Another good reason to recommend low-dose aspirin

Evidence shows that daily low-dose aspirin during pregnancy can safely lower the risk of preeclampsia and other adverse outcomes.

Sonia Oyola, MD; Katherine Kirley, MD, MS
University of Chicago, Department of Family Medicine

DEPUTY EDITOR
Bernard Ewigman, MD, MSPH
The University of Chicago, Department of Family Medicine

PRACTICE CHANGER

Prescribe low-dose aspirin (eg, 81 mg/d) to pregnant women who are at high risk for preeclampsia because it reduces the risk of this complication, as well as preterm birth and intrauterine growth restriction.[1]

STRENGTH OF RECOMMENDATION

A: Based on a systematic review and meta-analysis of 23 studies, including 21 randomized controlled trials.

Henderson J, Whitlock E, O'Connor E, et al. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2014;160:695-703.

ILLUSTRATIVE CASE

A 22-year-old G2P1 pregnant woman at 18 weeks gestation who has a history of preeclampsia comes to your office for a routine prenatal visit. On exam, her blood pressure continues to be in the 110s/60s, as it has been for several visits. Her history puts her at risk of developing preeclampsia again, and you wonder if anything can be done to prevent this from happening.

The incidence of preeclampsia, which occurs in 2% to 8% of pregnancies worldwide and 3.4% of pregnancies in the United States, appears to be steadily increasing.[2,3] Preeclampsia is defined as new-onset hypertension at >20 weeks gestation, plus proteinuria, thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and/or cerebral or visual symptoms.[4] The condition is associated with several adverse maternal and fetal outcomes, including eclampsia, abruption, intrauterine growth restriction (IUGR), preterm birth, stillbirth, and maternal death.[2,4] Risk factors for preeclampsia include previous preeclampsia, maternal age ≥40 years, chronic medical conditions, and multi-fetal pregnancy.[5]

The only effective treatment for preeclampsia is delivery.[4] Given the lack of other treatments, strategies for preventing preeclampsia would be highly valuable.

In 1996, the US Preventive Services Task Force (USPSTF) addressed this issue and concluded that there was insufficient evidence to recommend for or against using aspirin to prevent preeclampsia.[6] More recently, Henderson et al[1] conducted a systematic review and meta-analysis to support the USPSTF in a revision of its earlier recommendation.

STUDY SUMMARY

Aspirin use lowers risk of preeclampsia and preterm birth

Henderson et al[1] evaluated the impact of low-dose aspirin on maternal and fetal outcomes among pregnant women at risk for preeclampsia. The review of 23 studies included 21 randomized placebo-controlled trials that evaluated 24,666 patients. Slightly more than half of the studies that evaluated maternal and fetal health benefits were graded as good-quality, and 67% of those that evalu-

Researchers found no evidence of increased maternal postpartum hemorrhage with aspirin use.

ated maternal, perinatal, and developmental harms were rated good-quality.

Most women were white and ages 20 to 33 years. Aspirin doses ranged from 60 mg/d to 150 mg/d; most studies used 60 mg/d or 100 mg/d. Aspirin was initiated between 12 to 36 weeks gestation, with 9 trials initiating aspirin before 16 weeks. In most trials, aspirin was continued until delivery.

Among women at high preeclampsia risk (10 studies), the pooled relative risk (RR) for perinatal death was 0.81 (95% confidence interval [CI], 0.65-1.01) for low-dose aspirin compared to placebo. However, this finding was not statistically significant (*P*=.78).

Among women who received low-dose aspirin, researchers noted a 14% risk reduction for preterm birth (RR=0.86; 95% CI, 0.76-0.98); a 20% risk reduction for IUGR (RR=0.80; 95% CI, 0.65-0.99), and a 24% risk reduction for preeclampsia (RR=0.76; 95% CI, 0.62-0.95). The absolute risk reduction for preeclampsia was estimated to be 2% to 5%.

While the results for preterm birth, IUGR, and preeclampsia were statistically significant, the authors noted that these results could have been biased by small study effects (the tendency of smaller studies to report positive findings, which in turn can skew the results of a meta-analysis based primarily on such studies). The timing and dosage of aspirin had no significant effect on outcomes.

There was no evidence of increased maternal postpartum hemorrhage with aspirin use (RR=1.02; 95% CI, 0.96-1.09). Aspirin use did not seem to increase perinatal mortality among all risk levels (RR=0.92; 95% CI, 0.76-1.11; *P*=.65). No differences were noted in the toddlers' development at 18 months.

WHAT'S NEW

Low-dose aspirin use is now recommended

The 1996 USPSTF recommendation concluded that there was insufficient evidence to recommend aspirin use for preventing preeclampsia. This systematic review and meta-analysis, along with findings from a 2007 Cochrane review[7] and a meta-analysis from the PARIS Collaborative Group,[8] provide good-quality evidence that aspirin reduces negative maternal and fetal outcomes associated with preeclampsia. In 2014, the USPSTF cited this evidence when it decided to recommend using low-dose aspirin (81 mg/d) to prevent preeclampsia in women who are at high risk for preeclampsia (Grade B).[9] (For more on the USPSTF, see "Catching up on the latest USPSTF recommendations," on page 296.)

CAVEATS

Much of the data came from small studies

A substantial portion of the data in this systematic review and meta-analysis came from small studies with positive findings. Because small studies with null findings tend to not be published, there is concern that the results reported by Henderson et al[1] may be somewhat biased, and that future studies may push the overall observed effect toward a null finding.

Also, the criteria used to define "high risk" for preeclampsia varied by study, so it's unclear which groups of women would benefit most from aspirin use during pregnancy. Finally, there is a lack of high-quality data on the effects of aspirin use during pregnancy on long-term outcomes in children. Despite these caveats, the cumulative evidence strongly points to greater benefit than harm.

CHALLENGES TO IMPLEMENTATION

You need to determine which patients are at highest risk

The principle challenge lies in identifying which patients are at high risk for preeclampsia, and thus, will likely benefit from this intervention. This systematic review and meta-analysis used a large variety of risk factors to determine whether a woman was high risk. A 2013 American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy report defined high-risk as women with a history of preeclampsia in more than one previous pregnancy or women with a previous preterm delivery due to preeclampsia.[4]

The updated USPSTF recommendation suggests that women be considered high

risk if they have any of the following: 1) previous preeclampsia, 2) multifetal gestation, 3) chronic hypertension, 4) diabetes, 5) renal disease, or 6) autoimmune disease.[9] We consider both sets of criteria reasonable for identifying women who may benefit from low-dose aspirin during pregnancy. JFP

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