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FAST TRACK

Low-dose aspirin helps prevent preeclampsia in higher-risk patients

Does low-dose aspirin reduce preeclampsia and other maternal-fetal complications?

Evidence-based answer

Yes. The use of low-dose aspirin during pregnancy decreases the risk of preeclampsia for women considered at increased risk. The effect is smaller for women without risk factors (strength of recommendation [SOR]: **A**, based on randomized controlled trials [RCTs] and systematic reviews [SRs] of RCTs).

Rates of preterm delivery, perinatal death, and incidence of small-for-gestational age infants are decreased for women treated with low-dose aspirin (SOR: **A**, based on SRs and RCTs). A meta-analysis of RCTs has found no increased rates of harm from low-dose aspirin therapy, including placental abruption or other antepartum bleeding complications (SOR: **A**, based on SRs and RCTs).

Clinical commentary

I prescribe 81 mg/day of aspirin for women with previous severe preeclampsia

Confused about when to use aspirin in pregnancy? You're not alone. Over my 20 years of practice, I have reacted to disparate guidelines ranging from "never use aspirin in pregnancy" to "always use low-dose aspirin." This review helps simplify my clinical practice.

With the benefit of evidence from multiple RCTs over the past 7 years, I now personally use 81 mg of aspirin each day in 2 groups of women: those who had severe preeclampsia in a prior pregnancy, and those who develop signs of preeclampsia or strong risk factors for it before the third trimester in their current pregnancy.

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Evidence summary

Systematic reviews show aspirin lowers rates of preeclampsia

Four SRs published between 2001 and 2007[1–4] and a Cochrane Review updated in 2006[5] have demonstrated that low-dose aspirin helps to prevent preeclampsia, reduction in preterm delivery rates, and decreased perinatal mortality.

The **2001 SR by Duley**[1] included 39 trials and 30,563 patients. Patients were classified either as high-risk (previous severe preeclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease) or moderate-risk (remainder of subjects). Four individual studies (with a combined weight of 27%) did not support aspirin therapy. The largest trial not supporting aspirin therapy included 6275 subjects and had a relative risk of 1.14 (95% CI, 0.94–1.38).

Most studies in this review compared

TABLE

Low-dose aspirin reduces risk of preeclampsia, but how does it affect other maternal and fetal outcomes?

STUDY (YEAR)	DEVELOPMENT OF PREECLAMPSIA	PRETERM DELIVERY	NEONATAL DEATH	SGA OR LOW BIRTH WEIGHT	RISK OF ABRUPTION & BLEEDING
Duley (2001)[1]	*Moderate-risk patients:* 15% reduction *High-risk patients:* 15% reduction NNT=100	8% reduction NNT=72	14% reduction NNT= 250	8% reduction*	Not reported
Coomarasamy (2003)[2]	14% reduction	14% reduction	21% reduction	215-g weight gain in aspirin group	No significant clinical difference in risk (RR=0.98)
Ruano (2005)[3]	*Low-risk patients:* no significant reduction *High-risk patients:* 13% reduction				Not reported
Askie (2007)[4]	10% reduction	10% reduction	9% reduction	10% reduction	No significant clinical difference in risk (RR=0.90–1.15)
Cochrane (2007)[5]	19% reduction NNT=69 (overall), 118 (moderate risk), 18 (high-risk)	7% reduction NNT=83	16% reduction NNT=227	8% reduction*	No significant clinical difference in risk (RR=1.06)

* Borderline for statistical significance (RR=0.92).
SGA, small for gestational age; NNT, number needed to treat; RR, relative risk.

aspirin alone with placebo (28,802 subjects). However, 4 studies either compared combination therapy with aspirin or other thromboprophylaxis therapy (dipyridamole, heparin, or ozagrel). Although there were differences in risk stratification, variable doses of aspirin, and varied gestational age at trial entry, all studies reported an overall 15% reduction of preeclampsia (RR=0.85; 95% CI, 0.78–0.92).

The **2003 SR by Coomarasamy**[2] included 14 trials and 12,416 patients. The study exclusively evaluated high-risk pregnancies: women with history (or family history) of preeclampsia, chronic hypertension, gestational diabetes, or renal disease. The overall reduction in preeclampsia was 14% (relative risk [RR]=0.86; 95% confidence interval [CI], 0.76–0.96). Results were consistent across RCTs, and only 2 of the 14 studies (with a combined weight of 7.1%) did not support aspirin therapy.

Ruano's 2005 SR[3] included 22 trials with 33,598 subjects and specifically compared low-risk vs high-risk patients. The authors concluded that there was no significant reduction in preeclampsia with the use of low-dose aspirin in the low-risk arm (RR=0.95; 95% CI, 0.81–1.11), and a 13% reduction among high-risk subjects (RR=0.87; 95% CI, 0.79–0.96).[3]

A 2007 meta-analysis by Askie[4] included 31 trials with 32,217 women and their 32,819 infants. Main outcomes (regardless of initial maternal risks) were 1) onset of preeclampsia, 2) neonatal death, 3) preterm birth at <34 weeks gestation, 4) infant small for gestational age, and 5) pregnancy with serious adverse outcome. Results of these outcome measures consistently showed a relative risk reduction of 10% for subjects taking low-dose aspirin, except for neonatal deaths, which had a 9% reduction. This study also suggested that multiparous women and women with a history of hypertensive disorder of pregnancy may derive a larger benefit from low-dose aspirin.

A Cochrane Review[5] updated in 2007 demonstrated that low-dose aspirin pro-

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Low-dose aspirin does not appear to increase the risk of labor induction or neonatal bleeding

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Multiparous women and women with a history of hypertensive disorder of pregnancy may derive a larger benefit from low-dose aspirin

vided a moderate (19%) reduction in the overall risk of developing preeclampsia. New stratified analysis of the data indicates that in moderate-risk women, antiplatelet therapy is associated with a 15% reduction, and that high-risk women have a 27% reduction in the risk of developing preeclampsia. The effect on small-for-gestational-age infants revealed no overall clinically significant differences.

Aspirin dosing: One study recommends >75 mg/day

Studies varied in the aspirin dosage they used and duration of treatment. In all RCTs, the dose of aspirin ranged from 50 mg/day to 150 mg/day. Earlier trials used lower doses of aspirin (50–75 mg/day), while recent trials used 100 mg or more per day.

Early RCTs revealed no correlation between the dose of aspirin and the prevention of preeclampsia. However, Villar et al[6] showed a greater effect among women treated with doses greater than 75 mg/day of aspirin (RR=0.49; 95% CI, 0.38–0.63).[6]

No evidence of harm from aspirin

There is no evidence of harm from low-dose aspirin therapy—including placental abruption, antenatal admissions, fetal intraventricular hemorrhage and other neonatal bleeding complications, admission to neonatal care unit, induction of labor, or caesarean delivery—regardless of initial risk stratification.[7]

Recommendations from others

The 2002 American College of Obstetricians and Gynecologists Practice Bulletin states that low-dose aspirin in women at low risk has not been shown to prevent preeclampsia and therefore is not recommended. They make no specific statement regarding the use of low-dose aspirin in moderate- to high-risk pregnancies.[8]

The Australasian Society for the Study of Hypertension in Pregnancy conclude that low-dose aspirin for prevention of preeclampsia is reasonable for the following conditions: 1) prior fetal loss after first trimester due to placental insufficiency or severe fetal growth retardation, and 2) women with severe early onset preeclampsia in previous pregnancy necessitating delivery ≤32 weeks gestation. Despite difficulties in predicting who will deliver preterm, consider women who have had severe early-onset preeclampsia in a previous pregnancy for low-dose aspirin therapy.[9]

The Canadian Hypertension Society Consensus Panel concludes low-dose aspirin therapy is effective in decreasing the incidence of preterm delivery and early-onset preeclampsia among women at risk of developing the syndrome.[10] ■

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