Clinical Policy Title: Low-dose aspirin during pregnancy

Clinical Policy Number: CCP.1143

Effective Date: March 1, 2015
Initial Review Date: October 15, 2014
Most Recent Review Date: October 2, 2018
Next Review Date: October 2019

Related policies:
None

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of low-dose aspirin during pregnancy to be clinically proven and, therefore, medically necessary when all of the following criteria are met (American Academy of Family Physicians, 2014; American College of Obstetricians and Gynecologists, 2013; Bates, 2013; Bushnell, 2014; U.S. Preventive Services Task Force, 2014):

- Initiated in asymptomatic pregnant women at elevated risk of developing pre-eclampsia during pregnancy.
- Elevated risk is based on factors from either set of criteria below:
  - **Any** of the following single factors:
    - Hypertensive disease during prior pregnancy.
    - Multiple gestation pregnancy.
    - Chronic hypertension.
    - Type 1 or type 2 diabetes.
    - Renal disease.
    - Autoimmune disease (e.g., systemic lupus erythematosus or antiphospholipid syndrome).
  - **At least two** of the following risk factors:
    - Never having borne children.
- Obesity (e.g., body mass index > 30 kg/m²).
- Family history of pre-eclampsia (i.e., mother or sister).
- Sociodemographic characteristics (e.g., race or low socioeconomic status).
- Age ≥ 35 years.
- Personal history factors (e.g., born low birth weight or small for gestational age, previous adverse pregnancy outcome, > 10-year pregnancy interval).

- Patient has no history of adverse effects with, or contraindications to, low-dose aspirin.
- Aspirin is administered at dosages between 60 mg/d and 150 mg/d after 12 weeks of gestation.

**Limitations:**

All other uses of low-dose aspirin initiated during pregnancy are not medically necessary, including but not limited to the following:

- For women who undergo in vitro fertilization/intracytoplasmic sperm injection in the absence of other risk factors for pregnancy-related hypertension (Dentali, 2012; Groeneveld, 2013; Siristatidis, 2011).
- For women with a history of unexplained recurrent miscarriage, with or without inherited thrombophilia (American College of Obstetricians and Gynecologists,, 2015, updated 2017; de Jong, 2014).
- Administering low-dose aspirin at or earlier than 12 weeks of gestation as prophylaxis for pre-eclampsia (Roberge, 2013).

**Alternative covered services:**

- Pre-term delivery.
- Low molecular weight heparin.

**Background**

Hypertension is the most common medical problem encountered during pregnancy, complicating 5 percent to 10 percent of pregnancies. Elevated hypertension is defined as a systolic blood pressure of 120-139 mm Hg and a diastolic blood pressure less than 80 mm Hg (Whelton, 2017). Stage 1 hypertension is defined as either a systolic blood pressure of 130-139 mm Hg, a diastolic BP of 80-89 mm Hg or greater, or both. Stage 2 hypertension is defined as a systolic blood pressure of 140 mm Hg or greater, a diastolic BP of 90 mm Hg or greater, or both. Hypertensive disorders are associated with higher rates of maternal, fetal, and infant mortality, and severe morbidity (American College of Obstetricians and Gynecologists, 2013).

The genesis of hypertensive pregnancy disorders is an area of active research and theory development. Abnormal development and function of the placenta may play a critical role (Bujold, 2011). Abnormal placentation elicits inadequate utero-placental blood perfusion and ischemia. Placental ischemia and lowered placental perfusion cause the release of damaging factors (i.e., cellular debris, oxidized lipids, antiangiogenic factors, and soluble endoglin) into the maternal bloodstream, resulting in inflammation and oxidative stress.
with platelet aggregation and clotting system activation (Bujold, 2011).

The American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy (2013) classifies hypertensive disorders during pregnancy into four categories:

- Chronic hypertension (of any cause that predates conception or detected before 20 weeks of gestation).
- Pre-eclampsia/eclampsia.
- Pre-eclampsia superimposed on chronic hypertension.
- Gestational hypertension (new onset hypertension after 20 weeks of gestation, often near term, in the absence of proteinuria, or the failure of blood pressure to normalize postpartum).

Pre-eclampsia is the most common form of hypertension that complicates pregnancy, occurring in about 3 percent of pregnancies. It is one of the leading causes of maternal and perinatal morbidity (Hutcheon, 2011). Pre-eclampsia is a multisystem inflammatory syndrome with an unclear etiology and natural history. Most often, it occurs in the latter half of pregnancy (American College of Obstetricians and Gynecologists, 2013). American College of Obstetricians and Gynecologists defines pre-eclampsia clinically as hypertension in pregnancy associated with proteinuria (urinary protein excretion $\geq 300$ mg/24 h) or without proteinuria if one of the other multisystem features is present (e.g., thrombocytopenia [platelet count $< 100,000$/microliter], impaired liver function, progressive renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances). Severe pre-eclampsia comprises hemolysis, elevated liver enzymes, and low platelet count syndrome, and is associated with high rates of neonatal and maternal morbidity. Eclampsia is the convulsive phase of the disorder, and is among the more severe manifestations of the disease (American College of Obstetricians and Gynecologists, 2013).

Adverse pregnancy outcomes related to severe pre-eclampsia and eclampsia are caused largely by the need for preterm delivery (American College of Obstetricians and Gynecologists, 2013). Intra-uterine growth restriction (IUGR), placental abruption, and preterm birth are common and produce associated neonatal morbidities (Bujold, 2011).

**Aspirin:**

Aspirin (acetylsalicylic acid) is a salicylate drug often used as an analgesic to relieve minor aches and pains, an antipyretic to reduce fever, and an anti-inflammatory medication (American College of Obstetricians and Gynecologists, 2013). Aspirin in low doses is used as an antiplatelet drug to reduce the risk of heart attack and stroke either by interfering with platelet adhesion or by aggregating and preventing initial clot formation. Its anti-inflammatory and antiplatelet properties make it a potential option in the management of certain pregnancy-related conditions (American College of Obstetricians and Gynecologists, 2013).

Its mechanism of action to prevent pre-eclampsia remains unclear, but, theoretically, low-dose aspirin may enhance uterine and ovarian blood flow and tissue perfusion by decreasing platelet aggregation and inhibiting vasoconstriction (Bujold, 2011). Aspirin may have a beneficial effect on endothelial dysfunction later in gestation. This could provide more optimal conditions for invasion of the uterine spiral arterioles and
improved uteroplacental blood flow, which might prevent or delay development of pregnancy-induced hypertension or preterm delivery (Bujold, 2011). Antiplatelet medications, primarily low-dose aspirin, have been associated with modest but consistent and significant reductions in risk of preterm birth, fetal or neonatal deaths, and small-for-gestational age fetuses (Askie, 2007; Duley, 2007). However, uncertainty remains about who is most likely to benefit and when to initiate treatment and at what dose.

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on August 23, 2018. Search terms were: "aspirin" (MeSH) and "pregnancy" (MeSH).

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

For this policy, we identified six systematic reviews with meta-analyses and eight evidence-based practice guidelines. No cost-effectiveness studies were identified. One meta-analysis conducted by the Agency for Healthcare Research and Quality (AHRQ for the U.S. Preventive Services Task Force (USPSTF provides the most current and comprehensive analysis of the effectiveness of low-dose aspirin for women at elevated risk of developing pre-eclampsia (Henderson, 2014). One meta-analysis assessed the timing of low-dose aspirin administration on women at elevated risk of adverse perinatal outcomes (Roberge, 2013). Four meta-analyses considered two other populations of women in whom low-dose aspirin may be effective in preventing adverse perinatal and maternal outcomes. These populations were women with unexplained recurrent miscarriage with or without inherited thrombophilia (de Jong, 2014) and women who undergo IVF/ICSI (Groeneveld, 2013; Dentali, 2012; Siristatidis, 2011).

**The evidence is sufficient to support the use of well-established risk factors based on patient medical history to identify asymptomatic women at elevated risk of pre-eclampsia during pregnancy.** The challenge in applying the evidence on aspirin prophylaxis during pregnancy to clinical practice is predicting who is at risk
and most likely to benefit from treatment. Several risk factors have been implicated in hypertensive pregnancy disorders, specifically pre-eclampsia (Henderson, 2014). The most consistent risk factors resulting in the highest incidence of pre-eclampsia are based on patient medical history (Henderson, 2014). Table 1 lists risk factors that are considered well-established in the literature and were used as inclusion criteria in the meta-analyses by Henderson (2014). There is agreement among evidence-based guidelines in the use of these factors for risk assessment, with one exception being American College of Obstetricians and Gynecologists, which lists IVF as a risk factor for pre-eclampsia, while other evidence-based guidelines do not (Henderson, 2014; USPSTF, 2014; American College of Obstetricians and Gynecologists, 2013; Redman, 2011).

### Table 1. Risk factors for pre-eclampsia based on patient medical history

**High risk:** Presence of any single risk factor consistently associated with the greatest risk of pre-eclampsia. Hypertensive disease during prior pregnancy.

- Risk factors:
  - Multiple gestation pregnancy.
  - Chronic hypertension.
  - Type 1 or type 2 diabetes.
  - Renal disease.
  - Autoimmune disease (e.g., systemic lupus erythematosus, antiphospholipid syndrome).
  - IVFa.

**Moderate risk:** Presence of multiple moderate risk factors may identify women at high risk of pre-eclampsia.

- Never having borne children.
- Obesity (e.g., BMI > 30 kg/m²).
- Family history of pre-eclampsia (i.e., mother, sister).
- Sociodemographic characteristics (i.e., black race, low socioeconomic status).
- Age ≥ 35 years (or ≥ 40 yearsa, b).
- Personal history factors (e.g., born low birth weight or small for gestational age, previous adverse pregnancy outcome, or > 10-year pregnancy interval).

**Low risk:**

- Prior uncomplicated term delivery.

**Key:**

a American College of Obstetricians and Gynecologists (2013) only.

b Redman (2011) only.

Risk factors with less consistent supporting evidence that are the subject of ongoing research include changes in paternity between pregnancies, reduced exposure to paternal semen (IVF, sperm donation), inter-pregnancy weight change, history of migraine headaches, and various biomarkers and clinical readings (Henderson, 2014). A suitable physiologic or biochemical marker that can be used early in pregnancy to predict the development of pre-eclampsia with good test performance characteristics remains elusive. Few trials have been conducted in the United States or in black women, who suffer the highest disease
Consequently, risk factors based on these clinical tests are not recommended for routine use in clinical care to identify women at increased risk of pre-eclampsia (USPSTF, 2014; American College of Obstetricians and Gynecologists, 2013; Redman, 2011).

The evidence is sufficient to support the use of low-dose aspirin for asymptomatic women at elevated risk of developing pregnancy-related hypertensive disorders, primarily pre-eclampsia, and who have no prior adverse effects with or contraindications to low-dose aspirin. Evidence from multiple meta-analyses of large randomized controlled trials (RCTs) and individual patient data (IPD) shows aspirin is a safe, low-cost, and readily accessible treatment option that provides a modest but significant improvement in perinatal outcomes in this population. Evidence-based guidance that recommends low-dose aspirin to high-risk women for management of hypertensive disorders in pregnancy reflects these findings (American Academy of Family Physicians [AAFP, 2014; Bushnell, 2014; USPSTF, 2014; American College of Obstetricians and Gynecologists, 2013; Bates, 2013; Redman, 2011; World Health Organization [WHO] 2011).

The evidence is insufficient to support the use of low-dose aspirin for women who undergo IVF/ICSI in the absence of other risk factors. The limited evidence does not appear to improve procedural success with respect to perinatal outcomes (Groeneveld, 2013; Dentali, 2012; Siristatidis, 2011).

The evidence is insufficient to support the use of low-dose aspirin for women with a history of unexplained recurrent miscarriage, with or without inherited thrombophilia. Recurrent miscarriage is usually defined as three or more consecutive, spontaneous miscarriages occurring in the first trimester, with the same biological father (Duckitt, 2008). Limited evidence suggests no beneficial effect of anticoagulants on perinatal outcomes in this population (de Jong, 2014).

The evidence is sufficient to support initiating low-dose aspirin as prophylaxis after 12 weeks of gestation in women who are at elevated risk for pre-eclampsia. For RCTs of women at elevated risk of pre-eclampsia, all trials initiated treatment after 12 weeks of gestation (Henderson, 2014). The evidence did not suggest additional benefit when aspirin was started earlier (12 weeks to 16 weeks) rather than later (≥ 16 weeks) (Roberge, 2013). The evidence regarding when to stop aspirin prophylaxis is inconclusive (AAFP, 2014; Bushnell, 2014; USPSTF, 2014; American College of Obstetricians and Gynecologists, 2013; Bates, 2013; Redman, 2011; WHO, 2011).

The evidence is sufficient to support using low-dose aspirin at dosages between 60 mg/d and 150 mg/d to reduce the risk of pre-eclampsia and associated perinatal outcomes. There was no consistent effect of dosage on outcomes within this range. The most commonly used dosage was 100 mg/d, but the two largest trials contributing to the estimates of benefit used 60 mg/d (Henderson, 2014). In the United States, low-dose aspirin is available at a dose of 81 mg/d (AAFP, 2014; Bushnell, 2014; USPSTF, 2014; American College of Obstetricians and Gynecologists, 2013; Bates, 2013).

Policy updates:

We identified one new systematic review/meta-analysis (Bartsch, 2016) and two new evidence-based
guidelines (American College of Obstetricians and Gynecologists, 2015; Vayssiere, 2015). Bartsch (2016) identified several clinical risk factors for pre-eclampsia determined in early pregnancy, which are consistent with our earlier findings listed in Table 1. Commercially available predictive tests are limited by the low positive predictive value (PPV) for early-onset pre-eclampsia and the lack of data demonstrating improved clinical outcomes. A detailed medical history continues to be the best and only recommended screening approach for identifying pregnant women at risk of developing early-onset pre-eclampsia (American College of Obstetricians and Gynecologists, 2015). The French College of Gynaecologists and Obstetricians (FCGO) recommends prescribing low-dose aspirin to women with a history of pre-eclampsia before 34 weeks of gestation, and/or fetal growth restriction (FGR) below the fifth percentile with a probable vascular origin (Vayssiere, 2015). These results do not change previous findings. Therefore, no changes to the policy are warranted.

In 2017, American College of Obstetricians and Gynecologists reaffirmed their professional statements on early pregnancy loss and first-trimester risk assessment for early-onset preeclampsia. Two new analyses from the Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration (Mehta, 2017; Roberge, 2017) confirm the effects of low-dose aspirin on preventing preeclampsia and its complications, when initiated at or before 16 weeks gestation, but there is greater uncertainty regarding both the benefits of low dose aspirin when initiated after 16 weeks’ gestation and the optimal dosage. These results do not change the original findings, and no policy changes are warranted.

In 2018, we updated the guidelines for blood pressure evaluation and added the source reference to those guidelines to the policy reference list. We did not identify any other relevant publications. Policy ID changed from 12.02.03 to CCP.1143.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
| American College of Obstetricians and Gynecologists (2015, reaffirmed 2017) | **Early pregnancy loss**  
**Key points:**  
- The use of anticoagulants, aspirin, or both has not been shown to reduce the risk of early pregnancy loss in women with thrombophilia except in women with antiphospholipid syndrome (based on good and consistent scientific evidence [Level A]). |
| American College of Obstetricians and Gynecologists (2015 reaffirmed 2017) | **First-trimester risk assessment for early-onset preeclampsia**  
**Key points:**  
- American College of Obstetricians and Gynecologists does not recommend screening to predict pre-eclampsia beyond obtaining an appropriate detailed medical history due to the low PPV of current predictive tests. Evidence does not show that aspirin or other interventions reduce the incidence of pre-eclampsia for women at high risk based on first-trimester predictive tests.  
- Cost-effectiveness of screening strategies for first-trimester risk assessment will depend on tests demonstrating sufficient sensitivities and PPVs to accurately identify women who will develop pre-eclampsia and on interventions that improve clinical outcome in women who test positive. |
<p>| Meher (2017) for the | <strong>Key points:</strong> |</p>
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
| PARIS Collaboration | - A subgroup analysis of individual participant data from a previously published meta-analysis (Roberge, 2013) comparing gestation at randomization (< 16 weeks versus ≥ 16 weeks) to antiplatelet agents.  
- There was no significant between-group difference for any of the four prespecified outcomes: preeclampsia; death of baby; preterm birth prior to 34 weeks; and small-for-gestational-age baby. |
| Roberge (2017) for the PARIS Collaboration | **Key points:**  
- Systematic review and meta-analysis of 45 RCTs (20,909 total pregnant women) comparing the effect of daily 50-150 mg of aspirin or placebo (or no treatment) on preventing preeclampsia or FGR.  
- Significant reduction and a dose-response effect for prevention of preeclampsia and FGR with low-dose aspirin initiated at ≤ 16 weeks' gestation.  
- No risk reduction or dose-response effect with low-dose aspirin initiated at >16 weeks' gestation. |
| Siristatidis (2011, updated 2016) | **Key points:**  
- Systematic review and meta-analysis of 13 RCTs (2,653 total women).  
- Quality assessment — Mostly low or unclear risk of bias.  
- No significant differences found between the treatment and control groups for any of the outcomes assessed.  
- Aspirin versus control — No significant differences found for live birth rate (RR 0.91, 95% CI 0.72 - 1.15), clinical pregnancy rate (RR 1.03, 95% CI 0.91 - 1.17), ectopic rate (RR 1.86, 95% CI 0.75 - 4.63), or miscarriage rates (RR 1.10, 95% CI 0.68 - 1.77).  
- Evidence does not support use of aspirin for women undergoing IVF/ICSI. Adequately powered trials are needed. |
| Bartsch (2016) | **Key points:**  
- Systematic review and meta-analysis of 92 cohort studies (25,356,688 total pregnancies).  
- The pooled rate (%, 95% confidence interval [CI]) and relative risk (RR, 95% CI) for preeclampsia:  
  - Antiphospholipid antibody (pooled rate 17.3%, 6.8% - 31.4%).  
  - Prior pre-eclampsia (RR 8.4, 7.1 - 9.9).  
  - Chronic hypertension (pooled rate 16.0%, 12.6% - 19.7%) and (RR 5.1, 4.0 - 6.5).  
  - Pregestational diabetes (pooled rate 11.0%, 8.4% - 13.8%) and (RR 3.7, 3.1 - 4.3).  
  - Prepregnancy BMI >30 (7.1%, 6.1% - 8.2%) and (RR 2.8, 2.6 - 3.1).  
  - Use of assisted reproductive technology (pooled rate 6.2%, 4.7% - 7.9%) and (RR 1.8, 1.6 - 2.1). |
| Vayssiere (2015) for the FCGO | **Key points:**  
- Recommend prescribing low-dose aspirin to women with a history of pre-eclampsia < 34 weeks of gestation, and/or FGR below the fifth percentile with a probable vascular origin (professional consensus). |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson (2014) for AHRQ</td>
<td><em>Aspirin must be taken in the evening or at least eight hours after awakening (Grade B), before 16 weeks of gestation, at a dose of 100 – 160 mg/day (Grade A).</em></td>
</tr>
<tr>
<td>Prevention of pre-eclampsia</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td></td>
<td>• Systematic review and meta-analysis of one large U.S. study (2,539 total patients); one large international study based in the United Kingdom (9,364 total patients); 13 smaller trials for analysis of benefits; six RCTs; and two large observational studies for analysis of harms.</td>
</tr>
<tr>
<td></td>
<td>• Quality assessment: moderate to high; potential publication bias, many individual RCTs underpowered to detect some serious health outcomes.</td>
</tr>
<tr>
<td></td>
<td>• Effectiveness: For women at elevated risk of pre-eclampsia, prophylaxis with low-dose aspirin (60 mg - 150 mg) beginning after the first trimester of pregnancy &gt; 12 weeks of gestation modestly reduced risks of pre-eclampsia, preterm birth, IUGR, and possibly perinatal mortality, with a significant difference in birth weight noted. Perinatal health benefits likely due to reduction in pre-eclampsia incidence. No direct effects on maternal health found.</td>
</tr>
<tr>
<td></td>
<td>• Harms: potential increased risk of abruption, but not other bleeding-related complications (e.g., postpartum hemorrhage, maternal blood loss, and neonatal intracranial or intraventricular bleeding). Low risk of adverse longer-term outcomes for offspring from low-dose in utero aspirin exposure.</td>
</tr>
<tr>
<td></td>
<td>• Inconclusive evidence regarding when to stop aspirin prophylaxis.</td>
</tr>
<tr>
<td></td>
<td>• No consistent effect of dosage.</td>
</tr>
<tr>
<td></td>
<td>• Insufficient evidence to provide clear guidance on the ideal high-risk candidate for prophylaxis.</td>
</tr>
<tr>
<td>De Jong (2014) for Cochrane review</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Unexplained miscarriage with or</td>
<td>• Systematic review and meta-analysis of nine RCTs or quasi-RCTs (1,228 total women) evaluating effects of low molecular weight heparin (enoxaparin or nadroparin in varying doses), aspirin or a combination of both.</td>
</tr>
<tr>
<td>without thrombophilia</td>
<td>• Overall quality: moderate; three studies with high risk of bias, six with low risk of bias.</td>
</tr>
<tr>
<td></td>
<td>• Limited evidence suggests no beneficial effect of anticoagulants on perinatal outcomes in studies of low risk of bias.</td>
</tr>
<tr>
<td></td>
<td>• Inconclusive results.</td>
</tr>
<tr>
<td>Roberge (2013) and commentary by</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Meher (2013) for the PARIS</td>
<td>• Systematic review and meta-analysis of 42 RCTs (27,222 total women).</td>
</tr>
<tr>
<td>Collaboration</td>
<td>• Overall quality: low to moderate. Most studies with low or unclear risk of bias.</td>
</tr>
<tr>
<td>Early versus late administration</td>
<td>• Limited evidence with high uncertainty suggests low-dose aspirin initiated at ≤ 16 weeks of gestation reduces adverse perinatal outcomes (e.g., FGR, preterm birth, pre-eclampsia, perinatal death, and severe pre-eclampsia) than when initiated at &gt; 16 weeks.</td>
</tr>
<tr>
<td>of low-dose aspirin</td>
<td>• Confirmation using meta-analysis of IPD is warranted.</td>
</tr>
<tr>
<td>Groeneveld (2013)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Preconception administration of</td>
<td>• Meta-analysis of IPD on 268 pregnancies (131 treated with aspirin, 137 placebo) from four RCTs.</td>
</tr>
<tr>
<td>low-dose aspirin in IVF</td>
<td>• Overall quality: Moderate; variation in duration of low-dose aspirin therapy and degree of hypertension, underpowered.</td>
</tr>
</tbody>
</table>
Significantly fewer twin pregnancies in the aspirin group (odds ratio [OR] 0.55, 95% CI 0.30 - 0.98), but no significant differences for hypertensive pregnancy complications and preterm delivery for either singletons (OR 0.62, 95% CI 0.22 - 1.7 and OR 0.52, 95% CI 0.16 - 1.7), respectively, or twin pregnancies (OR 1.2, 95% CI 0.35 - 4.4 and OR 1.6 95% CI 0.51 - 5.0), respectively.

Evidence does not support starting low-dose aspirin preconceptionally to reduce the incidence of hypertensive pregnancy complications or preterm delivery in IVF women. Larger studies are warranted.

Low-dose aspirin in IVF/ICSI

Key points:

- Systematic review and meta-analysis of 17 RCTs (6,403 women).
- Overall quality — 10 of low quality, seven of high quality using Jadad scale.
- Timing and dosage of aspirin varied.
- Aspirin was not associated with improvement in live birth rate versus placebo or no treatment (OR 1.08, 95% CI 0.90 - 1.29). Pregnancy rates were significantly increased in patients randomized to low-dose aspirin (OR 1.19, 95% CI 1.01 - 1.39), but miscarriage rates were not (OR 1.18, 95% CI 0.82 - 1.68). Robust in sensitivity analyses in all considered endpoints.
- Evidence does not support low-dose aspirin to improve pregnancy outcomes in IVF/ICSI. Further high-quality studies evaluating the efficacy of aspirin in selected groups of patients are warranted.
- Timing of introduction of low-dose aspirin, especially when introduced at least one day before embryo transfer, may improve efficacy, but more study is needed.

References

Professional society guidelines/other:


**Peer-reviewed references:**

DOI: 10.1016/j.ajog.2016.09.076.


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>N40.0-N40.1</td>
<td>Benign prostatic hyperplasia</td>
<td></td>
</tr>
<tr>
<td>C61.</td>
<td>Malignant neoplasm of prostate</td>
<td></td>
</tr>
<tr>
<td>D68.61</td>
<td>Antiphospholipid syndrome</td>
<td></td>
</tr>
<tr>
<td>O10.011-O10.019</td>
<td>Pre-existing hypertension affecting pregnancy</td>
<td></td>
</tr>
<tr>
<td>O10.411-O10.419</td>
<td>Pre-existing secondary hypertension affecting pregnancy</td>
<td></td>
</tr>
<tr>
<td>O09.511-O09.519</td>
<td>Supervision of elderly primigravida</td>
<td></td>
</tr>
<tr>
<td>O09.521-O09.529</td>
<td>Supervision of elderly multigravida</td>
<td></td>
</tr>
<tr>
<td>O24.011-O24.019</td>
<td>Pre-existing diabetes mellitus, Type 1, in pregnancy</td>
<td></td>
</tr>
<tr>
<td>O24.111-O24.119</td>
<td>Pre-existing diabetes mellitus, Type 2, in pregnancy</td>
<td></td>
</tr>
<tr>
<td>O30.90-O30.93</td>
<td>Multiple gestation</td>
<td></td>
</tr>
<tr>
<td>O99.111-O99.119</td>
<td>Other diseases of the blood and blood-forming organisms and certain disorders involving the immune mechanism complicating pregnancies</td>
<td></td>
</tr>
<tr>
<td>O99.210-O99.213</td>
<td>Obesity complicating pregnancy</td>
<td></td>
</tr>
<tr>
<td>M32.9</td>
<td>Systemic lupus erythematosus</td>
<td></td>
</tr>
<tr>
<td>HCPCS Level II Code</td>
<td>Description</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>G8298</td>
<td>Aspirin</td>
<td></td>
</tr>
</tbody>
</table>