

Another Good Reason to Recommend Low-dose Aspirin

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

Sonia Oyola, MD, Katherine Kirley, MD, MS

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 for 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.¹

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 for 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 hyperten-

Sonia Oyola and Katherine Kirley are in the Department of Family Medicine at the University of Chicago.

sion 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 include previous preeclampsia, maternal age 40 or older, chronic medical conditions, and multifetal pregnancy.⁵

The only effective treatment for preeclampsia is delivery.⁴ Given the lack of other treatments, strategies for prevention 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 al¹ conducted a systematic review and meta-analysis to support the USPSTF in a revision of its earlier recommendation.

STUDY SUMMARY

Aspirin lowers risk for preeclampsia and preterm birth Henderson et al¹ 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 evaluated maternal, perinatal, and developmental harms were rated good quality.

Most study participants were white and ages 20 to 33. Aspirin doses ranged from 60 to 150 mg/d; most studies used doses of 60 or 100 mg/d. Aspirin was initiated between 12 to 36 weeks' gestation, with nine 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 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), a 20% risk reduction for IUGR (RR, 0.80), and a 24% risk reduction for preeclampsia (RR, 0.76). 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). Aspirin use did not seem to increase perinatal mortality among all risk levels (RR, 0.92; $P = .65$). 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 review⁷ 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 the complication (Grade B).⁹

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 not to be published, there is concern that the results reported by Henderson et al¹ 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 the identification of patients who 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 at high risk. A 2013 American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy report defined as *high risk* 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: previous preeclampsia, multifetal gestation, chronic hypertension, diabetes, renal disease, or auto-

immune disease.⁹ We consider both sets of criteria reasonable for identifying women who may benefit from low-dose aspirin during pregnancy. **CR**

REFERENCES

- 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 US Preventive Services Task Force. *Ann Intern Med.* 2014;160:695-703.
- Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. *Semin Perinatol.* 2012;36:56-59.
- Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ.* 2013;347:f6564.
- American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. *Obstet Gynecol.* 2013;122:1122-1131.
- Duckitt K, Harrington D. Risk factors for preeclampsia at antenatal booking: systematic review of controlled studies. *BMJ.* 2005;330:565.
- US Preventive Services Task Force. Aspirin prophylaxis in pregnancy. In: *Guide to Clinical Preventive Services: Report of the US Preventive Services Task Force.* 2nd ed. Washington, DC: US Department of Health and Human Services; 1996.
- Duley L, Henderson-Smart DJ, Meher S, et al. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev.* 2007(2):CD004659.
- Askie LM, Duley L, Henderson-Smart DJ, et al; PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet.* 2007;369:1791-1798.
- LeFevre ML; US Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia [recommendation statement]. *Ann Intern Med.* 2014;161:819-826.

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

Copyright © 2015. *The Family Physicians Inquiries Network.* All rights reserved.

Reprinted with permission from *The Family Physicians Inquiries Network* and *The Journal of Family Practice.* 2015;64(5):301-303.