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Medical Policy

Subject:	Serum Biomarker Tests for Risk of Preeclampsia		
Document#:	LAB.00040	**Publish Date:**	10/06/2021
Status:	New	**Last Review Date:**	08/12/2021

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. In addition, the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1), which tends to increase in preeclampsia and PIGF may be calculated to test for the presence or absence 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 investigational and not medically necessary.

Rationale

Prediction of Preeclampsia

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Asymptomatic pregnancies

A number of observational studies evaluating the predictive accuracy of PIGF 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 PIGF 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 PIGF 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, UtA-PI and MAP were measured and serum concentration of PIGF 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 PIGF 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 PIGF, 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 PIGF, 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 PIGF 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, mean arterial pressure (MAP) and the uterine artery pulsatility index (UtA-PI). The addition of PIGF did significantly improve the screening model compared with maternal factors alone and maternal factors and PAPP-A. Moreover, the performance of screening with PIGF, maternal factors, MAP and UtA-PI was superior to screening with PAPP-A, maternal factors, MAP and UtA-PI.

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 PIGF. The primary study objectives were to determine whether an sFLt-1:PIGF 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:PIGF 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 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 of 36.7% (95% CI, 28.4 to 45.7%).

A meta-analysis of studies evaluating the sFLt-1:PIGF 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: PIGF 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.

A 2020 study by Barton and colleagues enrolled 753 pregnant women with signs or symptoms of preeclampsia < 35 weeks' gestation. PIGF levels were retrospectively analyzed from plasma samples, with a normal level of PIGF 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 PIGF level, women with PIGF ≤ 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).

Clinical Utility of Serum Biomarker Tests

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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 PIGF 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 eclampsia was assessed using an algorithm that included maternal risk factors, MAP, the UtA-PL and the maternal serum biomarkers PAPP-A and PIGF. PIGF concentrations were measured using the PIGF 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. An earlier (Henderson, 2014) evidence review for the USPSTF recommendation on low-dose aspirin states "…Reviews and test performance studies of existing and candidate biomarkers and clinical tests do not yet support their use in routine clinical care to identify women at increased risk of preeclampsia."

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: thrombycytopenia, 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). In 2014, The USPSTF (LeFevre, 2014) 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 (PIGF) 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 PIGF 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 PIGF Preeclampsia Screening tests. The DELFIA® Xpress PlGF 1-2-3 kit quantifies the level of free PIGF 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^{SM} 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, PIGF as well as PAPP-A and AFP (alpha fetoprotein).

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.

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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**
81599	**Unlisted multianalyte assay with algorithmic analysis [when specified as a multiple biomarker test for risk of preeclampsia]** **Note: if billed with separate codes such as 82105, 84704, 84163 the test would be considered investigational and not medically necessary**
ICD-10 Diagnosis	
	All diagnoses, including, but not limited to:
Z34.80-Z34.93	**Encounter for supervision of normal pregnancy**
Z36.9	**Encounter for antenatal screening, unspecified**

References

Peer Reviewed Publications:

1. **Agrawal S, Cerdeira AS, Redman C, Vatish M. Meta-analysis and systematic review to assess the role of soluble FMS-like tyrosine kinase-1 and placenta growth factor ratio in prediction of preeclampsia: The SaPPPhirE Study. Hypertension. 2018; 71(2):306-316.**
2. **Agrawal S, Shinar S, Cerdeira AS et al. Predictive performance of PlGF (placental growth factor) for screening preeclampsia in asymptomatic women: a systematic review and meta-analysis. Hypertension. 2019; 74(5):1124-1135.**
3. **Barton JR, Woelkers DA, Newman RB et al. Placental growth factor predicts time to delivery in women with signs or symptoms of early preterm preeclampsia: a prospective multicenter study. Am J Obstet Gynecol. 2020; 222(3):259.e1-259.e11.**
4. **Kalousová M, Muravská A, Zima T. Pregnancy-associated plasma protein A (PAPP-A) and preeclampsia. Adv Clin Chem. 2014; 63:169-209.**
5. **Mazer Zumaeta A, Wright A et al. Screening for pre-eclampsia at 11-13 weeks' gestation: use of pregnancy-associated plasma protein-A, placental growth factor or both. Ultrasound Obstet Gynecol. 2020; 56(3):400-407.**

6. **Tan MY, Syngelaki A, Poon LC et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol. 2018; 52(2):186-195.**
7. **Rolnik DL, Wright D, Poon LCY et al.ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol. 2017; 50(4):492-495.**
8. **Zeisler H, Llurba E, Chantraine F et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016; 374(1):13-22.**

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.**
2. **American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin, Number 222. Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2020; 135(6):e237-e260.**
3. **Bibbins-Domingo K, Grossman DC, Curry SJ et al. Screening for Preeclampsia: US Preventive Services Task Force Recommendation Statement. JAMA. 2017; 317(16):1661-1667. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/preeclampsia-screening. Accessed July 20, 2021.**
4. **LeFevre ML; U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 161(11):819-26. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/low-dose-aspirin-use-for-the-prevention-of-morbidity-and-mortality-from-preeclampsia-preventive-medication. Accessed July 20, 2021.**
5. **Henderson, JT, Whitlock EP, O'Conner E. et al. Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. AHRQ Publication No. 14-05207-EF-1. Available at: https://www.ncbi.nlm.nih.gov/books/NBK196392/. Accessed July 20, 2021.**
6. **Poon LC, Shennan A, Hyett JA et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019; 145 Suppl 1(Suppl 1):1-33.**
7. **Society for Maternal and Fetal Medicine (SMFM) Patient Safety and Quality Committee. Combs CA, Montgomery DM. Society for Maternal-Fetal Medicine Special Statement: Checklists for preeclampsia risk-factor screening to guide recommendations for prophylactic low-dose aspirin. Am J Obstet Gynecol. 2020 Sep; 223(3):B7-B11.**

Websites for Additional Information

1. **National Institute of Child Health and Human Development (NICHD). Preeclampsia and Eclampsia. Available at: https://www.nichd.nih.gov/health/topics/preeclampsia. Accessed July 20, 2021.**

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Placental Growth Factor
Pregnancy-associated plasma protein-A

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
New	08/12/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

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