Medical Policy Manual Laboratory, Policy No. 75

Maternal Serum Analysis for Risk of Adverse Obstetric Outcomes

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Maternal serum tests have been proposed as a method for identifying risk of preterm birth and preeclampsia.

MEDICAL POLICY CRITERIA

Maternal serum analysis for predicting risk of preterm birth or preeclampsia is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Preimplantation Genetic Testing of Embryos, Genetic Testing, Policy No. 18
2. Noninvasive Prenatal Testing to Determine Fetal Aneuploidies and Microdeletions using Cell-Free DNA, Genetic Testing, Policy No 44
3. Invasive Prenatal (Fetal) Diagnostic Testing Using Chromosomal Microarray Analysis (CMA), Genetic Testing, Policy No. 78
4. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

BACKGROUND

PREECLAMPSIA

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.[1] 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.[2] 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).[3, 4] Currently, maternal serum biomarkers are not included in either USPSTF guidelines or ACOG risk factor assessment when determining appropriate candidates for aspirin prophylaxis.

Despite decades of research, accurate identification of women at risk of preeclampsia, particularly prior to the 20th week of gestation, remains challenging.[2] 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.[5] 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.[6] 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, resulting in reduced maternal and perinatal morbidity and mortality.

SPONTANEOUS PRETERM BIRTH

Preterm birth is defined as live birth before 37 weeks of gestation. 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.[7] 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. Preterm birth is associated with negative health outcomes for the mother and baby. For infants, there is greater risk of death and disability, as well health and development problems, including difficulties with breathing and feeding, cognitive, visual, and hearing problems, and developmental delay. Consequences for the

mother include increased risk for cardiovascular morbidity and mortality for years after the delivery.

Interventions to prevent or delay preterm birth are limited. Cerclage and progesterone are two interventions that have been evaluated in randomized trials for effectiveness in preventing preterm birth. These interventions may be recommended based on a history of spontaneous preterm birth or short cervical length, but preventive measures are not generally recommended outside of those clinical scenarios.

Risk factors associated with pre-term birth are varied and include social, personal and economic factors such as age, race, income, previous preterm birth, multiple gestation, and behavioral factors such as tobacco and substance use and stress. No effective risk scoring system, for example based epidemiologic, historical, and clinical risk factors, for prediction of preterm birth have been developed. Currently, prediction of pre-term birth relies on cervical length, which can be measured at the time of the fetal anatomic survey ultrasound between 18 and 24 weeks, and the presence of a dilated cervix before 24 weeks of gestation. The ACOG recommends ultrasonographic assessment of cervical length in the second trimester to identify women at an increased risk of preterm birth.[8]

The PreTRM® test is a prognostic test based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) measurement of proteins in maternal blood. The test determines the relative levels of two proteins, insulin-like growth factor binding protein 4 (IBP4) and sex hormone binding globulin (SHBG). These are used along with patient clinical data to predict the likelihood of preterm birth.

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.

Commercially produced, maternal serum biomarker tests for preeclampsia include the Triage PlGF™ (Quidel), Elecsys sFlt-1/PlGF™ (Roche Diagnostics), and DELFIA Xpress PIGF 1-2-3™ (PerkinElmer).[9] These commercially produced tests are not currently available in the United States.

The PreTRM® test by Sera Prognostics has not been approved or cleared by the U.S Food and Drug Administration (FDA) but is being offered as a laboratory-developed test. The laboratory performing this test is accredited by the Centers for Medicare and Medicaid (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

The B·R·A·H·M·S 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.[10] 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."

EVIDENCE SUMMARY

Validation of any new diagnostic technique involves three steps:

- Demonstration of its technical feasibility, including assessment of its reproducibility and precision. For comparison among studies, a common standardized protocol is necessary.
- An understanding of normal and abnormal values as studied in different clinical situations. For accurate interpretation of study results, sensitivities, specificities, and positive and negative predictive values compared to a gold standard must be known.
- The clinical utility of a diagnostic technique is related to how the results of the test can be used to guide patient management resulting in an improvement in net health outcomes. The clinical utility of both positive and negative tests must be assessed. Relevant outcomes of a negative test (i.e., suspected pathology is not present) may be avoidance of more invasive diagnostic tests or avoidance of an ineffective therapy. Relevant outcomes of a positive test (i.e., suspected outcome is present) may also include avoidance of a more invasive test plus the institution of specific, effective therapy.

MATERNAL SERUM ANALYSIS FOR PREDICTING RISK OF PREECLAMPSIA

Clinical Validity

Systematic Reviews

Vivek (2022) conducted a systematic review and meta-analysis to evaluate the changes in maternal circulatory irisin levels in preeclampsia as compared to normotensive healthy pregnant controls.[11] Compared with controls, preeclampsia patients showed significantly decreased serum irisin levels (SMD: -1.13; 95% confidence interval [CI]: -1.63 to -0.62, $p<0.0001$). The sub-group analysis showed that this decrease in irisin is regardless of body mass index (BMI) and gestational age of preeclampsia patients. The meta-regression analysis indicated that blood pressure is significantly associated with the observed results. There is still need for future studies to evaluate the diagnostic utility of this study.

Agrawal (2019) conducted a systematic review that included 40 observational studies (n=92,687) on the predictive ability of PlGF testing in women without known risk factors.[12] Studies that analyzed PlGF in conjunction with other biomarkers were excluded. The timing of PlGF testing was less than 14 weeks in 15 studies, greater than or equal to 14 weeks in 25 studies, and greater than or equal to19 weeks in 18 studies. Most studies (37/40) used a definition of preeclampsia that required presence of proteinuria. Two studies evaluated the Kryptor system. Six studies were conducted in the United States; two of these included first trimester populations. In all studies, the chosen PlGF cutoff was not predetermined but was calculated based on maximizing accuracy and ranged from 41 to 382 pg/mL in studies in which it was reported. Individual study sensitivity and specificity ranged from 7% to 93% and 51% to 97%, respectively. When all studies were included in a pooled analysis, sensitivity was 61% (95% CI 53 to 69%), specificity was 85% (95% CI 82 to 88%), and heterogeneity was high (I^2=99%).

A second systematic review conducted by Agrawal (2018) assessed the diagnostic accuracy of the sFlt-1/PlGF ratio for prediction of preeclampsia.[13] The review included 15 studies, all assessing risk after the 19th week of gestation. Among the 15 included studies (n=20,121), eight were conducted in women (n=19,038) at low risk of developing preeclampsia based on clinical characteristics. Sensitivity and specificity ranged widely in the individual studies, which reported sensitivities of 23% to 97% and specificities from 64% to 100%. When pooled, sensitivity was 77% (95% CI 61% to 88%) and specificity was 94% (95% CI 88% to 97%) with very high heterogeneity (I^2=94% and 100%, respectively). The review included seven studies conducted in women at high-risk of developing preeclampsia based on clinical characteristics (that is, with known risk factors). Among the included studies, sensitivity ranged from 67% to 100%, and specificity ranged from 68% to 100%. When pooled, sensitivity was 85% (95% CI 66% to 94%) and specificity was 87% (95% CI 76% to 93%). Heterogeneity was high for both measures (I^2=75% and 79%, respectively).

A systematic review published by Veisani (2019) included 15 studies measuring sFLT-1 or PlGF at gestational weeks 1 to 12 in one study and in the second or third trimester in the remaining 14 studies.[14] The review found serum sFlt-1 values above the study cut-off point were associated with an increased risk of preeclampsia based on three studies that reported odd ratios ranging from 2.20 to 7.50. The pooled odds ratio for sFlt-1 was 5.20 (95% CI 1.24 to 9.16) with high heterogeneity (I^2=82%). For PlGF, a serum level below the cut-off point was predictive of preeclampsia development based on four studies with individual odds ratios ranging from 2.30 to 4.28; pooled odds ratio was 2.53 (95% CI 1.33 to 3.75) with no heterogeneity (I^2=0%).

Randomized Controlled Trials

De Oliveira (2023) reported results of the PREPARE (Prematurity Reduction by Preeclampsia Care) trial (NCT03073317).[15] PREPARE was a stepped-wedge, cluster randomized controlled trial (RCT) conducted in seven tertiary centers in Brazil from 2017 to 2019. The trial enrolled 1,250 pregnant patients (singleton) between 20+0 and 36+6 weeks gestation with suspected or confirmed preeclampsia. The control group (n=566) was managed according to local treatment guidance. The intervention group (n=684) consisted of two risk stratification components. Risk of adverse maternal outcomes related to preeclampsia was estimated using an algorithm called fullPIERS which combines maternal symptoms, signs and laboratory tests. In addition, samples were collected for sFlt-1/PlGF ratio measured using the Elecsys test. If sFlt-1/PlGF was less than or equal to 38 and fullPIERS was less than 10%, patients were considered low risk and clinicians received recommendations to defer delivery, unless clinical conditions deteriorated, with repeat testing. If sFlt-1/PlGF was greater than 38 or fullPIERS was greater than or equal to 10%, patients were considered not low risk, and clinicians received recommendations to increase surveillance. The primary outcome was the proportion of patients with preterm preeclampsia who delivered earlier than 37 weeks' gestation. The median age of participants was 30 years, and the median gestational age at enrollment was 33 weeks. The ethnicities were reported as: 47% White, 15% Black, 37% Brown-mixed. 17% of participants received low dose aspirin supplementation. 60% of patients in the intervention group were classified as not low risk based on sFlt-1/PlGF or fullPIERS test; most of these were not low risk based on sFlt-1/PlGF alone. The authors acknowledged difficulties with statistical analyses. The denominators vary across outcomes between using the total number of deliveries at the sites and the number of deliveries for preeclampsia. For the primary outcome, 1.1% (375/35,129 total births) in the intervention group versus 1.4% (365/26,847 total births) delivered prior to 37 weeks; however, after adjustment for confounders, the

adjusted risk ratio indicated increased risk of the primary outcome in the intervention group (adjusted risk ratio=1.5; 95% CI, 1.0 to 2.0; p=0.03). When the denominator was limited to patients with preeclampsia, there was no difference in the proportion of deliveries before 37 weeks (72% vs 66%; adjusted p=.93). The median time from enrollment to delivery was longer in the control group (6.5 versus 9 weeks; adjusted p<0.01).

Nonrandomized Studies

Thadhani (2022) reported results of the largest study of the Kryptor system, PRAECIS (Preeclampsia Risk Assessment: Evaluation of Cut-offs to Improve Stratification NCT03815110).[16] PRAECIS was a prospective, blinded, multicenter study conducted in the United States between 2019 and 2021. PRAECIS enrolled 1,014 pregnant women with singleton pregnancies; 299 in a derivation cohort and 715 in a validation cohort. The participants were between 23+0 and 34+6 weeks gestation with a hypertensive disorder of pregnancy as defined by ACOG. The primary outcome was the development of preeclampsia with severe features within two weeks of enrollment which was adjudicated by a committee of maternal fetal medicine experts blinded to the local diagnosis. Preeclampsia with severe features was defined as: 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; and headache unresponsive to medication. Using the development cohort, a sFlt-1:PlGF ratio of greater than or equal to 40 was chosen as the cutoff that provided the highest sensitivity while maintaining specificity of 70%. The results that follow are for the validation cohort using the cutoffs of 40 for the sFlt-1:PlGF ratio. The validation cohort (n=556) was racially diverse including 6% Asian, 30% Black, 53% White and 16% Hispanic participants. The mean age was 32 years and the mean gestational age at enrollment was 30 weeks. 46% of participants had used aspirin during pregnancy. The incidence of the primary outcome was 33.5%. The overall performance characteristics of the test for predicting preeclampsia with severe features were: 94% sensitivity (95% CI, 89 to 96), 75% specificity (95% CI, 70 to 79), 65% PPV (95% CI, 59 to 71) and 96% NPV (95% CI, 93 to 98). In the subgroup of participants who identified as Black race (n=169), the positive and negative predictive values 66% (95% CI, 51 to 67) and 99% (95% CI, 94 to 100), respectively. Subgroup analyses were not reported by aspirin use during pregnancy. Given that aspirin lowers the risk of preeclampsia, the PPV might differ across subgroups of women who did and did not take aspirin during pregnancy. There were 51 adverse maternal outcomes. Adverse maternal outcomes occurred in 16% of the group with a ratio greater than or equal to 40 compared to 3% of the group with a ratio less than 40 (risk ratio, 5.8; 95% CI, 2.8 to 12.2). There were 288 adverse fetal and neonatal outcomes. Adverse fetal and neonatal outcomes occurred in 80% of the group with a ratio greater than or equal to 40 compared to 26% in the group with a ratio less than 40 (risk ratio, 3.1; 95% CI, 2.5 to 3.8). There were nine fetal deaths, eight of which were in the group with a ratio greater than or equal to 40.

Döbert (2022) conducted a prospective multicenter study of prediction of pre-eclampsia at delivery using a screening at 35 to 37 weeks' gestation using a competing risks model combining maternal risk factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), PlGF and sFlt-1.[17] Out of a population of 29,677 singleton pregnancies, of which 653 developed PE, the detection rate using maternal risk factors, MAP, PlGF and sFlt-1 and a 10% false-positive rate was 79% (95% CI 76 to 82%) and the AUC was 0.923 (95% CI 0.913 to 0.932). Adding UtA-PI to the model did not improve the prediction rate.

Wright (2022) conducted a multicenter study of prediction of pre-eclampsia.[18] As opposed to the Döbert study above, screening occurred in the first trimester and the aim was to predict PE at less than 37 weeks' gestation. Women with singleton pregnancies undergoing routine evaluation at 11^{+0} to 13^{+6} weeks' gestation were assessed for maternal risk factors and MAP, UtA-PI and either PlGF or pregnancy associated plasma protein-A (PAPP-A). Out of a population of 25,226 singleton pregnancies, of which 678 developed PE, 194 (0.8%) had preterm-PE. Adding PlGF to the model improved the detection rate of preterm-PE, using 10% screen positive rate, by 18.4% (95% CI 12.2 to 24.6) in screening by maternal risk factors, by 19.9% (95% CI 13.6 to 26.2) in screening by maternal factors and MAP, and by 7.0% (95% CI 2.3 to 11.6) in screening by maternal factors, MAP and UtA-PI. No significant improvement was observed when adding PAPP-A to any combination of biomarkers.

Mazer Zumaeta (2020) conducted a cohort study (published subsequent to the Agrawal 2019 systematic review) evaluating the diagnostic accuracy of adding measurement of PlGF and PAPP-A using the DELFIA Xpress assay system to standard clinical management.[19] The study included 60,875 pregnant women undergoing routine, first trimester aneuploidy screening. PlGF and PAPP-A measurement took place at 11 to 13 weeks gestation. The addition of PlGF to maternal clinical characteristics was associated with improvement in the detection rate of preeclampsia at less than 34 and at less than 37 weeks ($p<0.0001$ for both time points.) Inclusion of PAPP-A was not associated with improved detection of preeclampsia at less than 34 weeks ($p=0.08$) but did improve detection rate at less than 37 weeks ($p<0.04$).

McCarthy (2019) conducted a retrospective analysis of data from industry-sponsored, prospective cohort studies comparing the diagnostic accuracy of three commercially produced maternal serum biomarker tests (Triage PlGF, DELFIA XPress PlGF 1-2-3 and Elecsys sFlt-1/PlGF).[9] In this analysis, diagnostic accuracy was based on delivery within 14 days of testing due to preeclampsia in women less than 35 weeks gestation. Sensitivities were 81% (95% CI 61% to 93%), 88% (95% CI 68% to 97%), and 75% (95% CI 53% to 90%) for the Triage PlGF, DELFIA, and Elecsys tests, respectively. Corresponding specificities were 80% (95% CI 74% to 84%), 77% (95% CI 70% to 83%), and 90% (95% CI 85% to 94%). The area under the receiver operating characteristic (AUROC) was 0.85 (95% CI 0.75 to 0.95) for the Triage PlGF test, 0.86 (95% CI 0.76 to 0.95) for the DELFIA test and 0.88 (95% CI 0.78 to 0.97) for the Elecsys test.

Clinical Utility

Lim (2021) conducted a systematic review analyzing the clinical utility of sFlt-1 and PlGF individually and in combination as the sFlt-1/PlGF ratio in predicting adverse obstetric outcomes.[20] The review only included studies of women (n=9,246) with suspected or confirmed preeclampsia. All of the 33 included studies were observational (prospective cohort, retrospective cohort, or case control), and were heterogeneous in a number of important factors, including the definition of preeclampsia used in the study, the method of evaluating and cut-off values for biomarkers, the definition of adverse obstetric outcomes, and the methods for reporting results. The timing of biomarker testing ranged from 18 to 40 weeks gestation. Evidence on sFlt-1 was too limited to pool. Although both PlGF and the sFlt-1/PlGF ratio were associated with AUROC values that suggested acceptable statistical discrimination for the outcomes analyzed, the clinical utility of the results is limited by significant heterogeneity and/or imprecision for nearly all outcomes.

MATERNAL SERUM ANALYSIS FOR PREDICTING RISK OF PRETERM BIRTH

Clinical Validity

Khanam (2021) published a nested case control study of the IBP4/SHBG ratio for prediction of spontaneous preterm birth in subjects from Bangladesh, Pakistan and Tanzania enrolled in the Alliance for Maternal and Newborn Health Improvement (AMANHI) biorepository study.[21] A total of 300 subjects (100 sPTB cases less than 37 weeks of gestation and 200 control term deliveries greater than or equal to 37 weeks), all singleton pregnancies, were enrolled in the case-control study. Serum was collected between $17^{0/7}$ and $19^{6/7}$ weeks. This was significantly different from the U.S. cohort report by Saade (described below), as was body mass index (BMI). With no population adjustment for these factors, the IBP4/SHBG biomarker score did not significantly predict preterm birth (less than 37 weeks of gestation; p=0.069). When population adjustment was made for these factors, IBP4/SHBG significantly classified spontaneous preterm birth subjects (area under the curve [AUC] 0.64, 95% CI 0.57 to 0.71, p<0.001).

Markenson (2020) assessed the clinical validity of the IBP4/SHBG ratio for prediction of spontaneous preterm birth in The Multicenter Assessment of a Spontaneous Preterm Birth Risk Predictor (TREETOP) study.[22] A cohort of 5,011 subjects from 18 sites in the United States had blood drawn between $19^{1/7}$ and $20^{6/7}$ weeks gestational age. A randomly selected subset of 847 subjects were included in the planned substudy analysis. The ratio of IBP4 to SHBG was significantly predictive of birth at prior to $32^{0/7}$ weeks gestation (AUROC = 0.71; 95% CI 0.55 to 0.87; p=0.016). When stratification by body mass index (BMI) was included in the analysis, the AUC was 0.76 (95% CI 0.59 to 0.93; p=0.023).

Saade (2016) published the development and validation of a serum based IBP4/SHBG preterm birth predictor in the Proteomic Assessment of Preterm Risk (PAPR) study.[23] In this prospective study, 5,501 participants with singleton pregnancies were enrolled at 11 sites. All subjects were enrolled and blood was collected between $17^{0/7}$ and $28^{6/7}$ weeks gestational age. Information was collected regarding height, prepregnancy weight, past medical and pregnancy history, current pregnancy history, and concurrent medications, as well as maternal and infant outcomes and complications. Personnel, except the director of clinical operations and clinical data manager, were blinded to subject case, control, and gestational age at birth. The statisticians who completed the initial analysis and those who confirmed the analysis were blinded. Of the 217 spontaneous preterm births prior to $37^{0/7}$ weeks gestational age that were available for analysis, 86 were included in the discovery analysis, 50 in the verification analysis, and 81 in the validation analysis. Samples were analyzed for two serum proteins, insulin-like growth factor-binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG) and the log ratio of the measures of IBP4 and SHBG (IBP4/SHBG) was assessed as a predictor of spontaneous preterm delivery. In the verification analysis, the predictor for spontaneous preterm birth versus controls had an area under the receiver operating characteristic curve (AUROC) value of 0.75 and sensitivity and specificity of 0.75 and 0.74, respectively. The IBP4/SHBG predictor at this sensitivity and specificity had an odds ratio of 5.04 (95% CI 1.4 to 18) for spontaneous preterm delivery. In the validation analysis, the AUROC was 0.72 (95% CI 0.51 to 0.8).

Clinical Utility

Branch (2021) conducted an RCT that compared the rate of spontaneous preterm birth in low-risk women who underwent testing with PreTRM versus those who had no PreTRM testing.[24] PreTRM testing incorporates the IBP4/SHBG ratio and maternal clinical characteristics into an

algorithmic risk assessment. Women with a singleton pregnancy with cervical length greater than or equal to 2.5 cm and no clinical risk factors for spontaneous preterm birth were randomized to testing with PreTRM (n=595) or no testing (n=596). Women who were randomized to the PreTRM testing group and had a positive screen (33.3% [198/595]) were offered a preterm birth prevention protocol that included progesterone supplementation (either weekly intramuscular 17-hydroxyprogesterone 250 mg or daily vaginal progesterone 200 mg), serial measurement of cervical length, low-dose aspirin (81 mg/day), and additional clinical monitoring. Women randomized to PreTRM testing who had a negative screen received undefined standard obstetric care, as did women randomized to the no testing group and women in any group who had unusable serum samples.

No difference was found in the rate of spontaneous preterm birth among woman managed with PreTRM (2.7% [16/589]) versus without PreTRM (3.5% [21/593]; p=0.41). There was also no clear difference in neonatal gestational age at delivery (39.1 weeks for both groups) or in length of neonatal intensive care stay (0.7, standard deviation [SD] 3.8 days for the intervention group and 1.4, SD 9.5 days for the control group). The trial had numerous methodological limitations. Notably, the trial was terminated after 10 months due to insufficient funding. In addition, the study protocol was amended mid-study with a change to prespecified neonatal outcomes, Black women were underrepresented, the "standard obstetric care" comparator is undefined and may have varied according to study site, uptake of prevention protocol in screen-positive women was incompletely reported and varied according to protocol component, and positive screening result were derived from results of an unpublished pilot study.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS AND THE SOCIETY FOR MATERNAL-FETAL MEDICINE

The American College of Obstetricians and Gynecologists (ACOG) issued updated clinical practice guidelines in 2020 on preeclampsia,[4] and 2021 on preterm birth.[8] 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.[25]

SUMMARY

There is not enough evidence to show that the use of maternal serum analysis for predicting risk of preterm birth or preeclampsia improves health outcomes. Further, no clinical practice guidelines based on evidence recommend maternal serum analysis for predicting risk of these adverse obstetric outcomes. Therefore, the use of maternal serum analysis for predicting risk of preterm birth or preeclampsia is considered investigational.

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CODES

Codes	Number	Description
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
	0247U	Obstetrics (preterm birth), insulin-like growth factor–binding protein 4 (IBP4), sex hormone– binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth
	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
	0482U	Obstetrics (preeclampsia), biochemical assay of soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF), serum, ratio reported for sFlt-1/PlGF, with risk of progression for preeclampsia with severe features within 2 weeks
HCPCS	None	

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