

# Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia: U.S. Preventive Services Task Force Recommendation Statement

Michael L. LeFevre, MD, MSPH, on behalf of the U.S. Preventive Services Task Force\*

**Description:** Update of the 1996 U.S. Preventive Services Task Force (USPSTF) recommendation on aspirin prophylaxis in pregnancy.

**Methods:** The USPSTF reviewed the evidence on the effectiveness of low-dose aspirin in preventing preeclampsia in women at increased risk and in decreasing adverse maternal and perinatal health outcomes, and assessed the maternal and fetal harms of low-dose aspirin during pregnancy.

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

**Recommendation:** The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation)

*Ann Intern Med.* 2014;161:819-826. doi:10.7326/M14-1884

www.annals.org

For author affiliation, see end of text.

\* For a list of USPSTF members, see the **Appendix** (available at www.annals.org).

This article was published online first at www.annals.org on 9 September 2014.

**T**he U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

## SUMMARY OF RECOMMENDATION AND EVIDENCE

The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation)

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

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

**Appendix Table 1** describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

## RATIONALE

### Importance

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 both 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 >140/90 mm Hg) and proteinuria ( $\geq 0.3$  g of protein in the urine within a 24-hour period) during the second half of pregnancy (>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;

See also:

Summary for Patients. . . . . I-28  
Related article: *Ann Intern Med.* 2014;160:695-703.

### Web-Only

CME quiz  
Consumer Fact Sheet

*Figure.* Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: clinical summary of U.S. Preventive Services Task Force recommendation.

## Annals of Internal Medicine



### LOW-DOSE ASPIRIN USE FOR THE PREVENTION OF MORBIDITY AND MORTALITY FROM PREECLAMPSIA CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

<b>Population</b>	Asymptomatic pregnant women who are at high risk for preeclampsia
<b>Recommendation</b>	Prescribe low-dose (81 mg/d) aspirin after 12 weeks of gestation. Grade: B
<b>Risk Assessment</b>	Pregnant women are at high risk for preeclampsia if they have 1 or more of the following risk factors: <ul style="list-style-type: none"> <li>• History of preeclampsia, especially when accompanied by an adverse outcome</li> <li>• Multifetal gestation</li> <li>• Chronic hypertension</li> <li>• Type 1 or 2 diabetes</li> <li>• Renal disease</li> <li>• Autoimmune disease (i.e., systemic lupus erythematosus, the antiphospholipid syndrome)</li> </ul>
<b>Preventive Medication</b>	Low-dose aspirin (60 to 150 mg/d) initiated between 12 and 28 weeks of gestation reduces the occurrence of preeclampsia, preterm birth, and IUGR in women at increased risk for preeclampsia. The harms of low-dose aspirin in pregnancy are considered to be no greater than small.
<b>Balance of Benefits and Harms</b>	There is a substantial net benefit of daily low-dose aspirin to reduce the risk for preeclampsia, preterm birth, and IUGR in women at high risk for preeclampsia.
<b>Other Relevant USPSTF Recommendations</b>	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 µg) of folic acid. This recommendation is available at <a href="http://www.uspreventiveservicestaskforce.org">www.uspreventiveservicestaskforce.org</a> .

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to [www.uspreventiveservicestaskforce.org](http://www.uspreventiveservicestaskforce.org). IUGR = intrauterine growth restriction.

placental abruption or fetal death; maternal comorbid conditions (including type 1 or 2 pregestational diabetes, chronic hypertension, renal disease, and autoimmune diseases); and multifetal gestation (1).

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

#### Benefits of Preventive Medication

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

Low-dose aspirin (range, 60 to 150 mg/d) reduced the risk for preeclampsia by 24% in clinical trials and reduced the risk for 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 for placental abruption, postpartum hemorrhage, or fetal

intracranial bleeding. In a meta-analysis of randomized, controlled trials (RCTs) and observational studies of women at low/average or increased risk for preeclampsia, there was no significantly increased risk for these adverse events. In addition, there was no difference in the risk for placental abruption by aspirin dosage.

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

Evidence on long-term outcomes in offspring exposed in utero to low-dose aspirin is limited, but no developmental harms were 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 for preeclampsia, preterm birth, and IUGR in women at high risk for preeclampsia.

## CLINICAL CONSIDERATIONS

### Patient Population Under Consideration

This recommendation applies to asymptomatic pregnant women who are at increased risk for 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 for 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 the **Table**. This approach may help to identify a patient population with an absolute risk for 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 1 or more high-risk factors should receive low-dose aspirin. Women with several moderate-risk factors may also benefit from low-dose aspirin (**Table**), but the evidence is less certain for this approach. Clinicians should use clinical judgment in assessing the risk for preeclampsia and discuss the benefits and harms of low-dose aspirin use with their patients.

### Assessment of Risk for Adverse Effects

Low-dose aspirin use in women at increased risk for 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/d reduced the occurrence of preeclampsia, preterm birth, and IUGR in women at increased risk for preeclampsia in several randomized trials (1). The most commonly used dosage was 100 mg/d, but the 2 largest trials contributing to the estimates of benefit used 60 mg/d (1, 5–7). Although studies did not evaluate a dosage of 81 mg/d, 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 for 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 ( $\geq 16$  weeks) in pregnancy in women at increased risk for preeclampsia (1).

## OTHER CONSIDERATIONS

### Research Needs and Gaps

Research is needed on the effect of low-dose aspirin on the development of preeclampsia and how the magnitude of response to low-dose aspirin varies with individual or combined risk factors for preeclampsia. Research on how

**Table. Clinical Risk Assessment for Preeclampsia\***

Risk Level	Risk Factors	Recommendation
High†	History of preeclampsia, especially when accompanied by an adverse outcome Multifetal gestation Chronic hypertension Type 1 or 2 diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has $\geq 1$ of these high-risk factors
Moderate‡	Nulliparity Obesity (body mass index $>30$ kg/m <sup>2</sup> ) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (African American race, low socioeconomic status) Age $\geq 35$ y Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, $>10$ -y pregnancy interval)	Consider low-dose aspirin if the patient has several of these moderate-risk factors§
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 for preeclampsia. The preeclampsia incidence rate would be approximately  $\geq 8\%$  in a pregnant woman with  $\geq 1$  of these risk factors (1, 5).

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

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

to improve clinicians' ability to identify women at increased risk for preeclampsia, particularly those who would receive the greatest benefit from aspirin as preventive medication, is also needed. Efforts to validate the effectiveness of risk assessment tools using clinical history alone or combined with clinical testing may help clinicians better identify high-risk women who will benefit from aspirin as preventive medication, and help reduce the incidence of preeclampsia and its consequent outcomes.

Further research in populations that bear the highest disease burden for preeclampsia, including African American and nulliparous women, is needed. Multivariable risk prediction models that identify healthy nulliparous women who are likely to develop preeclampsia are in development, but further refinement and validation are needed. Additional research to further assess preeclampsia risk in pregnant women with 1 or more moderate-risk factors is needed. Future trials should recruit adequate numbers of women from racial/ethnic populations that are at disproportionate risk, such as African American women, in order to have sufficient power to determine the effectiveness of different aspirin dosages and timing of initiation in these high-risk groups.

Larger studies investigating aspirin use in the first or early second trimester may improve the evidence base on optimal timing of low-dose aspirin as preventive medication. Other areas of research include optimal therapies that individualize the aspirin dosage and timing of administration (e.g., morning vs. bedtime).

In addition, studies that explore less well-established risk factors that may better identify women at high risk for preeclampsia are needed. Further research should also investigate whether preeclampsia prevention with low-dose aspirin affects women's long-term risk for cardiovascular disease and whether there are benefits to continuing low-dose aspirin after delivery in women with 1 or more high-risk factors.

### Other Approaches to Prevention

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  $\mu$ g) of folic acid. More information is available at [www.uspreventiveservicestaskforce.org](http://www.uspreventiveservicestaskforce.org).

## DISCUSSION

### Burden of Disease

Preeclampsia is a multisystem inflammatory syndrome with an unclear etiology and natural history. It is one of the leading causes of maternal and perinatal morbidity and the second-leading cause of maternal mortality worldwide (1).

In 2010, preeclampsia affected 3.8% of deliveries in the United States (8). The rate of severe preeclampsia has increased over the past 3 decades. In the United States, 12% of maternal deaths are directly attributable to pre-

eclampsia and eclampsia. However, morbidity is more common than mortality, and it is estimated that more than one third of severe obstetric complications are related to preeclampsia (1).

Preeclampsia accounts for 15% of preterm births in the United States and is a leading cause of medically indicated preterm birth. Delivery is the only cure for preeclampsia (1). Early-onset preeclampsia is usually more severe and often requires preterm delivery. Preterm infants (<37 weeks of gestation) are at increased risk for morbidity and mortality, and complications increase with earlier delivery. Additional important threats to the fetus from preeclampsia include IUGR, being small for gestational age, placental abruption, neonatal intensive care unit admission, and neonatal death. It is estimated that perinatal mortality is about 2 times higher in pregnancies affected by preeclampsia (1).

There are racial/ethnic disparities in the prevalence of and mortality from preeclampsia. Non-Hispanic black women are at greater risk for preeclampsia than other women and bear a greater burden of maternal and infant morbidity and perinatal mortality. In the United States, the rate of maternal death from preeclampsia is higher in non-Hispanic black women than in non-Hispanic white women. Disparities in risk factors for preeclampsia, limited access to early prenatal care, and obstetric interventions may account for some of the differences in prevalence and clinical outcomes (1).

### Scope of Review

In 1996, the USPSTF reviewed the effectiveness of low-dose aspirin use to prevent preeclampsia (9). The current review included new evidence on the effectiveness of low-dose aspirin for preventing preeclampsia in women at increased risk and in decreasing adverse maternal and perinatal health outcomes, as well as assessing the maternal and fetal harms of low-dose aspirin during pregnancy.

### Effectiveness of Preventive Medication

The USPSTF considered 15 RCTs (8 good-quality) in women at increased risk for preeclampsia to evaluate maternal and perinatal health benefits and 13 RCTs (8 good-quality) to evaluate preeclampsia incidence. All trials were placebo-controlled (1). One large trial was conducted in the United States, and another large, multinational trial was coordinated from the United Kingdom. Thirteen smaller trials were conducted in various developed countries. Preeclampsia incidence in women at increased risk ranged from 8% to 30% across studies.

In general, trial participants were young (mean age range, 20.3 to 31 years) and white. Only 1 trial of women at increased risk for preeclampsia and 2 trials reporting harms included majority populations of black women. None of the trials initiated use of low-dose aspirin before 12 weeks of gestation, and 8 trials initiated prophylaxis before 16 weeks. The most common discontinuation date was upon delivery; however, 6 trials stopped aspirin use

before delivery, as early as 35 weeks of gestation or when preeclampsia developed. Aspirin dosages ranged from 60 to 150 mg/d, with most trials using 60 mg/d (6 RCTs) or 100 mg/d (8 RCTs) (1). Included trials defined “high risk” differently because a validated method for identifying women who are at increased risk for preeclampsia is lacking.

Two large RCTs, the Maternal-Fetal Medicine Units (MFMU) trial and the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), provided most of the data for pooled estimates of benefit (6, 7). The MFMU trial was conducted at 13 U.S. study sites in women at increased risk for preeclampsia ( $n = 2503$ ). The treatment group received 60 mg/d of aspirin, but was instructed to stop taking the medication if preeclampsia developed. Women were at 13 to 26 weeks of gestation and belonged to 1 of the following predefined preeclampsia risk categories: pregestational diabetes mellitus ( $n = 471$ ), chronic hypertension ( $n = 744$ ), current multifetal gestation ( $n = 688$ ), or preeclampsia in a prior pregnancy ( $n = 606$ ) (6).

CLASP was a multinational trial ( $n = 9364$ ) that included 16 sites (e.g., United Kingdom, United States, Canada, Germany, Spain, and Hong Kong). Women were enrolled to prevent or treat preeclampsia and IUGR on the basis of medical history. Risk factors for preeclampsia were prior IUGR or preeclampsia, chronic hypertension, renal disease, age, family history of preeclampsia, and multifetal gestation. Women were still eligible for study participation if their clinician was unsure whether they should receive low-dose aspirin. Two thirds of participants began taking aspirin before 20 weeks of gestation. Use of low-dose aspirin (60 mg/d) was continued until delivery (7).

### Perinatal Outcomes

The USPSTF found evidence of a 14% reduction in risk for preterm birth (pooled relative risk [RR], 0.86 [95% CI, 0.76 to 0.98]; 10 studies;  $I^2 = 33.2\%$ ) among women at increased risk for preeclampsia who received low-dose aspirin ( $n = 11\,779$ ). This reduction in risk for preterm birth resulted from a decrease in the number of women with preeclampsia, as well as a delay in the development of preeclampsia. Pooled estimates provided evidence of a 20% reduction in risk for IUGR (RR, 0.80 [CI, 0.65 to 0.99]; 13 studies;  $I^2 = 36.0\%$ ) in women at increased risk for preeclampsia ( $n = 12\,504$ ). Low-dose aspirin increased the mean birthweight of infants ( $n = 10\,712$ ) by a pooled weighted mean difference of 130.0 g (CI, 36.2 to 223.3 g;  $I^2 = 60\%$ ). There was no statistically significant reduction in perinatal mortality (pooled RR, 0.81 [CI, 0.65 to 1.01]; 10 studies;  $I^2 = 0\%$ ) in women at increased risk for preeclampsia ( $n = 12\,240$ ) (1).

### Maternal Outcomes

The USPSTF found evidence of a 24% reduction in risk for preeclampsia (pooled RR, 0.76 [CI, 0.62 to 0.95];

13 studies) with low-dose aspirin use in women at increased risk ( $n = 12\,184$ ). Heterogeneity was moderate across studies ( $I^2 = 40.5\%$ ). Stratified comparisons did not show that the timing of aspirin initiation (<16 weeks) or dosage had an effect on preeclampsia prevention (1).

Maternal complications of preeclampsia (e.g., the hemolysis, elevated liver enzymes, and low platelet count [HELLP] syndrome, organ system failure, eclampsia, or death) rarely occurred in studies and could not be evaluated. Pooled analysis of the outcome of cesarean delivery (10 studies;  $n = 10\,419$ ) indicated no difference in the cesarean delivery rate among women receiving aspirin compared with those receiving placebo (RR, 0.92 [CI, 0.79 to 1.08];  $I^2 = 24.9\%$ ) (1).

The number needed to treat was calculated from the event rate in the trial data at the lowest level of risk for the outcome. The number needed to treat to prevent 1 diagnosis of preeclampsia was 42 (CI, 26 to 200); it was 71 (CI, 41 to 1429) for IUGR, and 65 (CI, 38 to 455) for preterm birth. Absolute risk estimates based on observed event rates ranged from 2% to 5% for preeclampsia, 1% to 5% for IUGR, and 2% to 4% for preterm birth (1). Sensitivity analyses using an alternate method for estimating pooled random effects resulted in similar point estimates and CIs and did not change the statistical significance of results for benefits or harms (1).

Results from the USPSTF’s review are generally consistent with the findings from a Cochrane Collaboration systematic review (10) and an individual patient–data meta-analysis (Perinatal Antiplatelet Review of International Studies [PARIS]) (11). The Cochrane review included 59 trials (37 560 women), and the PARIS meta-analysis included data from 31 trials (32 217 women and 32 819 infants). Although there were differences in study inclusion criteria, the USPSTF found similar effect estimates for preeclampsia, IUGR, preterm birth, and perinatal mortality, particularly compared with results from the PARIS meta-analysis.

### Dosage and Timing

The USPSTF found no evidence from stratified comparisons that the timing of aspirin administration or the dosage had different effects. Comparison of dosage effects showed 1 outcome with a significant difference—preterm birth—when a cut-point of 75 mg/d was used. The reduction in risk for preterm birth was greater in studies using doses greater than 75 mg/d. However, the analyses were confounded by unequal distribution of sample sizes in different dosage categories because the largest studies (MFMU and CLASP) used 60 mg/d of aspirin. There was no evidence of a dose–response relationship (1, 5).

In 15 trials, use of low-dose aspirin was initiated between 12 and 28 weeks of gestation. None of the trials initiated use of aspirin before 12 weeks. In 8 trials, use of low-dose aspirin was initiated before 16 weeks. Evidence

did not demonstrate benefit of starting aspirin earlier (12 to 16 weeks) rather than later ( $\geq 16$  weeks) in pregnancy (1).

### Potential Harms of Preventive Medication

The USPSTF considered 19 RCTs (12 good-quality) and 2 good-quality observational studies to evaluate maternal, perinatal, and developmental harms. Studies of low- or average-risk pregnant women were included with trials of women at increased risk (1).

Low-dose aspirin use seemed to have no short-term harms during pregnancy. Eleven RCTs (23 332 women) reported on the outcome of placental abruption (6 trials in women with increased preeclampsia risk and 5 trials in women with low/average risk). Pooled analyses showed no statistically significant increase in abruption associated with aspirin (RR, 1.17 [CI, 0.93 to 1.48];  $I^2 = 36.4\%$ ).

Eighteen trials reported on the outcome of perinatal mortality (with 4 smaller studies reporting no events). Pooled analyses ( $n = 22\ 848$ ) on perinatal mortality (RR, 0.92 [CI, 0.76 to 1.11]; 14 studies;  $I^2 = 0\%$ ) suggested no harm from low-dose aspirin. When limited to women at increased risk for preeclampsia ( $n = 12\ 240$ ), the estimate approached statistical significance for a benefit (RR, 0.81 [CI, 0.65 to 1.01]; 10 studies;  $I^2 = 0\%$ ) (1).

Nine trials (6 in women at increased preeclampsia risk and 3 in women at low risk; 22 760 women in total) reported on the outcome of postpartum hemorrhage. There was no evidence of a treatment effect (RR, 1.02 [CI, 0.96 to 1.09]). Five trials (1 good-quality) in a total of 2748 women reported on the outcome of blood loss. No evidence demonstrated that low-dose aspirin affected blood loss. Studies found slightly lower mean blood loss or equivalent amounts of blood loss between study groups (1).

The pooled relative risk for intracranial hemorrhage in neonates (6 studies;  $n = 22\ 158$ ) was 0.84 (CI, 0.61 to 1.16), with low heterogeneity ( $I^2 = 27.1\%$ ;  $P = 0.23$ ). Maternal death was a rare outcome and could not be evaluated (1).

The USPSTF found limited evidence on long-term outcomes in offspring from in utero exposure to low-dose aspirin. One observational study of birth defects resulting from aspirin exposure showed that the rate of cryptorchidism did not differ between male infants exposed and unexposed to aspirin in utero (12). Another observational study on aspirin use during pregnancy had null findings for miscarriage (13). Follow-up data from the largest trial, CLASP, reported no differences in physical or mental developmental outcomes (e.g., gross motor development, height, weight, or hospital visits) in infants at 18 months of age (14).

Seven trials reported adverse events; however, most were determined to be unrelated to treatment. Two studies reported women withdrawing from treatment because of itching of the throat and epigastric pain (1).

### Estimate of Magnitude of Net Benefit

The USPSTF found adequate evidence that daily low-dose aspirin use in women at high risk for preeclampsia is associated with improved health outcomes through the reduction of risk for preeclampsia, preterm birth, and IUGR. The USPSTF found adequate evidence that low-dose aspirin use does not increase the risk for placental abruption, postpartum hemorrhage, fetal intracranial bleeding, or perinatal mortality. The USPSTF did not identify any harmful effects of low-dose aspirin use on long-term outcomes in offspring; however, evidence was limited.

Overall, the harms of low-dose aspirin use in pregnancy are considered to be no greater than small. Therefore, the USPSTF concludes with moderate certainty that the magnitude of net benefit of low-dose aspirin use to prevent morbidity and mortality from preeclampsia in women at high risk is substantial.

### How Does Evidence Fit With Biological Understanding?

Preeclampsia is a complex, multisystem inflammatory syndrome that can originate from multiple causes. It is believed to evolve from changes in placental development that result in placental ischemia. Poor placental perfusion may produce inflammation and oxidative stress. Preeclampsia may also develop as a result of overactive inflammatory responses to normal placentation. Preexisting inflammatory conditions are also believed to trigger systemic inflammatory and oxidative stress processes. The anti-inflammatory, antiangiogenesis, and antiplatelet properties of low-dose aspirin are believed to account for its preventive effect on preeclampsia.

### Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 8 April to 5 May 2014. Some comments requested clarification about risk factors for preeclampsia and the dosage and timing of initiation of low-dose aspirin. In response to these comments, the USPSTF added language about populations that are at risk for preeclampsia and aspirin dosages in the Clinical Considerations section. The USPSTF also added language to the **Table** to clarify the populations at risk. The USPSTF added language on the timing of initiation of low-dose aspirin in the Research Needs and Gaps section. Finally, the USPSTF provided more details about study characteristics and results in the Discussion section.

### UPDATE OF PREVIOUS USPSTF RECOMMENDATION

In 1996, the USPSTF concluded that evidence was insufficient to recommend for or against the routine use of aspirin for the prevention of preeclampsia or IUGR. Although a significant reduction in risk for preterm birth suggested benefits for infants, there was inadequate evidence that aspirin provided benefits for women at increased risk for preeclampsia. In addition, the studies avail-

able at that time indicated that aspirin use was associated with risk for placental abruption. As a result, the USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of aspirin use to prevent preeclampsia in pregnant women at increased risk for preeclampsia (9).

This recommendation updates the 1996 recommendation. It differs from the previous recommendation in that new evidence on the effectiveness and harms of low-dose aspirin on maternal and perinatal health outcomes now allows the USPSTF to recommend its use in women at high risk for preeclampsia. This recommendation also differs from the 1996 recommendation by defining “high preeclampsia risk” in pregnant women in more detail.

## RECOMMENDATIONS OF OTHERS

The American Congress of Obstetricians and Gynecologists recommends initiating use of low-dose aspirin (60 to 80 mg/d) during the late first trimester to prevent preeclampsia in women with a medical history of early-onset preeclampsia and preterm delivery (<34 weeks) or history of preeclampsia in more than 1 previous pregnancy (2).

The World Health Organization recommends the use of low-dose aspirin (75 mg/d) starting as early as 12 to 20 weeks of gestation for high-risk women (i.e., those with a history of preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multifetal pregnancies). It states that there is limited evidence regarding the benefits of low-dose aspirin in other subgroups of high-risk women (15).

The National Institute for Health and Care Excellence recommends that women at high risk for preeclampsia (i.e., those with a history of hypertension in a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or 2 diabetes, or chronic hypertension) take 75 mg/d of aspirin from 12 weeks until delivery. It recommends the same for women with more than 1 moderate-risk factor (first pregnancy, age  $\geq 40$  years, pregnancy interval >10 years, body mass index  $\geq 35$  kg/m<sup>2</sup>, family history of preeclampsia, or multifetal pregnancies) (16).

The American Heart Association and the American Stroke Association recommend that women with chronic primary or secondary hypertension or previous pregnancy-related hypertension take low-dose aspirin from 12 weeks until delivery (17).

The American Academy of Family Physicians recommends low-dose aspirin (81 mg/d) after 12 weeks of gestation in women who are at high risk for preeclampsia (18).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

**Disclaimer:** Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

**Financial Support:** The USPSTF is an independent, voluntary body. The U.S. Congress mandates that the Agency for Healthcare Research and Quality support the operations of the USPSTF.

**Disclosures:** Dr. Owens reports support from the Agency for Healthcare Research and Quality during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Authors followed the policy regarding conflicts of interest described at [www.uspreventiveservicestaskforce.org/methods.htm](http://www.uspreventiveservicestaskforce.org/methods.htm). Disclosures can also be viewed at [www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1884](http://www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1884).

**Requests for Single Reprints:** Reprints are available from the USPSTF Web site ([www.uspreventiveservicestaskforce.org](http://www.uspreventiveservicestaskforce.org)).

## References

- 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.
- American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Washington, DC: American College of Obstetricians and Gynecologists; 2013. Accessed at [www.acog.org/Resources\\_And\\_Publications/Task\\_Force\\_and\\_Work\\_Group\\_Reports/Hypertension\\_in\\_Pregnancy](http://www.acog.org/Resources_And_Publications/Task_Force_and_Work_Group_Reports/Hypertension_in_Pregnancy) on 31 July 2014.
- North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ*. 2011;342:d1875. [PMID: 21474517]
- Myatt L, Clifton RG, Roberts JM, Spong CY, Hauth JC, Varner MW, 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;119:1234-42. [PMID: 22617589]
- 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;160:695-703. [PMID: 24711050]
- Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rocco L, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med*. 1993;329:1213-8. [PMID: 8413387]
- Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, 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;338:701-5. [PMID: 9494145]
- Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ*. 2013;347:f6564. [PMID: 24201165]
- U.S. Preventive Services Task Force. Aspirin prophylaxis in pregnancy. In: *Guide to Clinical Preventive Services*. 2nd ed. Washington, DC: U.S. Department of Health and Human Services; 1996.
- Duley L, Henderson-Smith DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev*. 2007;(2):CD004659. [PMID: 17443552]
- Askie LM, Duley L, Henderson-Smith DJ, Stewart LA; PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet*. 2007;369:1791-8. [PMID: 17512048]
- Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP, et al. Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. *Epidemiology*. 2010;21:779-85. [PMID: 20805751]

13. Keim SA, Klebanoff MA. Aspirin use and miscarriage risk. *Epidemiology*. 2006;17:435-9. [PMID: 16755260]
14. Low dose aspirin in pregnancy and early childhood development: follow up of the Collaborative Low dose Aspirin Study in Pregnancy. CLASP Collaborative Group. *Br J Obstet Gynaecol*. 1995;102:861-8. [PMID: 8534620]
15. World Health Organization. WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia. Geneva: World Health Organization; 2011. Accessed at [http://whqlibdoc.who.int/publications/2011/9789241548335\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf) on 31 July 2014.
16. Redman CW. Hypertension in pregnancy: the NICE guidelines. *Heart*. 2011;97:1967-9. [PMID: 21990386]
17. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1545-88. [PMID: 24503673]
18. American Academy of Family Physicians. Recommendations for Clinical Preventive Services. Leawood, KS: American Academy of Family Physicians; 2014. Accessed at [www.aafp.org/patient-care/clinical-recommendations/cps.html](http://www.aafp.org/patient-care/clinical-recommendations/cps.html) on 31 July 2014.



## APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Michael L. LeFevre, MD, MSPH, *Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Kirsten Bibbins-Domingo, PhD, MD, *Co-Vice Chair* (University of California, San Francisco, San Francisco, California); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Karina W. Davidson, PhD, MAsc (Columbia University, New York, New York); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Matthew Gillman, MD, SM (Harvard

Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Alex R. Kemper, MD, MPH, MS (Duke University, Durham, North Carolina); Ann E. Kurth, PhD, RN, MSN, MPH (New York University, New York, New York); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); Maureen G. Phipps, MD, MPH (Brown University, Providence, Rhode Island); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina). Wanda Nicholson, MD, MPH, MBA, a former USPSTF member, also contributed to the development of this recommendation.

† For a list of current Task Force members, go to [www.uspreventiveservicestaskforce.org/members.htm](http://www.uspreventiveservicestaskforce.org/members.htm).

**Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice**

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

**Appendix Table 2. USPSTF Levels of Certainty Regarding Net Benefit**

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

\* The USPSTF defines *certainty* as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.