Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality from Preeclampsia: Recommendation Statement

This summary is one in a series excerpted from the Recommendation Statements released by the USPSTF. These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at http://www.uspreventiveservicestaskforce.org/.

This series is coordinated by Sumi Sexton, MD, Associate Medical Editor.

A collection of USPSTF recommendation statements published in *AFP* is available at http://www.aafp.org/afp/uspstf.

Summary of Recommendation and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends the use of low-dose aspirin (81 mg per day) as preventive medication after 12 weeks of gestation in women who are at high risk of preeclampsia *(Table 1)*. **B recommendation.**

See the Clinical Considerations section for additional information about risk factors, timing, and dosage.

Rationale

Preeclampsia is one of the most serious health problems affecting pregnant women. It is a complication in 2% to 8% of pregnancies worldwide, and contributes to maternal and infant morbidity and mortality. Preeclampsia also accounts for 15% of preterm births in the United States.[1] The disorder is defined by the onset of hypertension (blood pressure greater than 140/90 mm Hg) and proteinuria (0.3 g or more of protein in the urine within a 24-hour period) during the second half of pregnancy (after 20 weeks). In the absence of proteinuria, preeclampsia is classified as hypertension with any of the following: thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances.[2]

RECOGNITION OF RISK STATUS

Important risk factors for preeclampsia include history of preeclampsia (including early-onset preeclampsia), intrauterine growth restriction (IUGR), or preterm birth; placental abruption or fetal death; maternal comorbid conditions (including type 1 or 2 pregestational diabetes mellitus, chronic hypertension, renal disease, and autoimmune diseases); and multifetal gestation.[1]

Predictive models that combine risk factors to identify women at risk of preeclampsia, such as serum biomarkers, uterine artery Doppler ultrasonography, and clinical history and measures, are in development.[3,4] None has yet shown sufficient accuracy for clinical use.

BENEFITS OF PREVENTIVE MEDICATION

The USPSTF found adequate evidence of a reduction in risk of preeclampsia, preterm birth, and IUGR in women at increased risk of preeclampsia who received low-dose aspirin, thus demonstrating substantial benefit.

Low-dose aspirin (range, 60 to 150 mg per day) reduced the risk of preeclampsia by 24% in clinical trials and reduced the risk of preterm birth by 14% and IUGR by 20%.

HARMS OF PREVENTIVE MEDICATION

The USPSTF found adequate evidence that low-dose aspirin as preventive medication does not increase the risk of placental abruption, postpartum hemorrhage, or fetal intracranial bleeding. In a meta-analysis of randomized controlled trials and observational studies of women at low/average or increased risk of preeclampsia, there was no significantly increased risk of these adverse events. In addition, there was no difference in the risk of placental abruption by aspirin dosage.

The USPSTF also found adequate evidence that low-dose aspirin as preventive medication in women at increased risk of preeclampsia does not increase the risk of perinatal mortality.

Evidence on long-term outcomes in offspring exposed in utero to low-dose aspirin is limited, but no developmental harms were

Table 1. Low-Dose Aspirin for the Prevention of Morbidity and Mortality from Preeclampsia: Clinical Summary of the USPSTF Recommendation

Population	Asymptomatic pregnant women who are at high risk of preeclampsia
Recommendation	Prescribe low-dose (81 mg per day) aspirin after 12 weeks of gestation. Grade: B
Risk assessment	Pregnant women are at high risk of preeclampsia if they have one or more of the following risk factors: • History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes mellitus • Renal disease • Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)
Preventive medication	Low-dose aspirin (60 to 150 mg per day) initiated between 12 and 28 weeks of gestation reduces the occurrence of preeclampsia, preterm birth, and intrauterine growth restriction in women at increased risk of preeclampsia. The harms of low-dose aspirin in pregnancy are considered to be no greater than small.
Balance of benefits and harms	There is a substantial net benefit of daily low-dose aspirin use to reduce the risk of preeclampsia, preterm birth, and intrauterine growth restriction in women at high risk of preeclampsia.
Other relevant USPSTF recommendations	The USPSTF recommends that all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 mcg) of folic acid. This recommendation is available at http://www.uspreventiveservicestaskforce.org/.

NOTE: *For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, go to http://www.uspreventiveservicestaskforce.org/.*

USPSTF = U.S. Preventive Services Task Force.

identified by 18 months of age in the one study reviewed.

The USPSTF concludes that the harms of low-dose aspirin in pregnancy are no greater than small.

USPSTF ASSESSMENT

The USPSTF concludes with moderate certainty that there is a substantial net benefit of daily low-dose aspirin use to reduce the risk of preeclampsia, preterm birth, and IUGR in women at high risk of preeclampsia.

Clinical Considerations

PATIENT POPULATION

This recommendation applies to asymptomatic pregnant women who are at increased risk of preeclampsia and who have no prior adverse effects with or contraindications to low-dose aspirin.

ASSESSMENT OF RISK FOR PREECLAMPSIA

There are no validated methods of identifying women at high risk of preeclampsia on the basis of biomarkers, clinical diagnostic tests, or medical history. Most clinicians use medical history to identify women at high risk. Risk factors, based on medical history, may help guide clinicians and their patients in the decision to begin aspirin use.

Although clinical risk assessments were not systematically reviewed for this recommendation, a pragmatic approach is described in *Table 2*.[1,5] This approach may help to identify a patient population with an absolute risk of preeclampsia of at least 8%, which is consistent with the lowest preeclampsia incidence observed in control groups in studies reviewed by the USPSTF.[1] Women with one or more high-risk factors should receive low-dose aspirin. Women

Table 2. Clinical Risk Assessment for Preeclampsia*

Risk level	*Risk factors*	*Recommendation*
High†	History of preeclampsia, especially when accompanied by an adverse outcome	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
	Multifetal gestation	
	Chronic hypertension	
	Type 1 or 2 diabetes mellitus	
	Renal disease	
	Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)	
Moderate‡	Nulliparity	Consider low-dose aspirin if the patient has several of these moderate-risk factors§
	Obesity (body mass index > 30 kg per m^2)	
	Family history of preeclampsia (mother or sister)	
	Sociodemographic characteristics (black race, low socioeconomic status)	
	Age ≥ 35 years	
	Personal history factors (e.g., low birth weight or small for gestational age, previous adverse pregnancy outcome, > 10-year pregnancy interval)	
Low	Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

**—Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.*

†—Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or greater in a pregnant woman with one or more of these risk factors.[1,5]

‡—A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia. These risk factors are independently associated with moderate risk of preeclampsia, some more consistently than others.[1]

§—Moderate-risk factors vary in their association with increased risk of preeclampsia.

Information from references 1 and 5.

with several moderate-risk factors may also benefit from low-dose aspirin *(Table 2[1,5])*, but the evidence is less certain for this approach. Clinicians should use clinical judgment in assessing the risk of preeclampsia and talk with their patients about the benefits and harms of low-dose aspirin use.

ASSESSMENT OF RISK FOR ADVERSE EFFECTS

Low-dose aspirin use in women at increased risk of preeclampsia has not been shown to increase the occurrence of placental abruption; postpartum hemorrhage; or fetal harms, such as intracranial bleeding and congenital anomalies.

USE OF PREVENTIVE MEDICATION

The dosage and timing of initiation of low-dose aspirin varied across studies. However, the beneficial effects and small harms of low-dose aspirin were consistent across dosages and timing of initiation. It was not possible to determine from the evidence whether a specific dosage or timing of aspirin use conferred greater benefit over other dosages or intervals.

Dosage. Low-dose aspirin at dosages between 60 and 150 mg per day reduced the occurrence of preeclampsia, preterm birth, and IUGR in women at increased risk of preeclampsia in several randomized trials.[1] The most commonly used dosage was 100 mg per day, but the two largest trials contributing to the estimates of benefit used 60 mg per day.[1,6,7] Although studies did not evaluate a dosage of 81 mg per day, low-dose aspirin is available in the United States as 81-mg tablets, which is a reasonable dosage for prophylaxis in women at high risk of preeclampsia.

Timing. Use of low-dose aspirin was initiated between 12 and 28 weeks of gestation. Evidence did not suggest additional benefit when use of aspirin was started earlier (12 to 16 weeks) rather than later (after 16 weeks) in pregnancy in women at increased risk of preeclampsia.[1]

This recommendation statement was first published in *Ann Intern Med.* 2014;161(11):819-826.

The "Other Considerations," "Discussion," "Update of Previous USPSTF Recommendation," and "Recommendations of Others" sections of this recommendation statement are available at http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/low-dose-aspirin-use-for-the-prevention-of-morbidity-and-mortality-from-preeclampsia-preventive-medication.

REFERENCES

1. Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. Evidence synthesis no. 112. AHRQ publication no. 14-05207-EF-1. Rockville, Md.: Agency for Healthcare Research and Quality; 2014.
2. American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Washington, DC: American College of Obstetricians and Gynecologists; 2013. http://www.acog.org/Resources_And_Publications/Task_Force_and_Work_Group_Reports/Hypertension_in_Pregnancy (subscription required). Accessed July 31, 2014.
3. North RA, McCowan LM, Dekker GA, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ.* 2011;342:d1875.
4. Myatt L, Clifton RG, Roberts JM, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. First-trimester prediction of preeclampsia in nulliparous women at low risk. *Obstet Gynecol.* 2012;119(6):1234-1242.
5. Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. 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(10):695-703.
6. Sibai BM, Caritis SN, Thom E, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med.* 1993;329(17):1213-1218.
7. Caritis S, Sibai B, Hauth J, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med.* 1998;338(11):701-705. ■