Clinical Policy Title: Low-dose aspirin during pregnancy

Clinical Policy Number: 12.02.03

Effective Date: March 1, 2015
Initial Review Date: October 15, 2014
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Related policies:

None.

About this policy: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’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 AmeriHealth Caritas Pennsylvania 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. AmeriHealth Caritas Pennsylvania’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. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of low-dose aspirin during pregnancy to be clinically proven and, therefore, medically necessary when criteria from categories A, B, C, and D below are met:

A. Initiated in asymptomatic pregnant women at elevated risk of developing pre-eclampsia during pregnancy.

B. Elevated risk is based on factors from either section 1 or 2 below:

1. Any of the following single factors:
   i. Hypertensive disease during prior pregnancy.
   ii. Multiple gestation pregnancy.
   iii. Chronic hypertension.
   iv. Type 1 or type 2 diabetes.
   v. Renal disease.
   vi. Autoimmune disease (e.g., systemic lupus erythematosus or antiphospholipid syndrome).

2. At least two of the following risk factors:
i. Never having borne children.
ii. Obesity (e.g., body mass index [BMI] > 30 kg/m).
iii. Family history of pre-eclampsia (i.e., mother or sister).
   iv. Sociodemographic characteristics (e.g., race or low socioeconomic status).
       Age ≥ 35 years.
   v. Personal history factors (e.g., born low birth weight or small for gestational
       age, previous adverse pregnancy outcome, > 10-year pregnancy interval).
C. Patient has no history of adverse effects with, or contraindications to, low-dose aspirin.
D. 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:

- The use of low-dose aspirin for women who undergo in vitro fertilization
  (IVF)/intracytoplasmic sperm injection (ICSI) in the absence of other risk factors for
  pregnancy-related hypertension.
- The use of low-dose aspirin for women with a history of unexplained recurrent miscarriage,
  with or without inherited thrombophilia.
- Administering low-dose aspirin at or earlier than 12 weeks of gestation as prophylaxis for
  pre-eclampsia.

Alternative covered services:

Pre-term delivery and low molecular weight heparin.

Background

Hypertension is the most common medical problem encountered during pregnancy, complicating 5
percent to 10 percent of pregnancies. It is defined as either a systolic blood pressure (BP) 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 Congress of

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 ACOG Task Force on Hypertension in Pregnancy classifies hypertensive disorders during pregnancy into four categories (ACOG 2013):

- 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 BP 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 (ACOG 2013). ACOG defines pre-eclampsia clinically as hypertension in pregnancy associated with proteinuria (urinary protein excretion ≥ 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 (ACOG 2013).

Adverse pregnancy outcomes related to severe pre-eclampsia and eclampsia are caused largely by the need for preterm delivery (ACOG 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 (ACOG 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 (ACOG 2013).

The mechanism of action of aspirin 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 (Duley 2007, Askie 2007). However, uncertainty remains about who is most likely to benefit and when to initiate treatment and at what dose.

**Searches**

AmeriHealth Caritas Pennsylvania 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 (CMS).

We conducted searches on September 9, 2016. 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 ACOG, which lists IVF as a risk factor for pre-eclampsia, while other evidence-based guidelines do not (Henderson 2014, USPSTF 2014, ACOG 2013, Redman 2011).

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

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td>• Hypertensive disease during prior pregnancy.</td>
</tr>
<tr>
<td>Presence of any single risk factor consistently associated with the greatest risk of pre-eclampsia</td>
<td>• Multiple gestation pregnancy.</td>
</tr>
<tr>
<td></td>
<td>• Chronic hypertension.</td>
</tr>
<tr>
<td></td>
<td>• Type 1 or type 2 diabetes.</td>
</tr>
<tr>
<td></td>
<td>• Renal disease.</td>
</tr>
<tr>
<td></td>
<td>• Autoimmune disease (e.g., systemic lupus erythematosus, antiphospholipid syndrome).</td>
</tr>
<tr>
<td></td>
<td>• IVFa.</td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td>• Never having borne children.</td>
</tr>
<tr>
<td>Presence of multiple moderate risk factors may identify women at high risk of pre-eclampsia</td>
<td>• Obesity (e.g., BMI &gt; 30 kg/m²).</td>
</tr>
<tr>
<td></td>
<td>• Family history of pre-eclampsia (i.e., mother, sister).</td>
</tr>
<tr>
<td></td>
<td>• Sociodemographic characteristics (i.e., black race, low socioeconomic status).</td>
</tr>
<tr>
<td></td>
<td>• Age ≥ 35 years (or ≥ 40 yearsa,b).</td>
</tr>
<tr>
<td></td>
<td>• Personal history factors (e.g., born low birth weight or small for gestational age, previous adverse pregnancy outcome, or &gt; 10-year pregnancy interval).</td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>• Prior uncomplicated term delivery.</td>
</tr>
</tbody>
</table>

Note: a ACOG (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. (Henderson 2014). 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 (ACOG 2013, USPSTF 2014, 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 (USPSTF 2014, American Academy of Family Physicians [AAFP] 2014, Bushnell 2014, ACOG 2013, Bates 2013, World Health Organization [WHO] 2011, Redman 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) in pregnancy in women at increased risk for pre-eclampsia (Roberge 2013). The evidence regarding when to stop aspirin prophylaxis is inconclusive (USPSTF 2014, AAFP 2014, Bushnell 2014, ACOG 2013, Bates 2013, WHO 2011, Redman 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 (USPSTF 2014, AAFP 2014, Bushnell 2014, ACOG 2013, and Bates 2013).

Policy updates:

We identified one new systematic review/meta-analysis (Bartsch 2016) and two new evidence-based guidelines (ACOG 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 (ACOG 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.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
</table>
| 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 pre-eclampsia:  
    - Antiphospholipid antibody (pooled rate 17.3%, 6.8% to 31.4%).  
    - Prior pre-eclampsia (RR 8.4, 7.1 to 9.9).  
    - Chronic hypertension (pooled rate 16.0%, 12.6% to 19.7%) and (RR 5.1, 4.0 to 6.5).  
    - Pregestational diabetes (pooled rate 11.0%, 8.4% to 13.8%) and (RR 3.7, 3.1 to 4.3).  
    - Prepregnancy BMI >30 (7.1%, 6.1% to 8.2%) and (RR 2.8, 2.6 to 3.1).  
    - Use of assisted reproductive technology (6.2%, 4.7% to 7.9%) and (RR 1.8, 1.6 to 2.1). |
| ACOG (2015) | **Key points:**  
  - ACOG 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 interventions that improve clinical outcome in women who test positive. |
| 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).  
  - 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). |
| Henderson (2014) for AHRQ | **Key points:**  
  - 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 |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>eclampsia.</td>
<td>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 to 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 abruptio, 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>• No clear benefit of starting aspirin treatment before 16 weeks. 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) Cochrane review</td>
<td>Key points:</td>
</tr>
<tr>
<td></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></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>De Jong (2014) Cochrane review Unexplained miscarriage with or without thrombophilia.</td>
<td>Key points:</td>
</tr>
<tr>
<td>Roberge (2013) and commentary by Meher (2013) Early versus late administration of low-dose aspirin.</td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Systematic review and meta-analysis 42 RCTs (27,222 total women).</td>
</tr>
<tr>
<td></td>
<td>• Overall quality: low to moderate. Most studies with low or unclear risk of bias.</td>
</tr>
<tr>
<td></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></td>
<td>• Confirmation using meta-analysis of IPD is warranted.</td>
</tr>
<tr>
<td>Groeneveld (2013) Preconception administration of low-dose aspirin in IVF.</td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Meta-analysis of IPD on 268 pregnancies (131 treated with aspirin, 137 placebo) from four RCTs.</td>
</tr>
<tr>
<td></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 to 0.98), but no significant differences for hypertensive pregnancy complications and preterm delivery for either singletons (OR 0.62, 95% CI 0.22 to 1.7 and OR 0.52, 95% CI 0.16 to 1.7),
Evidence does not support starting low-dose aspirin pre-conceptionally to reduce the incidence of hypertensive pregnancy complications or preterm delivery in IVF women. Larger studies are warranted.

**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 to 1.29). Pregnancy rates were significantly increased in patients randomized to low-dose aspirin (OR 1.19, 95% CI 1.01 to 1.39), but miscarriage rates were not (OR 1.18, 95% CI 0.82 to 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.

**Key points:**

- Systematic review and meta-analysis of 13 RCTs (n = 2,653 women).
- Quality assessment — Not reported in abstract, underpowered.
- No significant differences found between the treatment and control groups for any of the outcomes assessed.
- Aspirin versus control — No significant differences found on live birth rate (RR 0.91, 95% CI 0.72 to 1.15), clinical pregnancy rate (RR 1.03, 95% CI 0.91 to 1.17), ectopic rate (RR 1.86, 95% CI 0.75 to 4.63), or miscarriage rates (RR 1.10, 95% CI 0.68 to 1.77).
- Evidence does not support use of aspirin for women undergoing IVF/ICSI. Adequately powered trials are needed.

**Glossary**

**Antiphospholipid syndrome** — An acquired form of thrombophilia caused by antibodies against constituents of the cell membrane. Regarded as an autoimmune disease and strongly associated with miscarriage.

**Eclampsia** — An acute and life-threatening complication of pregnancy characterized by the appearance of tonic-clonic seizures (convulsions), usually in a woman who has developed pre-eclampsia.

**Hemolysis, elevated liver enzymes, and low platelet count syndrome (HELLP)** — A life-threatening
complication often considered to be a variant or complication of pre-eclampsia. Usually begins during the third trimester and may occur after delivery.

**Intra-uterine growth restriction (IUGR)** — Refers to poor growth of a fetus during pregnancy. Most often involves poor maternal nutrition or lack of adequate oxygen supply to the fetus. Causes include multiple pregnancies, placental problems, and pre-eclampsia/eclampsia. IUGR can result in the baby being small for gestational age (SGA), most commonly defined as a weight below the 10th percentile for the gestational age and low birth weight.

**Meta-analysis of independent patient data (IPD)** — Analysis that uses raw patient data, rather than aggregated trial data as done in a standard meta-analysis, from each study. It permits researchers to perform subgroup analyses; improve consistency across studies (in inclusion criteria, outcome definition, and other factors); consider other outcomes; and identify predictors of an outcome. Increasingly used as an alternative to a standard meta-analysis.

**Placental abruption (placenta abruptio)** — Separation of the placenta from its attachment to the uterus wall before the fetus is delivered.

**Placentation** — Formation of a placenta in the uterus. It occurs seven to eight days after fertilization and implantation of the embryo into the uterine wall and involves the remodeling of spiral arteries to supply the needed amount of blood.

**Pre-eclampsia** — A multisystem inflammatory syndrome defined clinically as hypertension in pregnancy associated with proteinuria (urinary protein excretion \( \geq 300 \text{ mg/24 h} \)) 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) (ACOG 2013).

**Spiral arteries** — Small arteries that temporarily supply blood to the endometrium of the uterus during the luteal phase of the menstrual cycle.

**Thrombophilia** — Blood clotting abnormalities that increase the risk of thrombosis. May be hereditary or acquired later in life.

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on September 12, 2016, using term “preeclampsia” | Open Studies-recruiting | United States. 35 studies found, two relevant.

First Trimester Prediction of Preeclampsia and Fetal Growth Restriction. ClinicalTrials.gov website.
CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs 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>Comment</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>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>D68.61</td>
<td>Antiphospholipid syndrome</td>
<td></td>
</tr>
<tr>
<td>O10.011-O10.019</td>
<td>Pre-existing hypertension effecting pregnancy</td>
<td></td>
</tr>
<tr>
<td>O10.411-O10.419</td>
<td>Pre-existing secondary hypertension effecting pregnancy</td>
<td></td>
</tr>
<tr>
<td>O09.511-O09.519</td>
<td>O09.09.529</td>
<td>Supervision of elderly primigravida</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 I, 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>ICD-10 Code</td>
<td>Description</td>
<td>Comment</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>M32.9</td>
<td>Systemic lupus erythematos</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Level</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>G8298</td>
<td>Aspirin</td>
<td></td>
</tr>
</tbody>
</table>