

# Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality

## US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** Preeclampsia is one of the most serious health problems that affect pregnant persons. It is a complication in approximately 4% of pregnancies in the US and contributes to both maternal and infant morbidity and mortality. Preeclampsia also accounts for 6% of preterm births and 19% of medically indicated preterm births in the US. There are racial and ethnic disparities in the prevalence of and mortality from preeclampsia. Non-Hispanic Black women are at greater risk for developing preeclampsia than other women and experience higher rates of maternal and infant morbidity and perinatal mortality.

**OBJECTIVE** To update its 2014 recommendation, the USPSTF commissioned a systematic review to evaluate the effectiveness of low-dose aspirin use to prevent preeclampsia.

**POPULATION** Pregnant persons at high risk for preeclampsia who have no prior adverse effects with or contraindications to low-dose aspirin.

**EVIDENCE 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, small for gestational age/intrauterine growth restriction, and perinatal mortality in pregnant persons at high risk for preeclampsia.

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

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### Summary of Recommendation

Pregnant persons at high risk for preeclampsia	The USPSTF recommends the use of low-dose aspirin (81 mg/day) as preventive medication after 12 weeks of gestation in persons who are at high risk for preeclampsia.	B
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See the Practice Considerations section for information on high risk and aspirin dose. See the Figure for a more detailed summary of the recommendation for clinicians. USPSTF indicates US Preventive Services Task Force.

See the Summary of Recommendation figure.

### Importance

Preeclampsia is one of the most serious health problems that affect pregnant persons. It is a multisystem inflammatory syndrome that is often progressive but has an unclear etiology. Worldwide, preeclampsia is the second most common cause of maternal morbidity and mortality. It is a complication in approximately 4% of pregnancies in the US and contributes to both maternal and infant morbidity and mortality.<sup>1</sup> Preeclampsia also accounts for 6% of preterm births and 19% of medically indicated preterm births in the US.<sup>1</sup>

There are racial and ethnic disparities in the prevalence of and mortality from preeclampsia. Non-Hispanic Black women are at greater risk for developing preeclampsia than other women and experience higher rates of maternal and infant morbidity and perinatal mortality than other racial and ethnic groups. In the US, the rate of maternal death from preeclampsia is higher among non-Hispanic Black women than non-Hispanic White women.<sup>1,2</sup> Disparities in risk factors for preeclampsia, access to early prenatal care, and obstetric interventions may account for some of the differences in prevalence and clinical outcomes.<sup>1</sup> These disparities largely result from historical and current manifestations of

**Table 1. Clinical Risk Assessment for Preeclampsia<sup>a</sup>**

Risk level	Risk factors	Recommendation
High <sup>b</sup>	<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>Pregestational type 1 or 2 diabetes</li> <li>Kidney disease</li> <li>Autoimmune disease (ie, systemic lupus erythematosus, antiphospholipid syndrome)</li> <li>Combinations of multiple moderate-risk factors</li> </ul>	Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors
Moderate <sup>c</sup>	<ul style="list-style-type: none"> <li>Nulliparity</li> <li>Obesity (ie, body mass index &gt;30)</li> <li>Family history of preeclampsia (ie, mother or sister)</li> <li>Black persons (due to social, rather than biological, factors)<sup>d</sup></li> <li>Lower income<sup>d</sup></li> <li>Age 35 years or older</li> <li>Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, &gt;10-year pregnancy interval)</li> <li>In vitro conception</li> </ul>	Recommend low-dose aspirin if the patient has ≥2 moderate-risk factors Consider low-dose aspirin if the patient has 1 of these moderate-risk factors <sup>d</sup>
Low	Prior uncomplicated term delivery and absence of risk factors	Do not recommend low-dose aspirin

<sup>a</sup> Includes only risk factors that can be obtained from the patient medical history.

<sup>b</sup> Includes single risk factors that are consistently associated with the greatest risk for preeclampsia. Preeclampsia incidence would likely be at least 8% in a population of pregnant individuals having 1 of these risk factors.

<sup>c</sup> These factors are independently associated with moderate risk for preeclampsia, some more consistently than others. A combination of multiple moderate-risk factors may place a pregnant person at higher risk for preeclampsia.

<sup>d</sup> These factors are associated with increased risk due to environmental, social, and historical inequities shaping health exposures, access to health care, and the unequal distribution of resources, not biological propensities.

**Table 2. Summary of USPSTF Rationale**

Rationale	Assessment
Benefits of preventive medication	<ul style="list-style-type: none"> <li>There is adequate evidence of a reduction in risk for preterm birth, SGA/IUGR, and perinatal mortality in persons at increased risk for preeclampsia who received low-dose aspirin, thus demonstrating substantial benefit.</li> <li>There is also adequate evidence that use of low-dose aspirin in pregnant persons at increased risk for preeclampsia reduces risk for preeclampsia, which leads to improved maternal and perinatal outcomes, demonstrating substantial benefit.</li> </ul>
Harms of preventive medication	There is adequate evidence to bound the harms of low-dose aspirin as no greater than small based on the absence of evidence of harms associated with daily aspirin use.
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, SGA/IUGR, and perinatal mortality in persons at high risk for preeclampsia.

Abbreviations: IUGR, intrauterine growth restriction; SGA, small for gestational age; USPSTF, US Preventive Services Task Force.

structural racism that influence environmental exposures, access to health resources, and overall health status.<sup>1,3,4</sup>

## Recognition of Risk Status

Persons with a history of preeclampsia in a previous pregnancy, type 1 or type 2 diabetes, and chronic hypertension are at highest risk for preeclampsia. Additional conditions that place a person at high risk for preeclampsia include multifetal gestation, conception using assisted reproductive technology, autoimmune disease, and kidney disease. Other factors associated with increased preeclampsia risk include nulliparity, high prepregnancy body mass index, family history of preeclampsia, and advanced maternal age (35 years or older). In addition, Black persons have higher rates of preeclampsia and are at increased risk for serious complications due to various societal and health inequities (Table 1).<sup>1-3</sup>

## USPSTF Assessment of Magnitude of Net Benefit

The US Preventive Services Task Force (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, small for gestational age/intrauterine growth restriction, and perinatal mortality in pregnant persons at high risk for preeclampsia.

See Table 2 for more information on the USPSTF recommendation rationale and assessment and the eFigure in the Supplement for information on the recommendation grade. See the Figure for a summary of the recommendation for clinicians. For more details on the methods the USPSTF uses to determine the net benefit, see the USPSTF Procedure Manual.<sup>5</sup>

## Practice Considerations

### Patient Population Under Consideration

This recommendation applies to pregnant persons who are at high risk for preeclampsia and who have no prior adverse effects with or contraindications to low-dose aspirin.

### Definitions

Preeclampsia is a disease defined by hypertension (defined as office-based blood pressure ≥140/90 mm Hg on 2 separate occasions during the second half of pregnancy [>20 weeks]), accompanied by proteinuria. Proteinuria is defined as a 24-hour urine collection containing greater than 300 mg protein, a single voided urine protein to creatinine ratio of 0.3 or greater, or a urine dipstick

**Figure. Clinical Summary: Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality**

<b>What does the USPSTF recommend?</b>	<b>For pregnant persons:</b> Prescribe low-dose (81 mg/d) aspirin after 12 weeks of gestation to persons who are at high risk for preeclampsia. <b>Grade B</b> See "How to implement this recommendation?" for definition of high risk.
<b>To whom does this recommendation apply?</b>	Asymptomatic pregnant persons who are at high risk for preeclampsia and have no prior adverse events with low-dose aspirin. See "How to implement this recommendation?" for definition of high risk.
<b>What's new?</b>	This recommendation is consistent with the 2014 USPSTF recommendation. It is strengthened by new evidence from additional trials demonstrating reduced risks of perinatal mortality with aspirin use.
<b>How to implement this recommendation?</b>	<ol style="list-style-type: none"> <li><b>Assess Risk.</b> Determine if a pregnant person is at high risk for preeclampsia when obtaining the patient medical history. Pregnant persons 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</li> <li>• Multifetal gestation</li> <li>• Chronic hypertension</li> <li>• Pregestational type 1 or 2 diabetes</li> <li>• Kidney disease</li> <li>• Autoimmune disease (ie, systemic lupus erythematosus, antiphospholipid syndrome)</li> </ul> Combinations of multiple moderate-risk factors also may be used, such as nulliparity (having never given birth), obesity (ie, BMI &gt;30), family history of preeclampsia (ie, mother, sister), maternal age 35 years or older, personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, &gt;10-year pregnancy interval), in vitro fertilization conception, and lower income. Black persons are associated with increased risk due to environmental, social, and historical inequities shaping health exposures, access to health care, and the unequal distribution of resources, not biological propensities. </li> <li><b>Prescribe.</b> If patient is at high risk for preeclampsia, prescribe low-dose aspirin (81 mg/d) after 12 weeks of gestation.</li> </ol>
<b>How often?</b>	Once daily after 12 weeks of gestation
<b>What are 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 (400-800 µg) of folic acid. This and other recommendations for pregnant persons are available at <a href="https://www.uspreventiveservicestaskforce.org">https://www.uspreventiveservicestaskforce.org</a>
<b>Where to read the full recommendation statement?</b>	Visit the USPSTF website ( <a href="https://www.uspreventiveservicestaskforce.org">https://www.uspreventiveservicestaskforce.org</a> ) to read the full recommendation statement. This includes more details on the rationale of the recommendation, including benefits and harms; supporting evidence; and recommendations of others.

*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.*

BMI indicates body mass index; USPSTF, US Preventive Services Task Force.

reading of 2+ (used only if other quantitative methods are not available). In the absence of proteinuria, preeclampsia is diagnosed as hypertension with any of the following: thrombocytopenia, impaired liver function, kidney insufficiency, pulmonary edema, or cerebral or visual disturbances.<sup>6</sup>

### Assessment of Risk

Risk factors of preeclampsia can be categorized into those obtained by medical history, clinical examination, laboratory tests, and imaging. Most clinicians use medical history to identify pregnant persons at increased risk. Predictive models that combine risk factors to identify pregnant persons at risk for preeclampsia, such as serum biomarkers, uterine artery Doppler ultrasonography, and clinical history and measures, have been developed. However, there is limited evidence from external validation and implementation studies to demonstrate sufficient accuracy of predictive models for clinical use.<sup>1,7</sup>

Based on the risk assessment approaches used in the studies included in this review and the broader literature on clinical risk factors for preeclampsia, a pragmatic approach for identifying individuals who are candidates for aspirin prophylaxis is outlined in Table 1. 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.<sup>1</sup> Pregnant persons with 1 or more high-risk factors should receive low-dose aspirin. Pregnant persons with moderate-risk factors may also benefit from low-dose aspirin (Table 1). 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.

### Treatment or Intervention

Interventions to manage preeclampsia, such as antihypertensive medication, early delivery, and magnesium sulfate treatment can reduce complications and mortality. The definitive treatment for preeclampsia is delivery of the placenta. However, manifestations of preeclampsia may take days or weeks to resolve, with some cases presenting in the postpartum period and requiring additional intervention.<sup>1</sup> Evidence demonstrates that aspirin use reduces the risk of preeclampsia in high-risk populations.<sup>1,8-10</sup>

### Timing and Dosage

Effective dosages of low-dose aspirin range from 60 to 150 mg/d.<sup>1</sup> Although studies did not evaluate a dosage of 81 mg/d, low-dose

aspirin is available in the US as 81-mg tablets, which is a reasonable dose for prophylaxis in pregnant persons at high risk for preeclampsia.

Low-dose aspirin use should be initiated after 12 weeks of gestation (studies most often initiated before 20 weeks of gestation).

### Implementation

Risk factors, based on medical history, may help guide clinicians and their patients in the decision to begin aspirin use (Table 1). Pregnant persons with 1 or more high-risk factors should receive low-dose aspirin. Pregnant persons with 2 or more moderate-risk factors may also benefit from low-dose aspirin (Table 1), 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. In October 2020, the US Food and Drug Administration released a safety drug communication warning that the use of nonsteroidal anti-inflammatory drugs around 20 weeks of gestation or later may cause rare but serious kidney problems in unborn infants, resulting in low levels of amniotic fluid.<sup>11</sup> An exception to this warning is the use of an 81-mg dose of aspirin for certain pregnancy-related conditions under the direction of a health care clinician.<sup>11</sup>

## Other Related USPSTF Recommendations

The USPSTF has also issued recommendations for numerous conditions in pregnant persons, including screening for preeclampsia<sup>12</sup> and folic acid supplementation to prevent neural tube defects.<sup>13</sup> Other related USPSTF recommendations are available at <https://www.uspreventiveservicestaskforce.org/uspstf/>.

## Update of Previous USPSTF Recommendation

In the 2014 recommendation, the USPSTF recommended the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in persons at high risk for preeclampsia (B recommendation).<sup>14</sup> The current recommendation is consistent with the 2014 recommendation. It is strengthened by new evidence from additional trials supporting reduced risks of perinatal mortality with low-dose aspirin use.

## Supporting Evidence

### Scope of Review

The USPSTF commissioned a systematic review<sup>1,15</sup> to evaluate the effectiveness of low-dose aspirin use to prevent preeclampsia. The current review included evidence on the effectiveness of low-dose aspirin in preventing preeclampsia in pregnant persons 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 use during pregnancy.

### Benefits of Risk Assessment and Preventive Medication

The USPSTF considered 18 randomized clinical trials (RCTs) (n = 15 908) to assess maternal and perinatal health outcomes and 16 RCTs (n = 15 767; 10 good-quality) to assess prevention of

preeclampsia.<sup>1</sup> All trials were placebo-controlled.<sup>1</sup> The 3 largest trials included 1 conducted in the US and 2 large, multinational trials coordinated from the UK. Fifteen smaller trials were conducted in various developed countries.<sup>1,8,16-18</sup>

In general, trial participants were young (mean age range, 20.4 to 33.5 years) and White individuals. Only 3 trials included majority populations of Black individuals (range, 50% to 72%).<sup>1</sup> Studies most often initiated low-dose aspirin before 20 weeks of gestation, but initiation ranged from at 11 to 32 weeks of gestation and generally continued until delivery or near term. Nulliparous and multiparous participants were combined in most trials. Aspirin dosages ranged from 50 to 150 mg/d, with most trials using 60 mg/d (6 RCTs) or 100 mg/d (8 RCTs).<sup>1</sup> Included trials of selected participants at increased risk for preeclampsia used a variety of approaches to identify the study population.<sup>1</sup> The incidence of preeclampsia in the placebo groups therefore also varied considerably, but the proportion developing preeclampsia were generally 2 to 3 times higher than the average incidence in the US.

The USPSTF found evidence of a reduction in risk for preterm birth (pooled relative risk [RR], 0.80 [95% CI, 0.67-0.95]; 13 studies;  $I^2 = 49%$ ) among individuals at increased risk for preeclampsia who received low-dose aspirin (n = 13 619). Pooled estimates provided evidence of a reduction in risk for small for gestational age/intrauterine growth restriction (RR, 0.82 [95% CI, 0.68-0.99]; 16 studies;  $I^2 = 41.0%$ ) in individuals at increased risk for preeclampsia (n = 14 385). There was also a reduction in perinatal mortality (pooled RR, 0.79 [95% CI, 0.66-0.96]; 11 studies;  $I^2 = 0%$ ) in individuals at increased risk for preeclampsia (n = 13 860).<sup>1</sup> The USPSTF found evidence of a reduction in risk for preeclampsia (pooled RR, 0.85 [95% CI, 0.75-0.95]; 16 studies;  $I^2 = 0%$ ) with low-dose aspirin use in individuals at increased risk (n = 14 093). Maternal complications of preeclampsia (eg, eclampsia or death) rarely occurred in studies and could not be evaluated.

Stratified comparisons did not show consistent evidence for effect differences related to intervention or population characteristics such as the timing of aspirin initiation (<16 weeks of gestation), the dosage of aspirin used, or participant characteristics.<sup>1</sup>

### Harms of Risk Assessment and Preventive Medication

The USPSTF considered 21 RCTs (n = 26 757; 14 good-quality, 7 fair-quality) to assess maternal, perinatal, and developmental harms. Studies of average-risk pregnant individuals (5 trials) were included with trials of participants at increased risk (16 trials).<sup>1</sup> All trials were placebo-controlled, except 1 study in which participants in the control group received usual care with no placebo. Harms consistently reported across studies were placental abruption, postpartum hemorrhage, and fetal intracranial bleeding.<sup>1</sup>

Trials did not demonstrate evidence of harms from daily low-dose aspirin use during pregnancy. Bleeding harms were uncommon. Pooled results were not statistically significant for placental abruption (pooled RR, 1.15 [95% CI, 0.76-1.72];  $I^2 = 25%$ ; 10 trials; n = 24 970), postpartum hemorrhage (pooled RR, 1.03 [95% CI, 0.94-1.12];  $I^2 = 0%$ ; 9 trials; n = 23 133), or fetal intracranial bleeding (pooled RR, 0.90 [95% CI, 0.51-1.57];  $I^2 = 19%$ ; 6 trials; n = 23 719).<sup>1</sup>

The USPSTF found limited evidence on long-term child developmental outcomes in offspring from in utero exposure to

low-dose aspirin. Follow-up data from the largest trial, the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP), reported no differences in physical or developmental outcomes (eg, gross motor development, height, weight, or hospital visits) in infants at age 12 and 18 months.<sup>13</sup> No differences were found within a few studies reporting other rare perinatal harms (eg, congenital anomalies or malformations).<sup>1</sup>

The USPSTF also did not find a difference in harms by the aspirin dosage or timing of aspirin initiation or for specific populations based on limited subgroup comparisons.<sup>1</sup>

### How Does Evidence Fit With Biological Understanding?

Preeclampsia is a complex, multisystem inflammatory syndrome that can originate from multiple causes and is thought 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 because of overactive inflammatory responses to normal placentation. Pre-existing inflammatory conditions are also thought 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.<sup>1</sup>

### Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from February 23, 2021, to March 22, 2021. Comments asked for an explicit acknowledgment of the role of systemic racism in the prevalence of and mortality from preeclampsia. As a result, the USPSTF added language to the Importance section. Several comments asked for clarification of risk factors. In response, the USPSTF revised Table 1 and the Implementation section. A respondent asked about harms of aspirin; the USPSTF added language to the Implementation section. The USPSTF also added clarifying language to the Practice Considerations section.

### Research Needs and Gaps

There are several critical evidence gaps. Studies are needed that provide more information on the following.

- Research is needed on how to improve identifying pregnant persons at increased risk for preeclampsia. Research to further develop and evaluate the effectiveness of risk assessment tools using

clinical history alone or combined with clinical testing could help clinicians better identify pregnant persons who could benefit from aspirin as preventive medication.

- Further research is needed in populations that have the highest rates of preeclampsia, including Black persons. Future trials should recruit adequate numbers of persons from varying racial and ethnic populations, such as Black persons, to have sufficient power to determine the effectiveness of different aspirin dosages and timing of initiation in the populations that bear the greatest disease burden.
- Comparative effectiveness trials are needed to identify the specific aspirin protocol (eg, dosage, timing, continuation, and time of day) likely to have the greatest benefit.
- Studies are needed to more fully understand the populations most likely to benefit from aspirin prophylaxis and what risk threshold and factors should be used to identify eligible patient populations.
- Research is needed on aspirin effectiveness for all hypertensive disorders of pregnancy.
- Research is needed to improve effective and equitable implementation of clinical guidelines for aspirin use in pregnancy.

## Recommendations of Others

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine<sup>19</sup> recommend low-dose aspirin (81 mg/d) prophylaxis for persons at high risk of preeclampsia; the regimen should be initiated between 12 and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery.<sup>1</sup> Additionally, low-dose aspirin prophylaxis should be considered for individuals with more than 1 of several moderate-risk factors for preeclampsia. Persons at risk of preeclampsia are defined based on the presence of 1 or more high-risk factors (history of preeclampsia, multifetal gestation, kidney disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension) or more than 1 of several moderate-risk factors (first pregnancy, maternal age 35 years or older, a body mass index greater than 30, family history of preeclampsia, sociodemographic characteristics, and personal history factors). The World Health Organization<sup>20</sup> and the American Heart Association/American Stroke Association<sup>21</sup> also recommend low-dose aspirin use for the prevention of preeclampsia in persons at increased risk.

### ARTICLE INFORMATION

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**Author Contributions:** Dr Davidson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The USPSTF members contributed equally to the recommendation statement.

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**Additional Information:** The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious 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. Published by JAMA®—Journal of the American Medical Association under arrangement with the Agency for Healthcare Research and Quality (AHRQ). ©2021 AMA and United States Government, as represented by the Secretary of the Department of Health and Human Services (HHS), by assignment from the members of the United States Preventive Services Task Force (USPSTF). All rights reserved.

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