Anthem

Medical Policy

Subject: Serum Biomarker Tests for Risk of Preeclampsia
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Description/Scope

This document addresses serum biomarker testing to identify individuals at increased risk of preeclampsia during pregnancy. Serum biomarkers that can be used to predict preeclampsia include placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A), levels of which tend to drop during pregnancy in asymptomatic individuals who later develop preeclampsia. Moreover, the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1), which tends to increase in preeclampsia and PlGF may be calculated to test for the presence or absence of preeclampsia. In addition, there are other potential serum protein biomarkers, such as retinol-binding protein 4 (RBP4) and endoglin (ENG), the concentrations of which can be assessed and results combined into a risk-score to identify individuals at high risk of preeclampsia.

Note: This document does not apply to routine tests performed during pregnancy such as urine protein analysis, blood pressure, renal function labs, liver function labs and complete blood count (CBC).

Please see the following related document for additional information:

- ADMIN.00002 Preventive Health Guidelines

Position Statement

Investigational and Not Medically Necessary:

Serum biomarker tests to diagnosis, screen for, or assess risk of preeclampsia are considered**nvestigational and not medically necessary**.

Rationale

Prediction of Preeclampsia

Asymptomatic pregnancies

A number of observational studies evaluating the predictive accuracy of PlGF screening have been published and these have been evaluated in a meta-analysis. The study, by Agrawal and colleagues (2019), reviewed 40 observational studies published through May 23, 2018 that included participants with singleton pregnancies who had no signs or symptoms of preeclampsia at the time of PlGF testing. The studies had a total sample size of 92,687 women, and 3189 (3.4%) of these developed preeclampsia. In individual studies, the sensitivity of PlGF testing for predicting preeclampsia varied from 7% to 93%, and the specificities varied from 51% to 97%. When data were pooled, the overall sensitivity was 61% (95% confidence interval [CI], 0.53 to 0.69) and the overall specificity was 0.85 (95% CI, 0.82 to 0.88).

Data from several large prospective screening studies were published after the meta-analysis. Tan and colleagues (2018) reported on 61,174 singleton pregnancies, 1770 (2.9%) of which had developed preeclampsia. At an examination between 11 weeks 0 days to 13 weeks 6 days gestation, medical history was assessed, Uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP) were measured and serum concentration of PlGF and PAPP-A was assessed. The investigators calculated models predicting preeclampsia with various combinations of predictors. At a screen-positive rate of 10% for preeclampsia, the detection rate using maternal factors alone was 44.8% (95% CI, 40.5% to 69.2%) for preeclampsia < 37 weeks. The addition of PlGF to maternal factors increased the detection rate to 60.6% (95% CI, 56.3% to 64.9%), and the addition of PAPP-A to maternal factors increased it slightly to 48.5% (95% CI, 44.1% to 52.9%). The combination of MAP and UtA-PI and maternal factors increased the detection rate to 68.4% (95% CI, 64.1% to 72.3%). When PlGF, MAP and UtA-PI were considered, along with maternal factors, the detection rate was 74.8% (95% CI, 70.8% to 78.5%). The addition of PAPP-A rather than PlGF, to the model containing maternal factors, MAP and UtA-PI, did not improve the detection rate.

In 2020, Mazer Zumaeta and colleagues reported on 60,875 women with singleton pregnancies, 1736 (2.9%) of whom developed preeclampsia. Participants underwent a range of screening tests during their first routine first-trimester hospital visit, including serum concentrations of the biomarkers PlGF and PAPP-A (using a DELFIA Xpress system, PerkinElmer). In an analytic model with a fixed screen-positive rate of 10%, the addition of serum PAPP-A did not improve the prediction of preeclampsia beyond that provided by maternal factors, MAP and the UtA-PI. The addition of PlGF did significantly improve the screening model compared with maternal factors alone and maternal factors and PAPP-A. Moreover, the performance of screening with PlGF, maternal factors, MAP and UtA-PI was superior to screening with PAPP-A, maternal factors, MAP and UtA-PI.

No studies were identified that evaluated the mProbe preeclampsia test, which assesses levels of RBP4, endoglin and Kinase Insert Domain Receptor (KDR). However, studies have evaluated the association between levels of individual proteins assessed in the test and preeclampsia. In a 2019 study of 1002 pregnant women presenting with preeclampsia, higher serum concentrations of ENG were associated with risk of adverse maternal outcomes (Leaños-Miranda, 2019). A 2022 systematic review by Hamden and colleagues found that levels of RBP4 were significantly higher in pregnant women with preeclampsia compared with healthy controls.

Symptomatic pregnancies

In 2016, Zeisler and colleagues published findings from a prospective observational study including pregnant women age 18 and older with suspected preeclampsia. Participants were between 24 weeks 0 days to 36 weeks 6 days of gestation. This was a two-phase study, development and validation, each with data from 500 participants. Serum samples were collected and analyzed for levels of sFlt-1 and PlGF. The primary study objectives were to determine whether an sFLt-1:PlGF ratio at or below a defined cutpoint predicted the absence of preeclampsia, eclampsia or HELLP syndrome (Hemolysis, Elevated liver enzymes, LPw platelets counts) within 1 week of the baseline visit (rule out), and to determine whether a defined cutpoint predicted the presence of any of these outcomes within 4 weeks (rule in). In the development phase, a ratio of 38 was determined to be the optimal single cutoff value for both the rule out and rule in objectives. In the validation phase, the 38 cutoff point for the sFL-1:PlGF ratio had a sensitivity of 80%

(95% CI, 51.9 to 95.7%), a specificity of 78.3% (74.6 to 81.7%) and a negative predictive value (NPV) of 99% (95% CI, 97.9 to 99.9%) for predicting preeclampsia, eclampsia or HELLP syndrome within 1 week. For the prediction of one of these conditions within 4 weeks, the 38 cutoff point had a sensitivity of 66.2% (95% CI, 54.0 to 77.0%), specificity of 66.2% (95% CI, 54.0 to 77.0%) and a positive predictive value (PPV) of 36.7% (95% CI, 28.4 to 45.7%).

A 2020 study by Barton and colleagues enrolled 753 pregnant women with signs or symptoms of preeclampsia < 35 weeks' gestation. PlGF levels were retrospectively analyzed from plasma samples, with a normal level of PlGF defned as > 100 pg/mL. A total of 72% of women delivered at < 37 weeks' gestation and (47%) delivered at < 34 weeks' gestation. Compared with women with a normal PlGF level, women with PlGF ≤ 100 pg/ml had a significantly shorter time to delivery in multivariate models adjusting for gestational age and final diagnosis of preeclampsia (HR, 7.17, 95% CI, 5.08 to 10.13).

A 2022 study by Thadhani and colleagues evaluated the ThermoFisher BRAHMS PlGF and sFlt-1 KRYPTOR test. The prospective study included 1014 hospitalized women over 18 years old with singleton pregnancies between 23 weeks, 0 days and 34 weeks, 6 days' gestation who had a hypertensive disorder of pregnancy. The primary aim of the study was to validate the test, which measures the sFlt-1:PlGF ratio for predicting the development of preeclampsia with special features within 2 weeks of testing. Special features included severe hypertension, thrombocytopenia, impaired liver function, severe persistent right upper quadrant or epigastric pain, progressive renal insufficiency, pulmonary edema, new-onset cerebral or visual disturbances or medication-resistant headache. Initially, the test was evaluated in a derivation cohort. A total of 220 of 299 enrolled participants were included in the cohort; the remainder were excluded because they met criteria for special features at enrollment. From this derivation cohort, the investigators selected an sFlt-1:PlGF ratio of ≥ 40 for determining a positive test. For the validation cohort, 715 women were enrolled, of which 159 (22%) met criteria for special features at admission and were excluded, leaving 556 participants. The incidence of preeclampsia with special features within 2 weeks was 33.5%. Using the BRAHMS test with a cutoff of ≥ 40 for predicting preeclampsia with special features yielded a sensitivity of 94% (95% CI, 89 to 95%), a specificity of 75% (70 to 79%), a PPV of 65% (95% CI, 59 to 71%) and an NPV of 96% (95% CI, 93 to 98). The investigators also compared the performance of the sFlt-1:PlGF ratio to standard markers, including blood pressure, liver function tests, platelet counts and serum creatinine. They found an area under the curve (AUC) for the sFlt-1:PlGF ratio of 0.92. The AUC for the individual standard markers were as follows: systolic blood pressure, 0.67; diastolic blood pressure, 0.70; platelet count, 0.57; and creatinine, 0.65. The authors did not state whether the above markers were systematically accessed. The article did not discuss whether use of the BRAHMS test would change clinical management or improve health outcomes.

Several meta-analyses of studies evaluating the performance of biomarkers and prediction of adverse outcomes in preeclampsia have been published. A meta-analysis of studies evaluating the sFLt-1:PlGF ratio in singleton pregnancies both with and without suspected preeclampsia was published in 2018 by Agrawal and colleagues. The investigators included 15 observational studies with a total of 534 cases of preeclampsia and 19,587 controls. The pooled sensitivity of the sFLt-1:PlGF ratio for predicting preeclampsia was 80% (95% CI, 68 to 88%) and the pooled specificity was 92% (95% CI, 91 to 95%). Separate analyses were not conducted for studies that included women with suspected preeclampsia versus those that included women without suspected preeclampsia. In 2021, Lim and colleagues reviewed studies on the biomarkers sFLt-1, PlGF and the sFLt-1:PlGF ratio. A total of 33 studies were included in their analysis, all of which were observational and included women with suspected and/or confirmed preeclampsia or hypertensive disorders of pregnancy. A meta-analysis of 7 studies on PlGF found a pooled sensitivity of 76% (95% CI, 54% to 89%) and a pooled specificity of 71% (95% CI, 55% to 83%) for predicting preterm birth. A meta-analysis of 5 studies on the sFLt-1:PlGF ratio found a pooled sensitivity of 74% (95% CI, 59% to 85%) and a pooled specificity of 80% (95% CI, 67% to 89%) for predicting preterm birth. An analysis of the diagnostic accuracy of the sFLt-1:PlGF ratio for predicting adverse maternal outcomes included 5 studies and found a pooled sensitivity of 67% (95% CI, 46% to 82%) and a pooled specificity of 77% (95% CI, 66% to 86%).

Clinical Utility of Serum Biomarker Tests

No randomized controlled trials (RCTs) were identified that compared patient management or clinical outcomes in pregnant individuals screened for preeclampsia with maternal risk factors only versus individuals screened with maternal risk factors plus biomarkers such as PlGF or PAPP-A.

The ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial is a double-blind RCT comparing treatment with 150 mg per day of aspirin versus placebo from 11-14 until 36 weeks' gestation in individuals at increased risk (at least 1 in 100) of delivery with preterm (< 37 weeks' gestation) preeclampsia (Rolnik, 2017). Risk of preterm preeclampsia was assessed using an algorithm that included maternal risk factors, MAP, the UtA-PI and the maternal serum biomarkers PAPP-A and PlGF. PlGF concentrations were measured using the PlGF 1-2-3tm kits (PerkinElmer Inc). After initial exclusions, 25,797 individuals pregnant with singletons were screened for eligibility and 2707 (10.5%) individuals were eligible for participation. Of these, 1595 (59%) agreed to participate; n=785 were assigned to the aspirin group and n=806 were assigned to the placebo group. In the aspirin group, there were 13 (1.66%) observed cases of preterm preeclampsia and 53 (6.75%) cases of term preeclampsia. In the placebo group, there were 35 (4.34%) cases of preterm preeclampsia and 53 (6.56%) cases of term preeclampsia. The rate of preterm preeclampsia was 62% lower in the aspirin-treated group than the placebo group, but there was no significant difference in term preeclampsia between the groups. In the trial, only about 10% of individuals screened were found to be at increased risk of preterm preeclampsia. Moreover, the 62% risk reduction for preterm preeclampsia in the ASPRE trial was a relative risk; the absolute risk reduction was 2.68%. Furthermore, the study lacked a comparison between the maternal risk factors alone and maternal risk factors plus biomarkers.

Professional Organizations

Serum biomarker tests to screen for preeclampsia are not currently recommended by U.S.-based national organizations or professional societies.

The U.S. Preventive Services Task Force (USPSTF) recommendation on preeclampsia screening (Bibbins-Domingo, 2017) is: "screening for preeclampsia in pregnant women with blood pressure measurements throughout pregnancy. (B recommendation)." This document does not mention screening with biomarker tests.

In 2020, the American College of Obstetricians and Gynecologists (ACOG) stated, "biomarkers and ultrasonography cannot accurately predict preeclampsia and should remain investigational." The ACOG document stated:

> …Extensive work has identified some angiogenic factors (soluble fms-like tyrosine kinase-[sFlt-1], placental growth factor [PlGF], and soluble endoglin) in the second trimester as likely tools for the prediction of early-onset preeclampsia. However, no single test reliably predicts preeclampsia and further prospective investigation is required to demonstrate clinical utility. In the first trimester of pregnancy, it has been reported that a combination of low maternal serum concentrations of PlGF, high uterine artery pulsatility index, and other maternal parameters, identified 93.1% of patients who would develop preeclampsia requiring delivery before 34 weeks of gestation. However, the results of this study are based on mathematical modeling derived from a nested case-control study applied to a large cohort of almost 7,800 patients in which PlGF was measured only in the case-control group. The

> calculated positive predictive value was only 21.2%, indicating that approximately 79% of the women in the screen-positive group would not develop hypertensive disorders during pregnancy (82). Of note, a similar algorithm underperformed in a subsequent randomized trial performed by the same research group…

An international organization, the International Federation of Gynecology and Obstetrics (FIGO) (Poon, 2019) stated, “all pregnant women would be screened for preterm PE [preeclampsia] during early pregnancy by the first-trimester combined test with maternal risk factors and biomarkers as a one-step procedure...”. FIGO’s conclusion was based on results of the ASPRE trial, discussed above.

Background/Overview

Preeclampsia affects approximately 4% of pregnancies in the United States (USPSTF, 2017). Diagnostic criteria for preeclampsia are new-onset hypertension and proteinuria or, in the absence of proteinuria, new-onset hypertension in combination with any of the following: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema or unexplained new-onset headache unresponsive to medication (ACOG, 2020).

Standard practice regarding preeclampsia prevention is to screen for traditional risk factors for preeclampsia at the first prenatal visit. At subsequent prenatal visits, preeclampsia screening generally consists of measuring blood pressure. Measurement of blood pressure before 20 weeks can establish baseline values with which to compare values later in pregnancy (USPSTF, 2017). The USPSTF (2021) recommended that individuals with at least one high-risk factor receive low-dose aspirin to prevent preeclampsia. Factors suggesting high-risk include a history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease or an autoimmune disease (e.g. systemic lupus erythematous, antiphospholipid syndrome). Similarly, in 2018, ACOG and the Society for Maternal-Fetal Medicine (SMFM) recommended the following:

- Low-dose aspirin (81 mg/day) prophylaxis is recommended in women at high risk of preeclampsia and should be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery.
- Low-dose aspirin prophylaxis should be considered for women with more than one of several moderate risk factors for preeclampsia.

Individuals with preeclampsia are monitored for worsening of the condition. Preeclampsia can be a progressive disorder and impact multiple systems. ACOG (2020) identified the following maternal conditions that, if present, would indicate expedited delivery after stabilization:

- Uncontrolled severe-range blood pressures (persistent systolic blood pressure 160 mm Hg or more or diastolic blood pressure 110 mm Hg or more not responsive to antihypertensive medication
- Persistent headaches, refractory to treatment
- Epigastric pain or right upper pain unresponsive to repeat analgesics
- Visual disturbances, motor deficit or altered sensorium
- Stroke
- Myocardial infarction
- HELLP syndrome
- New or worsening renal dysfunction (serum creatinine greater than 1.1 mg/dL or twice baseline)
- Pulmonary edema
- Eclampsia
- Suspected acute placental abruption or vaginal bleeding in the absence of placenta previa

Screening for biomarkers in serum is proposed as a supplement to the assessment of risk factor screening. Levels of placental growth factor (PlGF) tend to drop during pregnancy in asymptomatic individuals who later develop pre-eclampsia, and this drop may precede the development of signs or symptoms of preeclampsia (Argawal, 2019). Moreover, the ratio of sFlt-1t o PlGF tends to be elevated in symptomatic pregnant individuals before the onset of overt preeclampsia (Zeisler, 2016). In addition, lower levels of PAPP-A, which has been used for several decades in screening for fetal aneuploidies, has been associated with increased risk of adverse pregnancy outcomes such as preeclampsia (Kalousová, 2014).

PerkinElmer Genetics offers two PlGF Preeclampsia Screening tests. The DELFIA® Xpress PlGF 1-2-3 kit quantifies the level of free PlGF in maternal serum. The kit is intended for use in the first trimester of pregnancy. PerkinElmer Genetics also offers the DELFIA® Xpress sFlt-1 kit, which is intended to be used in the second and third trimesters for individuals with signs or symptoms of preeclampsia. The second and third trimester test determines serum soluble FMS-like tyrosine kinase-1 (sFlt) and PlGF levels, and expresses them as a ratio (sFlt to PlGF ratio). An increased ratio can be used as an aid to identify preeclampsia.

Eurofins NTD Genetics offers the Preeclampsia Screen | T1℠ test to assess risk of early onset preeclampsia. Early onset preeclampsia is defined as preeclampsia that results in delivery before 34 weeks’ gestation. The test, which is performed between 10 weeks, 0 days and 13 weeks, 6 days gestation, calculates a risk score based on personal history, ultrasound markers, blood pressure, and three serum biomarkers, PlGF as well as PAPP-A and AFP (alpha fetoprotein).

The Elecsys® sFlt-1/PlGF (Preeclampsia) from Roche Diagnostics measures the sFlt-1/PlGF ratio. It is intended to be used with first trimester screening to aid in the diagnosis of preeclampsia and identify women who may benefit from prophylactic treatment with aspirin.

ThermoFisher’s BRAHMS sFlt-1/PlGF KRYPTOR Test measures the sFlt-1/PlGF ratio. The test is designed for use with women with singleton pregnancies between 23 weeks, 0 days and 34 weeks, 6 days gestation who are hospitalized for hypertensive disorders of pregnancy to identify cases likely to progress to preeclampsia with severe features. In 2023, the test received De Novo classification by the FDA as a Class II device. The FDA determined that the Class II device satisfied the requirement for Special Controls such as determining that test results were accurate. The FDA document stated, “FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type”. No data on clinical validity or clinical utility were reported.

mProbe’s preeclampsia test is another test designed to be used in the first trimester of pregnancy to identify women at increased risk of preeclampsia who might benefit from prophylactic aspirin therapy. The test examines three proteins (RBP4, endoglin and KDR, and uses a proprietary algorithm to develop a preeclampsia risk score.

Definitions

Preeclampsia: High blood pressure disorder related to pregnancy.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

0243U	Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia PlGF Preeclampsia Screen, PerkinElmer Genetics, Inc
0390U	Obstetrics (preeclampsia), kinase insert domain receptor (KDR), Endoglin (ENG), and retinol-binding protein 4 (RBP4), by immunoassay, serum, algorithm reported as a risk score PEPredictDx, OncoOmicsDx Laboratory, mProbe
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a multiple biomarker test for risk of preeclampsia] **Note:** if a multianalyte assay for risk of preeclampsia is billed with individual codes such as 82105, 84704, 84163 it would be considered investigational and not medically necessary

ICD-10 Diagnosis

	All diagnoses

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Government Agency, Medical Society, and Other Authoritative Publications:

1. American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal Fetal Medcine (SMFM). Committee Opinion No. 743: Low-Dose Aspirin Use During Pregnancy. Obstet Gynecol. 2018 Jul; 132(1):e44-e52.
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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Rationale, Background/Overview, References and Index sections updated. Updated Coding section to add CPT 0390U.
Reviewed	08/11/2022	MPTAC review. Rationale, Background/Overview and References sections updated.
New	08/12/2021	MPTAC review. Initial document development.
