BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.152 Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes

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Related Policies:

None

Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes

Description

Improved accuracy of the identification of pregnant people at risk of preeclampsia and spontaneous preterm birth has the potential to reduce maternal and perinatal morbidity and mortality. Assessment of historical risk and clinical factors represents the traditional approach to diagnosis and planning interventions. Maternal serum biomarker testing is proposed as an adjunct to standard screening to identify pregnant people at risk of preeclampsia and spontaneous preterm birth.

Preeclampsia

Hypertensive disorders in pregnancy affected approximately 1 in 7 delivery hospitalizations between 2017 and 2019 in the US with a prevalence of approximately 1 in 5 delivery hospitalizations among Black women and 1 in 3 among women aged 45 to 55 years.[1,] Preeclampsia is defined as new onset maternal hypertension and proteinuria or new onset hypertension and significant end-organ dysfunction (with or without proteinuria) after the 20th week of gestation.[2,]

Maternal complications of preeclampsia include progression to eclampsia, placental abruption, and a life-threatening complication known as the hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. In the fetus, preeclampsia can lead to fetal growth restriction and intrauterine fetal death. Preeclampsia can develop in nulliparous women with no known risk factors.[3,] Maternal factors associated with an increased risk of preeclampsia include advanced maternal age, presence of a chronic illness such as diabetes mellitus, chronic hypertension, chronic kidney disease, or systemic lupus erythematosus, obesity, multiple gestations, and a prior history of preeclampsia. Preeclampsia can also develop in the postpartum period. In women determined to be at increased risk of developing preeclampsia, the use of daily, low-dose aspirin beginning in the 12th week of gestation is associated with a reduction in risk and is recommended by the U.S. Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG).[4,5,]

Despite decades of research, accurate identification of women at risk of preeclampsia, particularly prior to the 20th week of gestation, remains challenging.[3,] Standard methods for preeclampsia risk-factor assessment are based on medical and obstetric history and clinical assessment, including routine maternal blood pressure measurement at each prenatal visit.[4,] The use of maternal serum biomarker assays as an adjunct to standard preeclampsia risk assessment has been suggested as a mechanism that could improve accurate identification of at-risk individuals. More accurate identification of risk could create an opportunity for additional assessment, surveillance, and interventions that would ultimately reduce the maternal and fetal or newborn morbidity and mortality associated with preeclampsia. Individual maternal serum biomarkers, such as serum placental growth factor (PlGF), soluble Fms-like tyrosine kinase 1 (s-Flt 1), and pregnancy-associated plasma protein A (PAPP-A) have been investigated as predictors of preeclampsia.[6,] Multivariable preeclampsia risk assessment tools have been developed that incorporate maternal serum biomarkers; several of these tools have been commercially produced (see Regulatory Status) but few have been externally validated.[7,] Clinically useful risk assessment using maternal serum biomarker testing would need to show increased predictive value over standard assessment of preeclampsia risk without serum biomarker testing.

Spontaneous Preterm Birth

Preterm birth is defined as birth occurring between the 20th and 37th week of pregnancy and can be spontaneous following preterm labor and rupture of membranes or iatrogenic due to clinical interventions for maternal or fetal medical indications. The preterm birth rate was estimated by the Centers for Disease Control (CDC) to be 10.1% (about 360,000 births were preterm among 3,600,000 births) in 2020 in the United States and has consistently been approximately 10% for over a decade.[8,] Preterm birth rates vary according to race and ethnicity independent of social determinants of health, ranging from 8.5% for Asian women to 14.4% for non-Hispanic Black women. Prior preterm birth is the strongest predictor of a subsequent preterm birth, although absolute risk varies according to the gestational age of the prior preterm birth and maternal clinical factors.[9,] Characteristics in a current pregnancy that increase the risk of preterm birth include cervical changes (shortened length and/or early dilation), vaginal bleeding or infection, and maternal age under 18 years or over 35 years. Smoking, pre-pregnancy weight, interpregnancy interval, maternal stress, and lack of social support have also been associated with an increased risk of preterm birth. Despite recognition of risk factors, most preterm births occur without clearly identifiable maternal risk factors.[10,] Maternal consequences of preterm delivery include intrapartum and postpartum infection. Psychosocial adverse effects including postpartum depression have been reported. Infants born preterm have an increased risk of death up to 5 years of age relative to full-term infants. Preterm birth is also associated with morbidity extending into adulthood.[11,]

Cervical length is one measure available to clinicians to assess risk of preterm birth. Shortened cervical length prior to 24 weeks gestation is associated with an increased risk of preterm birth. The ACOG recommends ultrasonographic assessment of cervical length in the second trimester to identify women at an increased risk of preterm birth.[11,] In women with a prior history of preterm birth, serial measurement of cervical length using transvaginal ultrasound is recommended, although optimal timing of measurements has not been clinically established. In women without a history of preterm birth or other risk factors, universal ultrasonographic screening of cervical length in women has not been demonstrated to be an effective strategy due to the overall low incidence in this group. In women determined to have a shortened cervix and therefore an increased risk of preterm birth, the use of either vaginal or intramuscular progesterone supplementation has been associated with a reduced risk of preterm birth. There are some limitations in assessment of cervical length in predicting risk of preterm birth. These limitations include uncertainty as to what constitutes “shortened” length, with transvaginal ultrasound measurements ranging from <15 mm to <25 mm implicated in indicating increased risk and uncertainty regarding ideal timing of ultrasonographic assessment.[11,]

Given the limitations of cervical length assessment in predicting risk of preterm birth, the use of other biomarkers has been suggested as a mechanism that could improve accurate identification of women at risk of preterm birth, including maternal serum biomarkers.[12,]

OBJECTIVE

The objective of this evidence review is to determine whether the use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia and spontaneous preterm birth as an adjunct to standard clinical management improves the net maternal and fetal health outcome.

POLICY STATEMENT

The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of preeclampsia is considered **investigational.**

The use of maternal serum biomarker tests with or without additional algorithmic analysis for prediction of spontaneous preterm birth is considered **investigational.**

POLICY GUIDELINES

None

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests. Therefore, maternal serum biomarker tests would be provided by CLIA licensed laboratories.

The BRAHMS sFlt-1/ PlGF KRYPTOR Test System (Thermo Fisher Scientific) was cleared for marketing by the FDA as a prognostic test through the De Novo process (DEN220027) in May 2023.[13,] The Test System includes quantitative determination of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in human serum and plasma. The clearance letter states that the Test System is to be used 'along with other laboratory tests and clinical assessments to aid in the risk assessment of pregnant women (singleton pregnancies between gestational age 23+0 to 34+6/7 weeks) hospitalized for hypertensive disorders of pregnancy (preeclampsia, chronic hypertension with or without superimposed preeclampsia, or gestational hypertension) for progression to preeclampsia with severe features (as defined by the American College of Obstetricians and Gynecologists (ACOG) guidelines) within 2 weeks of presentation.'

Commercially produced, maternal serum biomarker tests for preeclampsia include the Triage PlGF™ (Quidel), Elecsys sFlt-1/PlGF™ (Roche Diagnostics), and DELFIA Xpress PlGF 1-2-3™ (PerkinElmer).[14,] These commercially produced tests are not currently available in the United States.

The PreTRM™ test (Sera Prognostics)[15,] uses maternal serum biomarkers (insulin-like growth factor binding protein-4 [IBP4] and sex hormone binding globulin [SHBG]) in combination with biometric measures to assess the risk of spontaneous preterm birth. According to the manufacturer, the PreTRM test is only intended to be used in women aged 18 years or older, who are asymptomatic (that is, with no signs or symptoms of preterm labor, with intact membranes, and with no first trimester progesterone use) with a singleton pregnancy. The PreTRM test is performed via a single blood draw during the 19th week of gestation.

RATIONALE

Summary of Evidence

For individuals who are pregnant without known risk factors for preeclampsia who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes systematic reviews of observational clinical validity studies and a randomized controlled trial (RCT) that selected eligible participants based on an algorithm that included biomarker testing results. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. The clinical validity studies primarily included populations from Europe and tests that are not cleared for use in the United States (US). Placental growth factor (PlGF) cutoffs for identifying high risk pregnant people were not prespecified and varied significantly. The RCT used a test not cleared for use in the US to identify people for enrollment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pregnant with known risk factors for preeclampsia who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes systematic reviews of observational clinical validity studies and RCTs. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. Studies evaluating the predictive ability of maternal serum biomarker testing have found measurement of sFlt-1, PlGF, and the sFlt-1/PlGF ratio can identify women at risk of developing preeclampsia. One sFlt-1/PlGF ratio test system (KRYPTOR) has been cleared in the US. One prospective observational study (PRAECIS) has been conducted in a second and third trimester, US population reporting clinical validity of the KRYPTOR test system. PRAECIS included a racially diverse population reflective of US diversity. While PRAECIS proposed a cutoff for the sFlt-1:PlGF ratio of 40, other publications have proposed various cutoffs. The clinical decision that would be informed by the test is unclear. While 5 RCTs have been conducted using various biomarker tests, the KRYPTOR test system has not been used in any RCTs. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pregnant without known risk factors for spontaneous preterm birth who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes an RCT and cohort studies. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. Measurement of the insulin-like growth factor binding protein-4 (IBP4) and sex hormone binding globulin (SHBG) ratio demonstrated acceptable discrimination in identifying asymptomatic women who may be at risk of preterm birth, based on evidence from 2 industry-sponsored cohort studies. However, a randomized trial did not find a difference in risk of preterm birth with use of the commercially produced PreTRM test, which includes the IBP4/SHBG ratio as part of an algorithmic analysis, versus no use. There were also no differences in neonatal outcomes in infants of women who underwent PreTRM testing versus no testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pregnant with known risk factors for spontaneous preterm birth who receive maternal serum biomarker testing with or without additional algorithmic analysis, the evidence includes a systematic review of observational studies. Relevant outcomes are test validity, maternal and perinatal morbidity and mortality, symptoms, functional outcomes, quality of life, hospitalizations, and resource utilization. The systematic review did not identify any individual biomarker that adequately identified women at risk of spontaneous preterm birth based on high sensitivity and specificity. No studies assessing maternal serum biomarkers as part of an algorithmic analysis were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists and The Society for Maternal-Fetal Medicine

The American College of Obstetricians and Gynecologists (ACOG) issued practice bulletins in 2020 on preeclampsia[4,] and 2021 on preterm birth.[11,] Maternal serum biomarker screening is described as investigational and is not recommended by ACOG as a factor included in risk assessment for either preeclampsia or spontaneous preterm birth.

The 2021 joint ACOG-Society for Maternal-Fetal Medicine (SMFM) guidance on the use of aspirin for prevention of preeclampsia does not include results of maternal serum biomarker testing among the risk factors to be used to identify women at risk of preeclampsia.[42,]The guidance was reaffirmed in October 2022.

International Federation of Gynecology and Obstetrics

The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Preeclampsia (PE) published a guide for first trimester screening and prevention of preeclampsia in 2019.[6,]The writing committee included representation from the National Institutes of Health (US Department of Health and Human Services) and the Society for Maternal-Fetal Medicine (Washington, DC). The guideline states that 'All pregnant women should be screened for preterm PE during early pregnancy by the first-trimester combined test with maternal risk factors and biomarkers as a one-step procedure.' The guidance further states that 'The best combined test is one that includes maternal risk factors, measurements of mean arterial pressure (MAP), serum placental growth factor (PlGF) and uterine artery pulsatility index (UTPI).' The combined test referred to in the guidance is the Fetal Medicine Foundation (FMF) risk calculator.

International Society for the Study of Hypertension in Pregnancy

The International Society for the Study of Hypertension in Pregnancy (ISSHP) issued practice guidelines in 2021 on classification, diagnosis and management of hypertension in pregnancy.[43,] The ISSHP committee included US representation. The guidelines make the following recommendation: 'To the assessment of women suspected of having pre-eclampsia (<37 weeks), we recommend adding evaluation of angiogenic imbalance, when available, as a marker of uteroplacental dysfunction to be used in conjunction with other clinical tests.' The quality of the evidence for the recommendation was rated as 'Moderate' and the strength of recommendation was rated as 'Strong'. Angiogenic imbalance was defined as reduced PlGF (<5th centile for gestational age) or increased sFlt/PlGF ratio.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) published guidance in 2022 on PLGF-based testing to help diagnose suspected preterm pre-eclampsia.[44,] The guidance recommends use of four tests to help decide on care (to help rule in or rule out pre-eclampsia) for people with suspected preterm (between 20 weeks and 36 weeks and 6 days of pregnancy) pre-eclampsia. The tests are: DELFIA Xpress PLGF 1-2-3, DELFIA Xpress sFlt-1/PLGF 1-2-3 ratio, Elecsys immunoassay sFlt-1/PLGF ratio, Triage PLGF Test. The guidance states that "BRAHMS sFlt-1 KRYPTOR/BRAHMS PLGF plus KRYPTOR PE ratio is not recommended for routine use in the NHS. Further research is needed to show the accuracy of this test when using specified thresholds."

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USPSTF) issued updated recommendations in 2023 on screening for hypertensive disorders of pregnancy.[16,] The recommendation states: "Several models have been developed with the aim of identifying pregnant individuals who are at risk of developing preeclampsia. Many of these models include variables for medical history, patient characteristics, blood serum biomarkers (e.g., serum placental growth factor), mean arterial pressure (MAP), and ultrasound readings (e.g., Doppler uterine artery pulsatility index). The most extensively researched of these are various iterations of the Fetal Medicine Foundation (FMF) model. Currently, risk assessment and risk prediction tools are being used to inform the use of aspirin for prevention of preeclampsia; however, no randomized controlled trials (RCTs) have incorporated the use of a risk prediction model to evaluate the optimal frequencies or intervals of screening for hypertensive disorders of pregnancy. In the absence of clinical implementation studies, it is not yet clear whether screening informed by risk prediction models would necessarily be superior to risk evaluations based on clinical history taking. Moreover, it remains to be seen whether risk-based screening protocols, regardless of the risk-assessment approach used, could improve outcomes relative to usual care screening."

The USPSTF issued updated recommendations in 2021 on the use of aspirin for the prevention of preeclampsia.[5,] The USPSTF recommendation notes "predictive models that combine risk factors to identify pregnant persons at risk for preeclampsia, such as serum biomarkers, uterine artery Doppler ultrasonography, and clinical history and measures, have been developed. However, there is limited evidence from external validation and implementation studies to demonstrate sufficient accuracy of predictive models for clinical use."

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2022	New policy	Policy created with literature review through December 13, 2021. Policy statement revised to align with FEP benefit.
June 2023	Replace policy	Policy updated with literature review through December 21, 2022; references added. Policy statements unchanged.
June 2024	Replace policy	Policy updated with literature review through January 2, 2024; references added. Policy statements unchanged.