than the inhibition of vessel wall cyclooxygenase. Similar observations were made by Walsh *et al.* who examined ten women at high-risk of PE that were treated with 81 mg of aspirin daily from 9 weeks' gestation and reported selective inhibition of thromboxane without affecting prostacyclin levels.[43]

In the first randomized study on prevention of PE, the dose of aspirin used was 150 mg/day,[6] which is compatible with the results of basic research;[3,4,42] in most subsequent trials, less than 75 mg/day was used. Nevertheless, there is some evidence that the effects of aspirin may be dose dependent. Vainio *et al.* found a dose–response effect between 0.5 and 2.0 mg/kg, but their study did not have the power to evaluate the effect of aspirin on pregnancy outcomes.[24] Walsh *et al.* observed a dose-dependent effect of aspirin on the selective inhibition of thromboxane and prostacyclin and showed that doses of 50–60 mg daily are insufficient to inhibit placental thromboxane.[43,44] Such dose-dependent effect has also been observed in studies utilizing platelet function as a method of assessing responsiveness to aspirin. A study evaluating the use of low-dose aspirin in women at high-risk of adverse pregnancy outcomes, including PE and FGR, reported that the outcome was better in women who had a prolongation of the bleeding time, compared with those who were 'resistant' to the treatment and had a normal bleeding time.[45] Another study in women with antiphospholipid syndrome receiving 75 mg of aspirin daily reported that aspirin-resistant women were more likely to develop adverse pregnancy outcomes than those who were not resistant.[46] A study evaluating aspirin resistance in pregnant women reported that the incidence was approximately 30%, 10% and 5% when the dose of aspirin was 81, 121 and 162 mg, respectively.[47,48] Another study, in women who were resistant to 81 mg of aspirin, reported that an increase in the dose to 162 mg was associated with a lower rate of severe PE than in those who continued with 81 mg.[49] Unfortunately, most studies did not control for maternal weight, and the data are very limited regarding factors related to aspirin resistance in pregnant women. Diabetes and obesity are two risk factors for aspirin resistance, and it is likely that obese women would require higher dosages of aspirin.[50,51] Further research is required in this field.

Our recent meta-analysis did not show a significant effect of aspirin dosage (≤80 vs ≥100 mg) for the prevention of PE, but the analysis was limited by the size of the included studies.[13] Henderson *et al.* observed that the estimated risk reduction was greater in studies using more than 75 mg of aspirin (RR 0.58, CI 0.36–0.95) than in those using less than 75 mg (RR 0.85, CI 0.68–1.05), but the difference in the effect size was not significant.[9] However, a recent subgroup analysis of the participants recruited before 16 weeks in the large trial from Caritis *et al.* was published.[52] They observed no significant decrease of PE in high-risk women when 60 mg of aspirin daily was used. An ongoing randomized trial is comparing 80 versus 160 mg daily in pregnant women with a prior history of PE.

TIME OF THE DAY FOR ASPIRIN INTAKE

Data from three randomized trials strongly suggest that low-dose aspirin administered at bedtime, compared with taking the drug at awakening, is associated with a significant decrease in systolic and diastolic blood pressure throughout pregnancy and significant decrease in the risk of PE, FGR and preterm birth.[19,20,53]

Ayala *et al.* detailed the abundant literature on the differential circadian effect of low-dose aspirin.[20] Although this phenomenon has been demonstrated with the use of 100 mg aspirin taken daily, it could be another explanation for the heterogeneity of the results from the trials that used dosage below 80 mg. Most trials did not specify whether or not a specific time of the day was recommended to the participants. On the basis of the actual available evidence, we believe that we should recommend that low-dose aspirin should be taken at bedtime.

ADMINISTRATION OF LOW-DOSE ASPIRIN BEFORE CONCEPTION

We did not find randomized trials that compared the initiation of low-dose aspirin before and after conception. However, several trials examined the potential value of low-dose aspirin in the prevention of miscarriage in women undergoing *in vitro* fertilization. In most of these trials, aspirin was given from several weeks before pregnancy and stopped at the diagnosis of pregnancy or during the first trimester. A conventional meta-analysis and an individual patient data meta-analysis did not demonstrate a beneficial effect of aspirin in the odds of clinical pregnancy [odds ratio (OR) 1.07, 95% CI 0.81–1.41 and OR 0.86, 95% CI 0.69–1.15, respectively] or hypertensive pregnancy complications (OR 0.62, 95%CI 0.22–1.7).[54,55] Two trials randomized women undergoing *in vitro* fertilization to receive low-dose aspirin or placebo from before pregnancy to delivery; their results were inconclusive regarding the benefit of aspirin for the prevention of hypertensive disorders of pregnancy (RR 0.85, 95% CI 0.36–1.98 and RR 0.13, 95% CI 0.02–1.01, respectively).[56,57]

Another recent randomized trial reported that treatment with aspirin alone or aspirin combined with low-molecular-weight heparin, in women with recurrent miscarriage who were attempting to conceive or were less than 6 weeks pregnant at randomization, did not significantly reduce the risk of miscarriage or adverse pregnancy outcomes.[58]

SELECTION OF PREGNANCIES THAT COULD BENEFIT FROM LOW-DOSE ASPIRIN

In the randomized trials investigating the possible benefit of low-dose aspirin, the main method of selecting the study populations was a history of previous PE or medical disorders, including chronic hypertension, diabetes mellitus, chronic renal disease, systemic lupus erythematosus and antiphospholipid syndrome. Although these factors are associated with a high risk of developing PE and other impaired-placentation-related adverse pregnancy outcomes, the sensitivity of this approach is poor, with estimated detection rate of PE or preterm PE of about 40% at false positive rate of 10%.[59]

A better method of early identification of the high-risk group at high risk of preterm PE is by combining maternal factors with mean arterial pressure, uterine artery PI, serum PAPP-A and serum PLGF at 11–13 weeks' gestation. The estimated detection rate of preterm PE by such combined test is more than 75% at false positive rate of 10%.[59]

SAFETY OF ASPIRIN FOR THE FETUS

First trimester

The safety of first-trimester use of low-dose aspirin has been demonstrated in large cohort and case–control studies that reported that the drug is not associated with increase in risk of congenital heart defects or other structural or developmental anomalies.[60–63] Moreover, a very large case–control study did not find a significant association between aspirin use and miscarriage (adjusted OR ranging from 0.64 to 0.92 with 95% CI 0.34–1.38). However, in the absence of large randomized trials that confirm the safety and demonstrate benefit from the use of low-dose aspirin started before conception or in very early pregnancy, it would be advisable to postpone treatment until 8 weeks' gestation, when closure of the neural tube and major development of the heart and great arteries have been completed.[64]

Third trimester

Potential risks associated with aspirin therapy during the third trimester include premature closure of the ductus arteriosus and hemorrhagic complications. Aspirin readily crosses the placenta, and given near term, higher concentrations are found in the neonate than in the mother.[65,66]

A randomized study of 40 women at a median gestational age of 37 weeks demonstrated that the daily administration of 60–80 mg of aspirin selectively inhibits maternal platelet cyclooxygenase without affecting neonatal platelet aggregation, pulmonary arterial pressure and ductus arteriosus patency.[67] Prospective and case–control studies did not find an association between daily consumption of 60–150 mg of aspirin during the third trimester and prenatal closure of the ductus arteriosus.[68–70]

In regard to potential fetal hemorrhagic complications, the inhibition of platelet thromboxane A2 formation has been observed in the neonates of women taking 100 mg of aspirin daily.[71] At doses of 325–650 mg daily during the week before delivery, aspirin may affect the clotting ability of the newborn, and it has been suggested that aspirin is best avoided in the last month of pregnancy.[72,73] A meta-analysis including more than 26 000 women randomized to low-dose (60–150 mg) aspirin versus placebo or no treatment demonstrated that the use of aspirin during pregnancy was not associated with an increase in intra-ventricular hemorrhage or other neonatal bleeding, but most women received 100 mg or less.[7] Most of the beneficial effects of aspirin are attained by 36 weeks, and a large proportion of women would probably require dosage greater than 75–100 mg; consequently, administration of low-dose aspirin should be stopped at 36 weeks to avoid any potential adverse neonatal effects.

SAFETY OF ASPIRIN FOR THE MOTHER

A large population-based cohort study, involving 186 425 individuals being treated with low-dose aspirin and 186 425 matched controls without aspirin use, reported that aspirin use was significantly associated with an increased risk of major gastrointestinal or cerebral bleeding episodes (5.58 vs 3.60 per 1000 person-years.[74] Although such risk is small, we believe that prophylactic administration of aspirin should not be offered routinely, but such therapy should be reserved for women at high risk of deep-placentation-related disorders.

CONCLUSION

There is good evidence that in women at high risk for PE, it is safe to take 80–150 mg of aspirin daily at bedtime; the treatment can be initiated at 8–16 weeks' gestation and continued into the third trimester of pregnancy. Such treatment decreases the risk of the severe and preterm forms of PE, as well as the risk of FGR, preterm birth and perinatal death.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Low-dose aspirin taken during pregnancy is associated with a small but significant reduction in the risk of preeclampsia.

WHAT DOES THIS STUDY ADD?

- The risk of preeclampsia and other impaired-placentation-mediated complications is reduced by half when treatment with low-dose aspirin is started at 8–16 weeks' gestation.
- The dose of 80 mg of low-dose aspirin daily or less may be insufficient for the prevention of preeclampsia in some women.
- The beneficial effect of low-dose aspirin is optimized when the drug is taken at bedtime.

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