Antepartum Fetal Surveillance

- Clinical Policy Bulletins
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Number: 0088

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses antepartum fetal surveillance.

1. **Medical Necessity**

   Aetna considers in-office and in-hospital antepartum fetal surveillance with non-stress tests (NST), contraction stress tests (CST), biophysical profile (BPP), modified BPP, and umbilical artery and middle cerebral Doppler velocimetry medically necessary according to the American College of Obstetricians and Gynecologists (ACOG) Clinical Guideline on Antepartum Fetal Surveillance.

   The following medical necessity guidelines apply:

   1. Antepartum fetal surveillance using NST, CST, BPP, or modified BPP is considered medically necessary for women with risk factors for stillbirth due to utero-placental insufficiency. Accepted guidelines state that fetal testing should not begin until interventions can be undertaken. For most pregnancies at increased risk of stillbirth due to utero-placental insufficiency, testing is considered appropriate beginning at 32 to 34 weeks of gestation. Testing is considered medically necessary beginning at 26 weeks gestation for pregnancies with multiple or particularly worrisome high-risk conditions. Examples of such high-risk conditions include bleeding, chronic or pregnancy-induced hypertension, collagen vascular disease (including anti-phospholipid syndrome), fetal growth restriction, gestational diabetes, impaired renal function, maternal heart disease (New York Heart Association Class III or IV), oligohydramnios, significant isoimmunization, steroid-dependent or poorly controlled asthma (not an all-inclusive list).
   2. If the clinical condition that has prompted testing persists, repeat testing (either weekly or twice-weekly, depending on the test used and the presence of certain high-risk conditions) is considered medically necessary until delivery. Repeat testing is also considered medically necessary for any significant deterioration in the maternal medical status or any acute diminution in fetal activity, regardless of the amount of time that has elapsed since the last test.
   3. A CST or full BPP is considered medically necessary following an abnormal NST or modified BPP. (Subsequent management should then be predicated on the results of the CST or BPP, the gestational age, the degree of oligohydramnios (if assessed), and the maternal condition.)
   4. Recent, normal antepartum fetal test results should not preclude the determination that intrapartum fetal monitoring is medically necessary.
   5. Umbilical artery Doppler velocimetry is considered medically necessary for the following when criteria are met:

      1. In pregnancies complicated by intra-uterine growth restriction (defined as a fetus whose estimated fetal weight or abdominal circumference is less than the 10th percentile for its gestational age), or oligohydramnios*;
      2. In screening monochorionic twin pregnancies to monitor for development of twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), and/or discordant fetuses** beginning at 16 weeks of gestation (If used in this setting, accepted guidelines indicate that decisions regarding timing of delivery should be made using a combination of information from the Doppler ultrasonography and other tests of fetal well being, along with careful monitoring of maternal status).

   6. Middle cerebral artery Doppler velocimetry is considered medically necessary for the following when criteria are met:

1. In pregnancies complicated by twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), or suspected fetal anemia in conditions such as isoimmunization and parvovirus B-19 infection;
2. In screening monochorionic twin pregnancies to monitor for development of twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS) beginning at 16 weeks of gestation.

7. Measurement of preeclampsia sFlt-1/PIGF ratio (PERA) is considered medically necessary for pregnant women with singleton pregnancies hospitalized for hypertensive disorders of pregnancy at 23+0 to 34+6 weeks of gestation.

* Oligohydramnios is described in various ways, including absence of a vertical pocket of at least 2 cm and an amniotic fluid index (AFI) of less than 5 cm. However, best available evidence supports using the deepest vertical pocket method of measurement because it leads to fewer interventions with no increase in poor perinatal outcomes compared with use of the AFI. Only the deepest vertical pocket method should be used with multiple pregnancies.

** Discordant fetal growth is defined by a 15 to 25 % reduction in the estimated fetal weight of the smaller fetus when compared with the largest.

2. **Experimental, Investigational, or Unproven**

The following tests and procedures are considered experimental, investigational, or unproven because the effectiveness of these approaches has not been established (not an all-inclusive list):

1. Uterine artery Doppler studies for risk assessment or screening during pregnancies;
2. Antepartum fetal surveillance with NST, CST, BPP, modified BPP, and umbilical artery Doppler velocimetry for all other indications not listed in Section I;
3. Doppler studies of ductus venosus and vessels other than the middle cerebral artery and umbilical artery for fetal surveillance of impaired fetal growth;
4. Measurement of serum YKL-40 for evaluation of pre-eclampsia or small-for-gestational age fetuses;
5. Umbilical artery Doppler velocimetry for multiple gestations pregnancies, except in those conditions noted in Section I;
6. Ophthalmic artery Doppler for prediction of pre-eclampsia;
7. Preeclampsia Screen|T1 for prediction of risk for early onset preeclampsia;
8. Use of maternal serum ischemia-modified albumin as a biomarker for preeclampsia;
9. PIGF Preeclampsia Screen (a biochemical assay of placental growth factor);
10. Remote non-stress testing (e.g., home, tele-monitored, and virtual).

3. **Related Policies**

- CPB 0106 - Fetal Echocardiography and Magnetocardiography
- CPB 0127 - Home Uterine Activity Monitoring
- CPB 0199 - Ultrasound for Pregnancy

CPT Codes / HCPCS Codes / ICD-10 Codes

***Antepartum fetal surveillance using NST, CST, BPP, or modified BPP*:**

Code	Code Description
CPT codes covered if selection criteria are met:	
59020	Fetal contraction stress test
59025	Fetal non-stress test
76805	Ultrasound, pregnant uterus, real time with image documentation, fetal and maternal evaluation, after first trimester (> or = 14 weeks 0 days), transabdominal approach; single or first gestation
+ 76810	each additional gestation (List separately in addition to code for primary procedure)
76818	Fetal biophysical profile; with non-stress testing
76819	without non-stress testing
CPT codes not covered for indications listed in the CPB:	
***Maternal serum ischemia-modified albumin as a biomarker* - no specific code**	

Code	Code Description
0243U	Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia

ICD-10 codes covered if selection criteria are met (not all-inclusive):

D68.61	Antiphospholipid syndrome
E10.10 - E10.9	Type 1 diabetes mellitus
E11.00 - E11.9	Type II diabetes mellitus
I50.1 - I51.9	Heart failure
J45.20 - J45.998	Asthma [steroid dependent or poorly controlled]
M32.10	Systemic lupus erythematosus, organ or system involvement unspecified
O09.00 - O09.93	Supervision of high-risk pregnancy
O10.011 - O11.9 O12.10 - O16.9	Proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium
O20.0 - O20.9	Hemorrhage in early pregnancy
O24.011 - O24.33	Pre-existing diabetes mellitus in pregnancy, childbirth and the puerperium
O24.410 - O24.439	Gestational diabetes in pregnancy, childbirth and the puerperium
O28.0 - O28.9	Abnormal findings on antenatal screening of mother
O36.1110 - O36.1999	Maternal care for other isoimmunization
O36.20x0 - O36.23x9	Maternal care for hydrops fetalis
O36.5110 - O36.5199	Maternal care for known or suspected placental insufficiency
O36.5910 - O36.5999	Maternal care for other known or suspected poor fetal growth
O36.80x0 - O36.80x9	Pregnancy with inconclusive fetal viability
O36.8120 - O36.8199	Decreased fetal movements
O36.8310 - O36.8399	Maternal care for abnormalities of the fetal heart rate or rhythm
O40.1xx0 - O40.9xx9	Polyhydramnios
O41.00x0 - O41.03x9	Oligohydramnios
O44.00 - O46.93	Placenta previa, premature separation of placenta [abruptio placentae], antepartum hemorrhage, not elsewhere classified
O48.0	Post-term pregnancy
O48.1	Prolonged pregnancy
O99.111 - O99.119	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy [Antiphospholipid syndrome]
O99.280 - O99.285	Other endocrine, nutritional and metabolic diseases complicating pregnancy, childbirth and the puerperium
O99.411 - O99.419	Diseases of the circulatory system complicating pregnancy
O99.511 - O99.519	Diseases of the respiratory system complicating pregnancy, childbirth and the puerperium [asthma]
O99.810 - O99.815	Abnormal glucose complicating pregnancy, childbirth and the puerperium
O99.891 - O99.891	Other specified diseases and conditions complicating pregnancy, childbirth and the puerperium [systemic lupus erythematosus (SLE)]

ICD-10 codes not covered for indications listed in the CPB:

Z33.1	Pregnant state, incidental
Z34.00 - Z34.93	Encounter for supervision of normal pregnancy

***Umbilical artery Doppler velocimetry*:**

CPT codes covered if selection criteria are met:

76820	Doppler velocimetry, fetal; umbilical artery [not covered for studies of ductus venosus and vessels for surveillance of impaired fetal growth]

ICD-10 codes covered if selection criteria are met:

O30.00 - O30.93	Multiple gestations

Code	Code Description
O31.8X10 - O31.8X99	Other complications specific to multiple gestation
O36.5110 - O36.5999	Maternal care for other known or suspected poor fetal growth
O36.8210 - O36.8299	Maternal care for fetal anemia and thrombocytopenia
O41.00x0 - O41.03x9	Oligohydramnios
O43.021 - O43.029	Fetus-to-fetus placental transfusion syndrome

***Uterine artery Doppler studies*:**

CPT codes not covered for indications listed in the CPB:

93975	Duplex scan of arterial inflow and venous outflow of abdominal, pelvic, scrotal contents and/or retroperitoneal organs; complete study
93976	limited study

ICD-10 codes not covered for indications listed in the CPB:

O00.00 - O9A.53	Pregnancy, childbirth, and the puerperium
Z03.71 – Z03.79	Encounter for suspected maternal and fetal conditions ruled out
Z32.00 – Z32.3	Encounter for pregnancy test and childbirth and childcare instruction
Z33.1 – Z33.3	Pregnant state
Z34.00 – Z34.93	Encounter for supervision of normal pregnancy
Z36.0 – Z36.9	Encounter for antenatal screening of mother
Z3A.00 – Z3A.49	Weeks of gestation

***Middle cerebral artery Doppler velocimetry*:**

CPT codes covered if selection criteria are met:

76821	Doppler velocimetry, fetal; middle cerebral artery

ICD-10 codes covered if selection criteria are met (not all-inclusive):

O30.00 – O30.93	Multiple gestation [Twin anemia polycythemia sequence (TAPS)]
O31.8X10 - O31.8X99	Other complications specific to multiple gestation
O35.3xx0 - O35.3XX9	Maternal care for (suspected) damage to fetus from viral disease in mother
O36.0110 - O36.0999	Maternal care for rhesus isoimmunization
O36.1110 - O36.1999	Maternal care for other isoimmunization
O36.5110 - O36.5999	Maternal care for other known or suspected poor fetal growth
O43.011 - O43.019	Fetomaternal placental transfusion syndrome
O43.021 - O43.029	Fetus-to-fetus placental transfusion syndrome
O98.511 - O98.53	Other viral diseases complicating pregnancy, childbirth and the puerperium [parvovirus B-19 infection]

Preeclampsia sFlt-1/PlGF ratio (PERA):

CPT codes covered if selection criteria are met:

0482U	Obstetrics (preeclampsia), biochemical assay of soluble fmslike tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF), serum, ratio reported for sFlt1/PlGF, with risk of progression for preeclampsia with severe features within 2 weeks

ICD-10 codes covered if selection criteria are met (not all-inclusive):

O13.1 – O13.9	Gestational [pregnancy-induced] hypertension without significant proteinuria
O14.00 – O14.95	Pre-eclampsia
Z3A.23 - Z3A.40	Weeks of gestation [23 - 40]

***Serum YKL-40*:**

Code	Code Description
CPT codes not covered for indications listed in the CPB:	
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [not covered for serum YKL-40]
ICD-10 codes not covered for indications listed in the CPB:	
O11.1 - O11.9	Pre-existing hypertension with pre-eclampsia
O14.00 - O14.93	Pre-eclampsia
O36.5910 - O36.5999	Maternal care for other known or suspected poor fetal growth [small-for-gestational age fetuses]

***Ophthalmic Artery Doppler*:**

CPT codes not covered for indications listed in the CPB:	
93886	Transcranial Doppler study of the intracranial arteries; complete study [not covered for the prediction of pre-eclampsia]
93888	Transcranial Doppler study of the intracranial arteries; limited study [not covered for the prediction of pre-eclampsia]

Background

Antepartum fetal surveillance is used to assess the risk of adverse perinatal outcome associated with utero-placental insufficiency, and is recommended for pregnancies that are at risk for hypoxia and stillbirth. Common tests include fetal movement assessment, non-stress tests (NST), contraction stress tests (CST), biophysical profile (BPP), modified BPP, and umbilical artery Doppler velocimetry. Some of the conditions under which antepartum fetal surveillance may be appropriate include the following:

Maternal Conditions

- Anti-phospholipid syndrome
- Chronic renal disease
- Cyanotic heart disease
- Hemoglobinopathies (hemoglobin SS, SC, or S-thalassemia)
- Hypertensive disorders
- Hyperthyroidism (poorly controlled)
- Systemic lupus erythematosus
- Type 1 diabetes mellitus

Pregnancy-Related Conditions

- Decreased fetal movement
- Intrauterine growth restriction
- Isoimmunization (moderate-to-severe)
- Multiple gestation (with significant growth discrepancy)
- Oligohydramnios
- Polyhydramnios
- Post-term pregnancy (greater than 41 weeks gestation)
- Pregnancy-induced hypertension
- Previous fetal demise (unexplained or recurrent risk)

Fetal Movement Assessment

A decrease in the maternal perception of fetal movement often but not invariably precedes fetal death, in some cases by several days. This observation provides the rationale for fetal movement assessment by the mother ("kick counts") as a means of antepartum fetal surveillance.

In a review on fetal movement assessment, Froen and colleagues (2008) noted that while almost all pregnant women adhere to it, organized screening by fetal movements has seen variable popularity among health professionals. Early results of screening

were promising and fetal movement counting is the only antepartum testing method that has shown effect in reducing mortality in a randomized controlled trial comparing testing versus no testing. Although awareness of fetal movements is associated with improved perinatal outcomes, the quest to define a quantitative "alarm limit" to define decreased fetal movements has so far been unsuccessful, and the use of most such limits developed for fetal movement counting should be discouraged.

Non-Stress Test

The NST is based on the premise that the heart rate of a fetus that is not acidotic or neurologically depressed will temporarily accelerate with fetal movement. Heart rate reactivity is thought to be a good indicator of normal fetal autonomic function. Loss of reactivity is associated most commonly with the fetal sleep cycle but may result from any cause of central nervous system depression, including fetal acidosis and some medications.

To perform NST, the mother is asked to denote when the fetus moves. The fetal heart rate tracing is then evaluated for accelerations of the fetal heart rate corresponding with fetal movement. Alternatively, acoustic stimulation is applied to the maternal abdomen for 1 to 2 seconds and the fetal heart rate is recorded. The acoustic stimulation may be repeated up to 3 times, each time for progressively longer durations (up to 3 seconds), to elicit fetal heart rate accelerations.

Remote Nonstress Testing

Kerner, et al. (2004) evaluated the feasibility of high-risk pregnancy surveillance by patient-directed fetal heart rate (FHR) monitoring and transmission, and to assess patient satisfaction with this technology. Thirty-six women with high-risk pregnancies performed daily non-stress tests at home and transmitted the data to our perinatal care center by telephone. The investigators concluded that daily home FHR monitoring in high-risk patients is safe and feasible at all gestational ages, based on this initial pilot evaluation.

van den Heuvel, et al. (2020) conducted a feasibility pilot study to explore the usability and acceptability of telemonitoring with an aim to gain insight in experiences and preferences of high risk pregnant women regarding telemonitoring strategy opposed to women who were hospitalized in pregnancy. They conducted four online focus groups: two focus groups with women who were admitted during pregnancy (n = 11) and two with women who received home telemonitoring in the pilot phase (n = 11). The qualitative data were analyzed thematically. The investigators concluded that future studies should further investigate the safety and cost effectiveness of telemonitoring.

van den Heuvel, et al. (2020) conducted a study utilizing a web-based survey to assess the current practice and attitudes concerning home-based monitoring (with daily home visits by professionals) and telemonitoring (using devices and the internet for daily self-recorded measurements) in high-risk pregnancies requiring maternal and fetal monitoring in the Netherlands. The investigators noted that 3% (28/73) of hospitals offered either home-based monitoring or telemonitoring or both as an alternative to hospital admission.

Porter et al (2022) reported on 63 women who had paired clinic-based patient-administered, wireless, fetal heartbeat monitor (HBM) designed for home use and cardiotocographic (CTG) recordings, providing 6982 fetal heart rate measures for point-to-point comparison from 126 min of continuous recording. The investigators noted that HBM is as accurate as gold-standard CTG and provides equivalent clinical information enabling use in non-stress test analyses conducted outside of hospitals.

Zizzo et al (2022) conducted a retrospective study to evaluate the outcome and safety of extended remote self-monitoring of maternal and fetal health in intermediate- and high-risk pregnancies. The study reported on 400 singleton pregnancies complicated by preterm premature rupture of membranes (PPROM), fetal growth restriction, preeclampsia, gestational diabetes mellitus, high-risk of preeclampsia, or a history of previous fetal or neonatal loss. The investigators concluded that home-monitoring including remote self-monitoring of fetal and maternal well-being in intermediate- and high-risk pregnancies seems to be a safe alternative to inpatient or frequent outpatient care, which sets the stage for a new way of thinking of hospital care.

Bekker et al (2023) conducted a multicenter, randomized, controlled, non-inferiority trial to evaluate the safety, clinical effectiveness, patient satisfaction, and costs of home telemonitoring against hospital care in complicated pregnancies. Pregnant women (n=201) were randomly assigned to either hospital admission or telemonitoring in (1:1), stratified for the six diagnoses for inclusion and the six centers of inclusion, using block randomization (block sizes of four and six). The investigators concluded that this non-inferiority trial shows the first evidence that telemonitoring might be as safe as hospital admission for monitoring complicated pregnancies.

Hamm et al (2023) the clinical interpretability and usability of INVU, a novel FDA-cleared, remote, self-administered maternal-fetal monitoring solution, previously validated for fetal and maternal heart rates and uterine activity measurements. This was a prospective, open-label, single site study of a wireless, remote pregnancy monitoring system (INVU by Nuvo Group, Ltd) in high-risk pregnancies to remotely perform clinically indicated nonstress tests (NSTs) instead of in clinic NSTs. The investigators noted that >90% of NSTs performed remotely using INVU were acceptable for clinical utility, and >88% of NST appointments were completed without in-clinic evaluation. INVU also demonstrated an excellent safety profile and good patient usability.

Li et al (2023) conducted a systematic review and meta-analysis of randomized controlled trials or quasi-experimental trials of remote fetal monitoring. Nine studies were included in the systematic review and meta-analysis (n=1128). The investigators concluded that remote fetal monitoring seems to reduce the incidence of neonatal asphyxia and health care costs compared with routine fetal monitoring. Further well-designed studies are necessary, especially in high-risk pregnant women, such as pregnant women with diabetes, pregnant women with hypertension, etc.

Suemitsu et al (2023) conducted a single-center, retrospective case series of patients with fetal growth restriction (FGR). Seventeen women diagnosed with FGR were enrolled. Patients performed mobile cardiotocography (iCTG) for 1 hour twice daily to examine their fetuses; data were uploaded and saved on the cloud. The investigators concluded that using iCTG reduces the economic burden of hospitalization for patients.

Contraction Stress Test

The CST measures the response of the fetal heart rate to uterine contractions. It relies on the premise that fetal oxygenation will be transiently worsened by uterine contractions. This test is rarely used in clinical practice at this time.

To perform CST, the fetal heart rate and uterine contractions are simultaneously recorded with an external fetal monitor. The test lasts until the mother has had 3 moderate strength contractions within a 10-min period. If contractions are not happening on their own, they may be induced using an intravenous dose of oxytocin

Biophysical Profile

BPP is comprised of 5 components:

- Amniotic fluid index (determination of the amniotic fluid volume)
- Fetal breathing movements
- Fetal movement
- Fetal tone
- Non-stress test.

Each component is assigned 2 points, resulting in a score ranging from 0 to 10, with scores from 8 to 10 considered normal, 6 considered borderline, and below 6 considered problematic.

A Cochrane review on BPP for fetal assessment in high-risk pregnancies (Lalor et al, 2008) concluded that there is currently insufficient evidence from randomized trials to support the use of BPP as a test of fetal wellbeing in high-risk pregnancies.

Modified Biophysical Profile

Modified BPP combines the NST (with the option of acoustic stimulation), as a short-term indicator of fetal acid-base status, with the amniotic fluid index as an indicator of long-term placental function.

Uterine Artery Doppler

Abnormal uterine artery Doppler studies in the first and second trimester have been associated with subsequent adverse pregnancy outcomes including preeclampsia, fetal growth restriction, and perinatal mortality. However, there is insufficient evidence in the peer-reviewed published medical literature and from evidence-based clinical guidelines for the use of uterine artery Doppler in assessment of either average-risk or high-risk pregnancies. A Cochrane systematic evidence review (Neilson et al, 2003) of Doppler ultrasound for fetal assessment of high-risk pregnancies found that most randomized trials have examined ultrasound of the umbilical artery, not the uterine artery. Only 1 randomized study examined the clinical impact of uterine artery blood flow; in that study, both uterine artery and umbilical artery blood flow were measured. Based on the lack of evidence on the clinical utility of uterine artery blood flow measurements, the Cochrane reviewers concluded: "It is not clear if the study of utero-placental arteries makes any real contribution or not. Fetal vessels other than the umbilical artery can also be studied, especially using pulsed wave Doppler with or without color flow imaging; as yet, there is no evidence from controlled studies that these studies are of clinical value."

Guidelines from the ACOG have concluded that uterine artery Doppler is not an effective method for identifying women at risk for eclampsia. The ACOG guidelines on eclampsia and preeclampsia (2002) state that "Doppler velocimetry of the uterine arteries was reported not to be a useful test for screening pregnant women at low risk for preeclampsia." The ACOG guidelines on intrauterine growth restriction (2000) state that umbilical artery ultrasounds may be useful in the evaluation of the growth restricted fetus; however, these guidelines indicate no particular role for uterine artery Doppler ultrasound in the evaluation and management of intrauterine growth restriction pregnancies.

A review of the evidence for uterine artery Doppler studies prepared for the Society for Maternal Fetal Medicine (Scicione and Hayes, 2009) found that the predictive value of Doppler testing in a low-risk population of women appears to be low, and currently there are no available interventions to prevent adverse outcomes based on an abnormal result. The review found that

effective interventions to prevent late pregnancy complications (e.g., preeclampsia, growth restrictions, and perinatal mortality) in women considered at low-risk with abnormal early pregnancy uterine artery Doppler studies are needed. The review concluded that, "[u]ntil such time as these are available, routine uterine artery Doppler screening of women considered at low risk is not recommended."

The review found that uterine artery Doppler screening of high-risk women (e.g., history of chronic hypertension or preeclampsia, prior fetal growth restriction, or stillbirth) with singleton gestations appears to identify those at substantially increased risk for adverse pregnancy outcomes (Scicione and Hayes, 2009). The review stated that abnormal testing in these women could potentially lead to increased surveillance (e.g., earlier and more frequent assessment of fetal growth and maternal clinical condition) and interventions that might improve clinical outcomes. Normal Doppler studies could potentially lead to a reduction in such testing and interventions. The review noted, however, that further study is needed to determine which high-risk conditions are amenable to such screening, what testing regimen is optimal for a normal or abnormal test in these women, and what interventions based on these findings will improve pregnancy outcomes.

The review concluded: "At this time, the evidence does not support routine screening with uterine artery Doppler in any particular group of patients. Use of umbilical artery Doppler should be individualized, and a plan of management based on the results should be put in place. Because standards for the study technique, gestational age, and criteria for an abnormal test are lacking, uterine artery Doppler studies should not be considered to be a required medical practice in low or high risk populations."

Pedrosa and Matias A (2011) performed a systematic review of screening for pre-eclampsia (PE) with the combination of uterine artery Doppler (UAD), maternal history, mean arterial pressure and/or maternal serum markers. These researchers identified eligible studies through Medline searches, and, for each included study, they assessed the risk of bias and extracted relevant data. They reported the performance of screening tests according to the target population (low- or high-risk), the trimester of screening (first and/or second) and the subset of PE screened for (early and late). Several tests provided moderate or convincing prediction of early PE, but screening for late PE was poor. Although UAD is more accurate in the second trimester, these investigators found encouraging results for first-trimester screening when it was combined with other markers. Performance of screening was consistently lower in populations with risk factors for PE in the maternal history. The authors presented encouraging results for the prediction of early PE, even in the first trimester of pregnancy. The different performance of tests in screening for early versus late PE, and of low- versus high-risk populations, supports the concept that PE is a heterogeneous disease.

In a systematic review, Kuc et al (2011) examined the literature on the predictive potential of first-trimester serum markers and of UAD velocity waveform assessment (uterine artery [Ut-A] Doppler). Literature on the 7 most studied serum markers (A-disintegrin and metalloprotease 12 [ADAM 12], free β-subunit of human chorionic gonadotropin [fβ-hCG], Inhibin A, Activin A, PP13, placental growth factor [PlGF], and pregnancy-associated plasma protein A [PAPP-A]) and Ut-A Doppler was primarily selected. In the selected literature, a combination of these markers was analyzed, and where relevant, the value of maternal characteristics was added. Measurements of serum markers and Ut-A Doppler were performed between week 8 + 0 and 14 + 0 gestational age (GA). Low levels of PP13, PlGF, and PAPP-A and elevated level of Inhibin A have been found to be significantly associated with the development of PE later in pregnancy. The detection rates of single markers, fixed at 10 % false-positive rate, in the prediction of early-onset PE were relatively low, and ranged from 22 % to 83 %. Detection rates for combinations of multiple markers varied between 38 % and 100 %. Therefore, a combination of multiple markers yields high detection rates and is promising to identify patients at high-risk of developing PE. However, the authors stated that large scale prospective studies are needed to evaluate the power of this integrated approach in clinical practice.

In a prospective cohort study, Bezircioglu et al (2012) examined the diagnostic value of blood flow measurements in endometrial, myometrial and uterine vasculature by trans-vaginal Doppler ultrasonography in the differentiation of the neoplastic endometrial pathologies in women with post-menopausal bleeding. A total of 106 women who presented with post-menopausal bleeding were enrolled in this study. Endometrial thickness, pulsatility and resistance indices (PI and RI) of the uterine, myometrial and endometrial vasculature, endometrial histopathology were measured by trans-vaginal Doppler sonography. Dilatation and curettage were performed for all women. Sonographic and histopathological results were evaluated. Endometrial malignancy was diagnosed in 24 of the patients (22.7 %). Endometrial thickness was found to be higher in the patients with malign histopathology compared with the patients of benign histopathology. Statistically, uterine artery PI, RI, radial artery PI, spiral artery PI, and RI were also significantly lower in patients with malign histopathology. According to receiver-operating characteristics (ROC) curve analysis the endometrial thickness of 5 mm, uterine artery PI of 1.450, uterine artery RI of 0.715, radial artery PI of 1.060, and radial artery RI of 0.645 were defined as the cut-off points. In multi-variate regression model, only uterine artery PI was identified as independent determinant of malignant endometrium. The authors concluded that blood flow of uterine artery and also myometrial and endometrial vasculature displayed lower impedance in patients with malignant endometrium, but these lower indices are not already adequate for using as diagnostic tests.

The Society for Maternal-Fetal Medicine Publications Committee’s report on "Doppler assessment of the fetus with intrauterine growth restriction" (Berkley et al, 2012) provided evidence-based guidelines for utilization of Doppler studies for fetuses with IUGR. Relevant documents were identified using PubMed (US National Library of Medicine, 1983 through 2011) publications, written in English, which describe the peri-partum outcomes of IUGR according to Doppler assessment of umbilical arterial, middle cerebral artery, and ductus venosus. Additionally, the Cochrane Library, organizational guidelines, and studies identified through review of the above were utilized to identify relevant articles. Consistent with US Preventive Task Force suggestions, references were evaluated for quality based on the highest level of evidence, and recommendations were graded. Summary of

randomized and quasi-randomized studies indicated that, among high-risk pregnancies with suspected IUGR, the use of umbilical arterial Doppler assessment significantly decreases the likelihood of labor induction, cesarean delivery, and perinatal deaths (1.2 % versus 1.7 %; relative risk, 0.71; 95 % confidence interval: 0.52 to 0.98). Antepartum surveillance with Doppler of the umbilical artery should be started when the fetus is viable and IUGR is suspected. Although Doppler studies of the ductus venous, middle cerebral artery, and other vessels have some prognostic value for IUGR fetuses, currently there is a lack of randomized trials showing benefit. Thus, Doppler studies of vessels other than the umbilical artery, as part of assessment of fetal well-being in pregnancies complicated by IUGR, should be reserved for research protocols.

Goetzinger et al (2013) estimated the efficiency of first trimester Ut-A Doppler, ADAM12, PAPP-A, and maternal characteristics in the prediction of PE. These researchers conducted a prospective cohort study of patients presenting for first trimester aneuploidy screening between 11 and 14 weeks' gestation. Maternal serum ADAM12 and PAPP-A levels were measured by an immunoassay, and mean Ut-A Doppler PIs were calculated. Outcomes of interest included PE, early PE (defined as requiring delivery at less than 34 weeks' gestation), and gestational hypertension. Logistic regression analysis was used to model the prediction of PE using ADAM12 multiples of the median (MoM), PAPP-A MoM, and Ut-A Doppler PI MoM, either individually or in combination. The sensitivity, specificity, and area under the receiver operating characteristic curves were used to compare the screening efficiency of the models using nonparametric U statistics. Among 578 patients with complete outcome data, there were 54 cases of PE (9.3 %) and 13 cases of early PE (2.2 %). Median ADAM12 levels were significantly lower in patients who developed PE compared to those who did not (0.81 versus 1.01 MoM; p = 0.04). For a fixed false-positive rate of 10 %, ADAM12, PAPP-A, and Ut-A Doppler parameters in combination with maternal characteristics identified 50 %, 48 %, and 52 % of patients who developed PE, respectively. Combining these first trimester parameters did not improve the predictive efficiency of the models. The authors concluded that first trimester ADAM12, PAPP-A, and Ut-A Doppler characteristics are not sufficiently predictive of PE. Combinations of these parameters do not further improve their screening efficiency.

An UpToDate review on "Prediction of preeclampsia" (Norwitz, 2014) states that "Studies of uterine artery Doppler velocimetry for prediction of preeclampsia are difficult to compare because investigators have used different Doppler sampling techniques, definitions of abnormal flow velocity waveform, populations, gestational age at examination, and criteria for the diagnosis of preeclampsia …. Although meta-analyses show that uterine artery Doppler analysis can predict women at increased risk of preeclampsia, we and most experts do not recommend these studies for screening purposes. Close clinical monitoring for preeclampsia is already a major component of prenatal care; improved identification of women at increased or decreased risk of a disease that cannot be prevented and has no treatment other than delivery is unlikely to improve maternal or fetal outcome. Furthermore, the false positive rate of this test is quite high, leading to excessive patient anxiety and health care costs. Further research is needed before screening with uterine artery Doppler can be recommended".

Seravalli et al (2014) noted that first trimester screening for subsequent delivery of a small for gestational age (SGA) infant typically focuses on maternal risk factors and Ut-A Doppler. These investigators examined if incorporation of fetal umbilical artery (UA) and ductus venosus (DV) Doppler improves SGA prediction. They performed a prospective screening study of singletons at 11 to 14 weeks. Maternal characteristics, serum concentrations of PAPP-A and free β-hCG were ascertained and Ut-A Doppler, UA, and DV Doppler studies were performed. These parameters were tested for their ability to predict subsequent delivery of a SGA infant. Among 2,267 enrolled women, 191 (8.4 %) delivered an SGA infant. At uni-variate analysis women with SGA neonates were younger, more frequently African-American (AA), nulliparous, more likely to smoke, have lower PAPP-A and free β-hCG levels. They had a higher incidence of Ut-A Doppler bilateral notching, higher mean Ut-A Doppler-PI z-scores (p < 0.001) and UA PI z-scores (p = 0.03), but no significant difference in DV-PI z-scores or in the incidence of abnormal qualitative UA and DV patterns. Multi-variate logistic regression analysis identifies nulliparity and AA ethnicity (p < 0.001), PAPP-A multiple of the median and bilateral notching (p < 0.05) as determinants of SGA infant. Predictive sensitivity was low; receiver operating characteristic curve analysis yields areas under the curve of 0.592 (95 % confidence interval [CI]: 0.548 to 0.635) for the combination of Ut-A Doppler and UA PI z-scores. The authors concluded that delivery of a SGA infant is most frequent in nulliparous women of AA ethnicity. Moreover, they stated that despite the statistical association with Ut-A Doppler first trimester SGA prediction is poor and not improved by the incorporation of fetal Doppler.

In a Cochrane review, Alfirevic et al (2015) examined the effects of routine fetal and umbilical Doppler ultrasound on obstetric practice and pregnancy outcome in unselected and low-risk pregnancies. These investigators searched the Cochrane Pregnancy and Childbirth Group Trials Register (February 28, 2015) and reference lists of retrieved studies. Randomized and quasi-randomized controlled trials of Doppler ultrasound for the investigation of umbilical and fetal vessels waveforms in unselected pregnancies compared with no Doppler ultrasound were selected for analysis. Studies where uterine vessels have been assessed together with fetal and umbilical vessels have been included. Two review authors independently assessed the studies for inclusion, assessed risk of bias and carried out data extraction. In addition to standard meta-analysis, the 2 primary outcomes and 5 of the secondary outcomes were assessed using GRADE software and methodology. These researchers included 5 trials that recruited 14,624 women, with data analyzed for 14,185 women. All trials had adequate allocation concealment, but none had adequate blinding of participants, staff or outcome assessors. Overall and apart from lack of blinding, the risk of bias for the included trials was considered to be low. Overall, routine fetal and umbilical Doppler ultrasound examination in low-risk or unselected populations did not result in increased antenatal, obstetric and neonatal interventions. There were no group differences noted for the review's primary outcomes of perinatal death and neonatal morbidity. Results for perinatal death were as follows: (average risk ratio (RR) 0.80, 95 % CI: 0.35 to 1.83; 4 studies, 11,183 participants). Only 1 included trial assessed serious neonatal morbidity and found no evidence of group differences (RR 0.99, 95 % CI: 0.06 to 15.75; 1 study, 2,016 participants). For the comparison of a single Doppler assessment versus no Doppler, evidence for group

differences in perinatal death was detected (RR 0.36, 95 % CI: 0.13 to 0.99; 1 study, 3,891 participants). However, these results were based on a single trial, and the authors would recommend caution when interpreting this finding. There was no evidence of group differences for the outcomes of caesarean section, neonatal intensive care admissions or pre-term birth less than 37 weeks. When the quality of the evidence for the main comparison of "All Doppler versus no Doppler" was assessed with GRADE software, the outcomes of perinatal death and serious neonatal morbidity data were graded as of low quality. Evidence for the outcome of stillbirth was graded according to regimen subgroups -- with a moderate quality rating for stillbirth (fetal/umbilical vessels only) and a low quality rating for stillbirth (fetal/umbilical vessels + uterine artery vessels). Evidence for admission to neonatal intensive care unit was assessed as of moderate quality, and evidence for the outcomes of caesarean section and pre-term birth less than 37 weeks was graded as of high quality. There was no available evidence to assess the effect on substantive long-term outcomes such as childhood neurodevelopment and no data to assess maternal outcomes, particularly maternal satisfaction. The authors concluded that existing evidence does not provide conclusive evidence that the use of routine UAD ultrasound, or combination of umbilical and UAD ultrasound in low-risk or unselected populations benefits either mother or baby. They stated that future studies should be designed to address small changes in peri-natal outcome, and should focus on potentially preventable deaths.

Allen et al (2016) evaluated the predictive accuracy for stillbirth of second trimester UAD. These investigators searched MEDLINE, EMBASE and Cochrane databases from inception until March 2015 without language restrictions. Included studies were those that assessed the association of abnormal UAD parameters and stillbirth. Two independent reviewers selected studies, extracted data and assessed quality. Results for studies that were performed in the second trimester were pooled and summary estimates of sensitivity, specificity, likelihood ratios and their 95 % CIs were obtained. Overall summary of test accuracy was provided by the diagnostic odds ratio (OR). Literature searches returned 338 relevant citations with 32 considered in full; 13 studies met search criteria, (85, 846 women, 508 stillbirths) and were included in the review. Bi-variate pooled estimate for sensitivity was 65 % (95 % CI: 38 to 85 %) and for specificity it was 82 % (95 % CI: 72 to 88 %). The positive likelihood ratio was 3.5 (95 % CI: 2.3 to 5.5) and negative likelihood ratio 0.43 (95 % CI: 0.22 to 0.85); the diagnostic OR was 8.3 (95 % CI: 3 to 22.4). The authors concluded that abnormal UAD indices are associated with a 3- to 4-fold increase in the risk of stillbirth. However, the heterogeneity was particularly high in the high-risk group rendering it impossible to draw firm conclusions.

Levine and colleagues (2016) stated that maternal prenatal stress is associated with pre-term birth, IUGR, and developmental delay. However, the impact of prenatal stress on hemodynamics during pregnancy remains unclear. These researchers carried out a systematic review to evaluate the quality of the evidence available to-date regarding the relationship between prenatal stress and maternal-fetal hemodynamics. The PubMed/Medline, Embase, PsycINFO, Maternity and Infant Care, Trip, Cochrane Library, and CINAHL databases were searched using the search terms pregnancy; stress; fetus; blood; Doppler; ultrasound. Studies were eligible for inclusion if prenatal stress was assessed with standardized measures, hemodynamics was measured with Doppler ultrasound, and methods were adequately described. A specifically designed data extraction form was used. The methodological quality of included studies was assessed using well-accepted quality appraisal guidelines. Of 2,532 studies reviewed, 12 met the criteria for inclusion; 6 reported that prenatal stress significantly affected maternal or fetal hemodynamics; 6 found no significant association between maternal stress and circulation. Significant relationships between prenatal stress and uterine artery RI and PI, umbilical artery RI, PI, and systolic/diastolic ratio, fetal MCA PI, cerebroplacental ratio (CPR), and umbilical vein volume blood flow were found. The authors concluded that there is limited evidence that prenatal stress is associated with changes in circulation. They stated that more carefully designed studies with larger sample sizes, repeated assessments across gestation, tighter control for confounding factors, and measures of pregnancy-specific stress are needed to clarify this relationship.

Also, an UpToDate review on "Overview of antepartum fetal surveillance" (Signore and Spong, 2016) states that "A number of investigators have explored the use of uterine artery Doppler for third trimester fetal assessment among women with complicated pregnancies, but its role in these settings has not been clearly defined".

Martinez-Portilla and colleagues (2020) examined the predictive ability for adverse perinatal outcome of abnormal third-trimester UAD in late SGA fetuses. These researchers carried out a systematic search to identify relevant observational studies and RCTs evaluating the performance of abnormal third-trimester UAD for the prediction of adverse perinatal outcome in suspected SGA fetuses and SGA neonates. Abnormal UAD was defined as uterine artery PI of greater than 95th percentile or greater than or equal to 2 SD above the mean, or bilateral uterine artery notching. Hierarchical summary ROC curves were constructed using random-effects modeling. Bayesian analysis was used to calculate the posterior probability of adverse perinatal outcome following an abnormal or normal UAD assessment. A total of 17 observational studies (including 7,552 fetuses either diagnosed with suspected SGA (n = 3,461) or later diagnosed as a SGA neonate (n = 4,091)) met the inclusion criteria; no RCTs met the inclusion criteria. Summary ROC curves showed that, among suspected SGA fetuses, the best predictive accuracy of abnormal third-trimester UAD was for perinatal mortality and the worst was for composite adverse perinatal outcome, with areas under the summary ROC curves of 0.90 and 0.66, respectively. The corresponding positive and negative likelihood ratios (PLRs and NLRs) were 16.5 and 0.6 for perinatal mortality and 2.82 and 0.65 for composite adverse perinatal outcome, respectively. Following an abnormal versus normal UAD assessment, the posterior risks for composite adverse perinatal outcome, admission to the neonatal intensive care unit (ICU), Cesarean section for intrapartum fetal compromise, 5-min Apgar score of less than 7, neonatal acidosis and perinatal death were: 52.3 % versus 20.2 %, 48.6 % versus 18.7 %, 23.1 % versus 15.2 %, 3.59 % versus 1.32 %, 9.15 % versus 5.12 % and 31.4 % versus 1.64 %, respectively. The authors concluded that abnormal UAD in the third trimester appeared to be moderately useful in predicting perinatal death in pregnancies with suspected SGA. However, because

of its limited predictive ability as a stand-alone test, UAD should be used in combination with other tests to guide clinical decisions.

The authors stated that this study had several drawbacks. First, due to the study design, these findings were applicable only to late SGA (greater than or equal to 32 weeks). Second, most of the included studies were hampered by lack of blinding of the UAD measurements. Third, it could be argued that the use of multiple likelihood ratios would be an inadequate approach, as they may not be totally independent from each other (e.g., CPR values may also depend on uterine perfusion reflected by UAD). The clinical findings of other studies that the association of UAD with adverse outcome was independent of brain Doppler made a strong correlation between these parameters unlikely.

Umbilical Artery Doppler Velocimetry

A variety of fetal and maternal blood vessels have been evaluated by Doppler wave form analysis to assess the risk of adverse perinatal outcome. The most commonly interrogated vessels are the umbilical arteries.

Umbilical artery Doppler flow velocimetry has been adapted for use as a technique of fetal surveillance, based on the observation that flow velocity waveforms in the umbilical artery of normally growing fetuses differ from those of growth-restricted fetuses. Abnormal flow velocity waveforms have been correlated histopathologically with small-artery obliteration in placental tertiary villi and functionally with fetal hypoxia and acidosis, as well as with perinatal morbidity and mortality.

At least 3 randomized clinical trials (RCTs) have evaluated the utility of umbilical artery Doppler velocimetry as a technique of antepartum fetal surveillance in pregnancies complicated by suspected intrauterine growth restriction. Women assigned to antepartum umbilical artery Doppler velocimetry have been shown to require less frequent antenatal monitoring and shorter durations of maternal hospitalization. The results of 1 RCT showed significantly lower rates of obstetric interventions in patients assigned to Doppler, such as antepartum admission and labor induction. Umbilical artery Doppler velocimetry has not been shown to impact other perinatal outcomes, such as gestational age at birth, birth-weight, Apgar scores, and cesarean birth rates.

Guidelines from the American College of Obstetricians and Gynecologists (ACOG, 1999) have concluded that, "[o]n balance, the available evidence suggests that primary antepartum surveillance of suspected intrauterine growth restriction with umbilical artery Doppler velocimetry can achieve at least equivalent (and possibly better) fetal and neonatal outcomes as primary antepartum surveillance based on results of the NST [non-stress test]. Furthermore, frequency of antepartum testing and certain aspects of obstetric intervention are reduced with use of Doppler." ACOG guidelines (1999) state that, "[i]f umbilical artery Doppler velocimetry is used, decisions regarding timing of delivery should be made using a combination of information from the Doppler ultrasonography and other tests of fetal well-being, such as amniotic fluid volume assessment, NST, CST [contraction stress test], and BPP [biophysical profile], along with careful monitoring of maternal status."

According to ACOG guidelines, "[n]o benefit has been demonstrated for umbilical artery velocimetry for conditions other than suspected intrauterine growth restriction, such as post term gestation, diabetes mellitus, systemic lupus erythematosus, or anti-phospholipid syndrome. Doppler ultrasonography has not been shown to be of value as a screening test for detecting fetal compromise in the general obstetric population, and its use for this purpose cannot be recommended."

American College of Obstetricians and Gynecologists (2000) guidelines on intra-uterine growth retardation (IUGR) reached the following conclusions about the clinical utility of Doppler ultrasound of the umbilical artery:

"Although Doppler velocimetry of the umbilical arteries is not useful as a screening technique for IUGR, it has been demonstrated to be useful once IUGR has been diagnosed. Not only are Doppler velocimetry findings normal in growth-restricted fetuses with chromosomal or other structural etiologies but Doppler velocimetry has been shown to both reduce interventions and improve fetal outcome in pregnancies at risk for IUGR. Thus, once IUGR is suspected or diagnosed, Doppler velocimetry may be useful as a part of fetal evaluation. Fetuses with normal flow patterns seem less likely to benefit from consideration of early delivery than do their counterparts with abnormal studies."

The American College of Radiology (2001) has concluded that Doppler studies are, in general, not indicated for the initial assessment to determine if there is (probable) intrauterine growth retardation.

"Extensive research on Doppler analysis of uterine, umbilical, and various intra-fetal vessels confirms a strong correlation between high resistance arterial wave form patterns (e.g., low, absent, or reversed diastolic flow in the umbilical artery) and subsequent IUGR, hypoxemic fetal morbidity, and mortality. The correlation is greatest in high-risk pregnancies, but insufficiently predictive in general, low-risk populations to be useful as a primary screening test. Some have argued that since Doppler appears to be applicable primarily in a population already defined as high risk, the clinical decisions as to when a fetus is distressed and requires emergent delivery will be made based on the BPP and heart rate monitoring, making the Doppler superfluous. A recently published meta-analysis of 20 controlled trials of Doppler ultrasonography found, however, that there is "compelling evidence" that knowledge of the Doppler findings improved perinatal outcome in high-risk pregnancies, reducing antenatal admissions, inductions of labor, and cesarean sections for fetal distress, and reducing the odds of perinatal death by 38 %."

Goffinet et al (1997) reviewed RCTs of umbilical artery Doppler velocimetry in average-risk pregnancies, and concluded that there is inadequate evidence to support its use in that clinical context:

"There is no evidence that routine umbilical Doppler in a general or low-risk population leads to any improvement in the health of women or their infants. Although other trials would be desirable before asserting a definite lack of benefit (due to the problem of statistical heterogeneity and lack of power), umbilical Doppler examination cannot be recommended as a routine test in low- risk pregnancies."

In a Cochrane review, Alfirevic and colleagues (2010) evaluated the effects on obstetric practice and pregnancy outcome of routine fetal and umbilical Doppler ultrasound in unselected and low-risk pregnancies. These investigators searched the Cochrane Pregnancy and Childbirth Group Trials Register (May 2010). Randomized and quasi-RCTs of Doppler ultrasound for the investigation of umbilical and fetal vessels waveforms in unselected pregnancies compared to no Doppler ultrasound were selected. Studies where uterine vessels have been assessed together with fetal and umbilical vessels have been included. Two authors independently assessed the studies for inclusion, assessed risk of bias, as well as carried out data extraction. These researchers included 5 trials involving 14,185 women. The methodological quality of the trials was generally unclear because of insufficient data included in the reports. Routine fetal and umbilical Doppler ultrasound examination in low-risk or unselected populations did not result in increased antenatal, obstetric and neonatal interventions, and no overall differences were detected for substantive short-term clinical outcomes such as perinatal mortality. There is no available evidence to assess the effect on substantive long-term outcomes such as childhood neurodevelopment and no data to assess maternal outcomes, particularly psychological effects. The authors concluded that existing evidence does not provide conclusive evidence that the use of routine umbilical artery Doppler ultrasound, or combination of umbilical and uterine artery Doppler ultrasound in low-risk or unselected populations benefits either mother or baby. They stated that future studies should be designed to address small changes in perinatal outcome, and should focus on potentially preventable deaths.

Umbilical Artery Doppler Velocimetry for Multiple Gestations Pregnancies

In a prospective, clinical study, Musilova and Hodík (2007) evaluated the clinical utility of Doppler velocimetry as a comprehensive test for the prediction of discordant twins. Biometrical measurements and Doppler velocimetry of umbilical artery (UA) and middle cerebral artery (MCA) were performed in twins in third trimester. Inter-twin differences in biometrical parameters delta BPD, delta AC, delta FL, delta EFW and in pulsatility indexes of studied vessels delta UA a delta MCA were expressed. Discordance was identified by the birth weight difference from 20 %. Studied parameters were evaluated using ROC analysis. Among the 63 sets of twins studied, 33 pars fulfilled the study criteria; 21 pars were bi-chorionic, 7 mono-chorionic and 5 with unknown chorionicity; 10 sets of twins were discordant (303 %). The mean gestational age at delivery was 35.9 +/- 1.7 weeks. Overall the best discordancy predictor was delta EFW with sensitivity and specificity values of 100 % and 95.7 %, respectively, for the cut-off value delta EFW 17.9 %. The more accurate one of Doppler parameters was MCA, with sensitivity and specificity values of 85.7 % and 77.9 %, respectively, for the cut-off value delta MCA 25 %. UA had sensitivity and specificity 70 % and 47.8 %, respectively, for most suitable cut-off value delta UA 16.7 %. The authors concluded that it is possible to predict the discordant twins birth using MCA Doppler velocimetry, but the EFW assessment remains the most accurate method. The authors noted that umbilical artery Doppler velocimetry did not appeared as effective.

American College of Gynecology (ACOG)’s Practice Bulletin No. 175: "Ultrasound in pregnancy" (2016) stated that "Umbilical artery Doppler velocimetry used in conjunction with standard fetal surveillance, such as non-stress tests, biophysical profiles, or both, is associated with improved outcomes in fetuses with fetal growth restriction. Absent or reversed end-diastolic flow in the umbilical artery is associated with an increased risk of perinatal mortality. The rate of perinatal death is reduced by as much as 29 % when umbilical artery Doppler velocimetry is added to standard antepartum testing in the setting of fetal growth restriction". It does not mention the use of umbilical artery Doppler velocimetry for multiple gestations pregnancies.

Also, an UpToDate review on "Doppler ultrasound of the umbilical artery for fetal surveillance" (Maulik, 2017) states that "The principles of managing a high risk pregnancy utilizing UA Doppler velocimetry in conjunction with other fetal surveillance test findings are described below. These recommendations are based upon current evidence and should be used to guide patient management with individualization of care as dictated by the specific clinical circumstance (algorithm 1). Umbilical artery Doppler assessment is most useful in pregnancies complicated by fetal growth restriction and/or preeclampsia. Doppler velocimetry is recommended as a primary surveillance tool for monitoring these pregnancies. Doppler investigation identifies the fetal cardiovascular response to progressive hypoxia and acidosis and assists in discriminating small, but constitutionally normal, fetuses from those compromised by placental insufficiency". It does not mention "multiple pregnancies" as an indication for UA Doppler velocimetry.

In an UpToDate review "Twin-twin transfusion syndrome: Screening, prevalence, pathophysiology, and diagnosis", Papanna and Bergh (2024) state that twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS) are serious complications of monochorionic (MC) twin gestations. TAPS is an atypical chronic form of TTTS in which blood flows unequally between twins that share a placenta (monochorionic [MC]), resulting in anemia of one twin (donor) and polycythemia of the co-twin (recipient). The authors state that in MC twin pregnancies, serial fetal ultrasound examinations are necessary to monitor for development of TTTS/TAPS. Doppler studies of the umbilical artery, umbilical vein, and ductus venosus are needed for classification of disease severity. Screening typically begins at 16 weeks of gestation to monitor for TTTS/TAPS, and continues through 36 weeks.

In October 2024, the Society for Maternal-Fetal Medicine provided updated guidance on twin-twin transfusion syndrome and twin anemia-polycythemia sequence. Recommendations include the following:

- Ultrasound surveillance for twin-twin transfusion syndrome begin at 16 weeks of gestation for all monochorionic-diamniotic twin pregnancies and continue at least every 2 weeks until delivery, with more frequent monitoring indicated with clinical concern (GRADE 1C);
- Routine sonographic surveillance for twin-twin transfusion syndrome minimally include assessment of amniotic fluid volumes on both sides of the intertwin membrane and evaluation for the presence or absence of urine-filled fetal bladders, and ideally incorporate Doppler study of the umbilical arteries (GRADE 1C);
- Fetoscopic laser surgery as the standard treatment for stage II through stage IV twin-twin transfusion syndrome presenting between 16 and 26 weeks of gestation (GRADE 1A);
- Expectant management with at least weekly fetal surveillance for asymptomatic patients continuing pregnancies complicated by stage I twin-twin transfusion syndrome, and consideration for fetoscopic laser surgery for stage I twin-twin transfusion syndrome presentations between 16 and 26 weeks of gestation complicated by additional factors such as maternal polyhydramnios-associated symptomatology (GRADE 1B);
- Individualized approach to laser surgery for early- and late-presenting twin-twin transfusion syndrome (GRADE 1C);
- All patients with twin-twin transfusion syndrome qualifying for laser therapy be referred to a fetal intervention center for further evaluation, consultation, and care (Best Practice).

Middle Cerebral Artery Peak Systolic Velocity (MCA PSV) Doppler

Amniocentesis for amniotic fluid bilirubin levels is the most widely used test to predict the severity of fetal disease in red-cell alloimmunization. Many textbooks and guidelines recommend serial amniocentesis to monitor these pregnancies. However, the reliability of amniotic fluid bilirubin measurements has been questioned and these tests are of limited value in the second trimester. Furthermore, critical appraisal of the very few prospective studies is hampered by limitations in design or insufficient data given by the authors. Two strategies have been proposed by investigators as useful indicators of fetal anemia. Some advocate liberal or primary use of fetal blood sampling, while others promote the use of non-invasive ultrasonography and Doppler assessment of umbilical venous and middle cerebral artery peak systolic velocity (MCA PSV).

The most promising of these methods appears to be MCA PSV. Studies have shown a very good correlation between MCA PSV and the degree of fetal anemia in red blood cell allo-immunized pregnancies known to cause immunological hydrops, that is, a low fetal hematocrit is associated with an increase in MCA PSV and the need to perform a transfusion. This screening method has been shown to have an overall sensitivity of 93 % to detect severe anemia, and a sensitivity of 88 % for moderate anemia. Specificity has been reported to be about 75 %. The false positive rate has been shown to increase following 33 weeks gestation. These high sensitivities and acceptable false-positive rates support the potential clinical applicability of the method to reduce the reliance on, and even replace, cordocentesis and amniocentesis with its attendant complications in Rh maternal alloimmunization pregnancies.

In October 2024, the Society for Maternal-Fetal Medicine provided updated guidance on twin-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS). Recommendations include the following:

- Prenatal diagnosis of TAPS minimally require either Doppler MCA-PSV values >1.5 MoM and <1.0 MoM in donor and recipient twins, respectively, or an intertwin Δ MCA-PSV >0.5 MoM (GRADE 1C)
- That providers consider incorporating Doppler MCA-PSV determinations into all monochorionic (MC) twin ultrasound surveillance beginning at 16 weeks of gestation (GRADE 1C)
- Fetoscopic laser surgery as the standard treatment for stage II through stage IV TTTS presenting between 16 and 26 weeks of gestation (GRADE 1A)
- Consultation with a specialized fetal care center is recommended when TAPS progresses to a more advanced disease stage (≥II) before 32 weeks of gestation or when concern arises for coexisting complications such as TTTS (Best Practice).

In an UpToDate review "Twin-twin transfusion syndrome: Screening, prevalence, pathophysiology, and diagnosis", Papanna and Bergh (2024) state that, at 16 to 18 weeks of gestation, middle cerebral artery-peak systolic flow velocity (MCA-PSV) is needed to evaluate for TAPS (defined by MCA-PSV >1.5 multiples of median [MoM] in one twin and <0.8 MoM in the other twin), which sometimes coexists with TTTS.

Serum YKL-40 (Chondrex/Chitinase 3-Like Protein 1)

YKL-40, a 38-kDA macrophage-derived glycoprotein, is a member of the "mammalian chitinase-like proteins". It is expressed and secreted by several types of solid tumors; however, the exact function of YKL-40 in cancer is unclear. YKL-40 exhibits growth factor activity for cells involved in tissue re-modeling processes; it may have a role in cancer cell proliferation, survival, and invasiveness, angiogenesis, and re-modeling of the extracellular matrix. Retrospective studies of patients with 8 different types of primary or advanced solid tumors suggested that serum concentration of YKL-40 may be a new biomarker in cancer patients. YKL-40 is neither organ- nor tumor-specific. Moreover, the pattern of its expression in certain tissues (e.g., human liver or cartilage) suggested that YKL-40 may also serve as an inflammatory marker involved in inflammatory states and vascular processes (Johansen et al, 2006).

In a prospective, case-control study, Madazli et al (2008) compared macrophage activation in normal and pre-eclamptic pregnancies by determining YKL-40 concentration and chitotriosidase activity in maternal and cord serum. Samples of maternal peripheral blood and umbilical venous blood were collected from 28 pre-eclamptic and 24 normotensive pregnant women and their newborns. YKL-40 concentration and chitotriosidase activity were determined by enzyme-linked immunoassay and fluorometry, respectively. Chitotriosidase activity in maternal and cord serum and YKL-40 concentration in cord serum were significantly higher in pre-eclamptic pregnancies ($p < 0.001$), but there was no significant difference in maternal serum levels of YKL-40 between the case and control groups ($p > 0.05$). There was a significant positive correlation between diastolic blood pressure and

1. chitotriosidase activity in both maternal and cord serum and
2. cord serum concentration of YKL-40 ($r = 0.61$, $r = 0.84$, and $r = 0.58$, respectively).

The authors concluded that this study may be the first to demonstrate maternal and fetal macrophage activation in pre-eclampsia.

In a prospective, cohort study, Gybel-Brask et al (2014) examined if serum YKL-40 is increased in women developing pre-eclampsia or small-for-gestational age fetuses. These researchers also assessed the association between uterine artery pulsatility index, notching and serum YKL-40 levels. A total of 1,214 unselected pregnant women enrolled at nuchal translucency examination between 11(+3) and 13(+6) weeks of gestation were included in this study. All women had ultrasound and blood sample collection at the nuchal translucency scan, a 20-week malformation scan and 25-week and 32-week fetal growth examinations. Uterine artery Doppler was assessed and outcome was registered from medical records. Main outcome measures were pre-eclampsia, hypertension, and small-for-gestational age. Serum YKL-40 was associated with increasing maternal age ($p < 0.0001$), body mass index (BMI; $p = 0.0002$), primiparity ($p = 0.0003$), and hypertension ($p = 0.015$). Serum YKL-40 increased from 12 to 20 weeks and decreased from 20 to 25 and 25 to 32 weeks of gestation. No association was found between pre-eclampsia and serum YKL-40. Small-for-gestational-age at birth was significantly associated with a 5.4 % increase in serum YKL-40 at 32 weeks of gestation (95 % CI: 1.5 to 9.3, $p = 0.005$). An association was found between uterine artery pulsatility index at 32 weeks and small-for-gestational age ($p = 0.0015$); but not between YKL-40 and uterine artery notching ($p = 0.83$). The authors concluded that serum YKL-40 was not associated with pre-eclampsia. Increasing serum YKL-40 was related to maternal age, BMI and small-for-gestational age and may reflect an exaggerated inflammatory response.

Kucur et al (2014) examined if alterations in the serum levels of apelin and YKL-40 differ between early and late onset pre-eclampsia and whether there is a correlation between apelin and YKL-40 in women who subsequently develop early and late pre-eclampsia. A total number of 80 pregnant women, 40 with normal pregnancy and 40 with pre-eclampsia, were included in the present study. Both the normal pregnant and pre-eclamptic subjects were subdivided into 2 groups. Serum YKL-40 and apelin concentrations were measured. Mean maternal serum YKL-40 levels were lower in women who subsequently developed early (87.45 ± 3.07 versus 103.40 ± 4.29) or late (96.43 ± 4.06 versus 99.87 ± 3.63) pre-eclampsia than those who remained normotensive. The difference was significant in early-onset pre-eclamptic women ($p < 0.05$) rather than late-onset pre-eclamptic ones ($p > 0.05$). Mean maternal serum apelin levels were both higher in women who subsequently developed early (8.6 ± 3.6 versus 5.7 ± 1.2) or late (9.6 ± 2.5 versus 8.1 ± 1.8) pre-eclampsia than those who remained normotensive. The difference was significant in early-onset pre-eclamptic women ($p < 0.05$) rather than late-onset pre-eclamptic ones ($p > 0.05$). There was a significant negative correlation between serum apelin and YKL-40 levels ($r = -0.48$, $p = 0.001$). The authors concluded that circulating levels of apelin were significantly increased in early-onset pre-eclampsia, indicating the role of apelin in the discrimination of the early-onset of pre-eclampsia. On the other hand, maternal serum YKL-40 levels were not elevated significantly, indicating that adipose-derived apelin was primarily involved in the vascular pathogenesis of early-onset pre-eclampsia than macrophage-derived YKL-40.

Furthermore, UpToDate reviews on "Preeclampsia: Clinical features and diagnosis" (August and Sibai, 2015), "Prediction of preeclampsia" (Norwitz), and "Fetal growth restriction: Evaluation and management " (Resnik, 2015) do not mention the use of YKL-40 as a biomarker.

Ophthalmic Artery Doppler for Prediction of Pre-Eclampsia

Matias and associates (2014) tested the hypothesis that ophthalmic artery Doppler velocimetry is predictive of the development of PE. This was a prospective cohort study that included pregnant women in the second trimester who had risk factors for PE. A total of 7 ophthalmic artery Doppler parameters, in addition to uterine artery (UtA) Doppler and clinical variables, were examined for their prognostic value with respect to PE. A total of 347 women were recruited, of whom 40 developed PE. A comparison of the mean ophthalmic artery Doppler parameter values between women with and those without PE showed statistically significant differences in several parameters: peak systolic velocity, end-diastolic velocity, mean velocity, peak meso-diastolic velocity (PMDV) and peak ratio. After adjusting for confounding variables, only PMDV remained statistically significant ($p < 0.001$), with an area under the receiver-operating characteristics curve (AUC) of 0.73. The best cut-off for predicting PE was a PMDV of greater than 22.11 cm/s, with sensitivity of 70 %, specificity of 75 %, positive likelihood ratio of 2.8, negative likelihood ratio of 0.4, positive predictive value (PPV) of 28 % and negative predictive value (NPV) of 95 %. The AUC increased from 0.72 to 0.78 when the PMDV was incorporated into a prediction model based on clinical variables, demonstrating that this marker increased the discriminatory capability of the model. The performance of ophthalmic artery Doppler was similar to that of UtA Doppler for predicting PE. Additionally, the AUC increased significantly from 0.82 to 0.88 when the PMDV was incorporated into the model

containing clinical variables and UtA Doppler indices. The authors concluded that a high ophthalmic artery PMDV in the second trimester of pregnancy was an independent predictor of PE that increased the discriminatory ability of clinical markers, as well as of models that included clinical variables and UtA Doppler indices.

The authors stated that the main drawback of this study was that it studied a sample of pregnant women with risk factors for PE, thus, the results could not be extrapolated to the general screening of pregnant women. They stated that further studies should be performed to confirm these findings and to verify the discriminatory capability of ophthalmic artery Doppler relative to the occurrence of PE in the general population. Accordingly, another cohort would be needed to validate the new model. These researchers stated that an understanding of the mechanism behind the increase in PMDV might be the key to using this parameter as a prognostic marker for pregnancy and post-partum recovery or as a screening test for the early detection of PE.

In a prospective, observational, cohort study, Gurgel and co-workers (2018) determined the performance of a multi-parametric test comprising maternal risk factors, uterine artery Doppler and ophthalmic artery Doppler in the first trimester of pregnancy for the prediction of PE. This trial recruited patients in the first trimester of pregnancy. Maternal uterine artery and ophthalmic artery Doppler assessments were performed in 440 singleton pregnancies at 11 to 14 weeks of gestation. Additional history was obtained through participant questionnaires, and follow-up occurred to discharge post-delivery. The normotensive and pre-eclamptic groups were compared using parametric (Student's t-test) and non-parametric (Mann-Whitney U-test) tests. Uni-variable and multi-variable logistic regression analyses were performed to determine which biophysical factors, and which of the factors among the maternal characteristics and medical and obstetric history, had a significant contribution to the prediction of PE in a multi-parametric model. A total of 31 (7 %) patients developed PE, including 9 (2 %) who needed delivery before 34 weeks (early PE) and 22 (5 %) with late PE. There were statistically significant differences in uterine artery pulsatility index (UtA-PI) and ophthalmic artery first diastolic peak (PD1) mean values between the PE and control groups. In a multi-parametric model, both UtA-PI and PD1 achieved a 67 % detection rate for early PE, although when combined, the detection rate only increased to 68 %. The authors concluded that the efficiency of ophthalmic artery PD1 in the first trimester as a predictive marker for the later development of PE was approximately equal to that described for uterine artery Doppler. They stated that although these findings did not support the replacement of uterine artery Doppler analysis in multi-parametric predictive models for PE, they provided novel insights into first-trimester maternal systemic vascular changes that preceded the clinical development of this condition.

The authors concluded that the main drawback of this study was its sample size, which yielded only 9 cases of early-onset PE. Furthermore, ophthalmic artery Doppler indices were not adjusted for maternal factors such as alcohol consumption (although the rates of such factors were similar between cases and controls), and raw values rather than multiples of the median (MoM) were used in statistical analyses.

In a systematic review and meta-analysis, Kalafat and colleagues (2018) determined the accuracy of ophthalmic artery Doppler in pregnancy for the prediction of PE. Medline, Embase, CINAHL and the Cochrane Library were searched for relevant citations without language restrictions. Two reviewers independently selected studies that evaluated the accuracy of ophthalmic artery Doppler to predict the development of PE and extracted data to construct 2 × 2 tables. Individual patient data were obtained from the authors if available. A bi-variate random-effects model was used for the quantitative synthesis of data. Logistic regression analysis was employed to generate ROC curves and obtain optimal cut-offs for each investigated parameter, and a bi-variate analysis was employed using pre-determined cut-offs to obtain sensitivity and specificity values and generate summary ROC curves. A total of 87 citations matched the search criteria of which 3 studies, involving 1,119 pregnancies, were included in the analysis. All included studies had clear description of the index and reference tests, avoidance of verification bias and adequate follow-up. Individual patient data were obtained for all 3 included studies. First diastolic peak velocity of ophthalmic artery Doppler at a cut-off of 23.3 cm/s showed modest sensitivity (61.0 %; 95 % CI: 44.2 to 76.1%) and specificity (73.2 %; 95 % CI: 66.9 to 78.7 %) for the prediction of early-onset PE (AUC, 0.68; 95 % CI: 0.61 to 0.76). The first diastolic peak velocity had a much lower sensitivity (39.0 %; 95 % CI: 20.6 to 61.0 %), a similar specificity (73.2 %; 95 % CI: 66.9 to 78.7 %) and a lower AUC (0.58; 95 % CI: 0.52 to 0.65) for the prediction of late-onset PE. The pulsatility index of the ophthalmic artery did not show a clinically useful sensitivity or specificity at any cut-off for early- or late-onset PE. Peak ratio above 0.65 showed a similar diagnostic accuracy to that of the first diastolic peak velocity with an AUC of 0.67 (95 % CI: 0.58 to 0.77) for early-onset PE and 0.57 (95 % CI: 0.51 to 0.63) for late-onset disease. The authors concluded that ophthalmic artery Doppler is a simple, accurate and objective technique with a standalone predictive value for the development of early-onset PE equivalent to that of uterine artery Doppler evaluation. The relationship between ophthalmic Doppler indices and PE could not be a consequence of trophoblast invasion and may be related to maternal hemodynamic adaptation to pregnancy. They stated that the findings of this review justify efforts to elucidate the effectiveness and underlying mechanism whereby 2 seemingly unrelated maternal vessels can be used for the prediction of a disease considered a "placental disorder".

Furthermore, an UpToDate review on "Early pregnancy prediction of preeclampsia" (Norwitz, 2018) does not mention the use of ophthalmic artery Doppler as a management option.

In a prospective, observational study, Sarno and associates (2021) examined the potential value of maternal ophthalmic artery Doppler at 35 to 37 weeks' gestation in combination with the established biomarkers of PE, including MAP) UtA-PI, serum PlGF and sFlt-1, in the prediction of subsequent development of PE. This trial included women attending for a routine hospital visit at 35+0 to 36+6 weeks' gestation. This visit included recording of maternal demographic characteristics and medical history, ultrasound (US) examination for fetal anatomy and growth, assessment of flow velocity waveforms from the maternal ophthalmic arteries, and measurement of MAP, UtA-PI, serum PlGF and serum sFlt-1. The competing risks model was used to estimate the

individual patient-specific risks of delivery with PE at any time and at less than 3 weeks from assessment by a combination of maternal demographic characteristics and medical history with biomarkers. The AUC and DR of delivery with PE, at 10 % FPR, after screening by maternal factors, ophthalmic artery second to first PSV ratio and combinations with MAP, UtA-PI, serum PlGF and serum sFlt-1 were determined. The modelled performance of screening for PE was also estimated. The study population of 2,287 pregnancies contained 60 (2.6 %) that developed PE, including 19 (0.8 %) that delivered with PE at less than 3 weeks from assessment. The PSV ratio improved the prediction of PE with delivery at any stage after assessment provided by maternal factors alone (from 25.4 % to 50.6 %), maternal factors plus MAP (54.3 % to 62.7 %), maternal factors, MAP, plus PlGF (68.3 % to 70.8 %) and maternal factors, MAP, PlGF plus sFlt-1 (75.7 % to 76.7 %), at FPR of 10 %. The PSV ratio also improved the prediction of PE with delivery at less than 3 weeks from assessment provided by maternal factors alone (from 31.0 % to 69.4%), maternal factors plus MAP (74.1 % to 83.4 %), maternal factors, MAP plus UtA-PI (77.1 % to 85.0 %) and maternal factors, MAP plus PlGF (88.6 % to 90.7 %). The empirical results on DR at 10 % FPR were consistent with the modelled results. Screening by a combination of maternal factors with MAP and second to first PSV ratio also detected 60.9 % (56.8 % to 81.2 %) of GH with delivery at any stage after assessment, and 80.0 % (95 % CI: 66.9 % to 98.7 %) of GH with delivery at less than 3 weeks from assessment. The authors concluded that ophthalmic artery Doppler could potentially improve the performance of screening for PE at 35 to 37 weeks, especially imminent PE with delivery within 3 weeks of assessment; however, further studies are needed to validate these findings.

In a prospective, observational study, Sapantzoglou and colleagues (2021) examined the potential value of maternal ophthalmic artery Doppler at 19 to 23 weeks' gestation on its own and in combination with the established biomarkers of PE, including UtA-PI, MAP, serum PlGF and serum sFlt-1, in the prediction of subsequent development of PE. This trial included women attending for a routine hospital visit at 19+1 to 23+3 weeks' gestation. This visit included recording of maternal demographic characteristics and medical history, US examination for fetal anatomy and growth, assessment of flow velocity waveforms from the maternal ophthalmic arteries, and measurement of MAP, UtA-PI, serum PlGF and serum sFlt-1. Waveforms were obtained in sequence from the right eye, left eye, and again right and then left eye. These researchers recorded the average of the 4 measurements, 2 from the right and 2 from the left eye, for the following 4 indices: first PSV, second PSV, PI, and ratio of second to first PSV. The measurements of the 4 indices were standardized to remove the effects of maternal characteristics and elements from the medical history. The competing risks model was used to estimate the individual patient-specific risks of delivery with PE at less than 37 and greater than or equal to 37 weeks' gestation and determine the AUC and DR, at 10 % FPR, in screening by a combination of maternal demographic characteristics and medical history with biomarkers. The modelled performance of screening for PE was also estimated. The study population of 2,853 pregnancies contained 76 (2.7 %) that developed PE, including 18 (0.6 %) that delivered with PE at less than 37 weeks' gestation. The ophthalmic artery second to first PSV ratio was significantly increased in PE pregnancies and the PE effect depended on gestational age at delivery; the deviation from normal was greater for early than late PE. The second PSV was also increased in PE pregnancies; however, the effect did not depend on gestational age at delivery. The other 2 ophthalmic artery indices of first PSV and PI were not significantly affected by PE. The PSV ratio improved the prediction of preterm PE provided by maternal factors alone (from 56.1 % to 80.2 %), maternal factors, MAP plus UtA-PI (80.7 % to 87.9%), maternal factors, MAP, UtA-PI plus PlGF (85.5 % to 90.3 %) and maternal factors, MAP, UtA-PI, PlGF plus sFlt-1 (84.9 % to 89.8 %), at FPR of 10 %. The PSV ratio also improved the prediction of term PE provided by maternal factors alone (from 33.8 % to 46.0 %), maternal factors, MAP plus UtA-PI (46.6 % to 54.2 %), maternal factors, MAP, UtA-PI plus PlGF (45.2 % to 53.4 %) and maternal factors, MAP, UtA-PI, PlGF plus sFlt-1 (from 43.0 % to 51.2 %), at FPR of 10 %. The empirical results on DR at 10 % FPR were consistent with the modelled results. The second PSV did not improve the prediction of either preterm or term PE provided by maternal factors alone. The authors concluded that ophthalmic artery PSV ratio at 19 to 23 weeks' gestation, both on its own and in combination with other biomarkers is potentially useful for prediction of subsequent development of PE, especially preterm PE; however, larger studies are needed to validate these findings.

Maternal Serum Ischemia-Modified Albumin as a Biomarker for Preeclampsia

Ozdemir and associates (2018) stated that pre-eclampsia (PE) carries an increased risk for maternal and/or fetal mortality or serious morbidity; and PE is associated with ischemia and increased oxidative stress in the placenta, which may lead to modification of plasma albumin to ischemia-modified albumin (IMA). These investigators examined IMA and hematological parameters in mothers and in premature infants in normal and in pre-eclamptic pregnancies. A total of 25 pregnant women with PE and their premature newborns were categorized as the PE group, and 25 normotensive pregnant women and their premature newborns as the control group. Preterm infants are classified as SGA or non-SGA according to the Fenton preterm growth chart. Serum IMA, complete blood count (CBC), liver function tests (LFT), renal function tests (RFT), albumin, and C-reactive protein (CRP) were measured in the mothers immediately before birth, and in the cord blood and serum of the newborns at 6 and 24 hours after birth. Clinical and demographic data were recorded for both groups. While IMA, LFT and RFT were significantly increased in the PE group compared with the control group, albumin and CBC were significantly lower in the PE group. A total of 40 % of PE newborns were SGA, 30 % of whom had severe SGA (birth-weight of less than third percentile). Cord IMA was significantly increased in all preterm neonates in the PE group compared with the control group. No mothers or neonates died. The authors concluded that serum IMA in addition to the prevalence of SGA were significantly increased in the PE group; thus, cord blood IMA might be a predictive biomarker for SGA in PE pregnancies.

Seshadri and colleagues (2019) noted that IMA has been widely accepted as a serological biomarker; and it has been proposed as a simple and novel marker of oxidative stress in PE. In a systematic review and diagnostic test accuracy meta-analysis, these researchers examined the diagnostic accuracy of this novel serological biomarker, IMA to detect PE. They carried out a

systematic search of major databases to identify all published diagnostic accuracy studies on IMA. Risk of bias and applicability concerns were assessed for included studies. Summary estimates; the pooled sensitivity, specificity, and the diagnostic odds ratio (DOR) of IMA for the diagnosis of PE were computed using random-effects models. The overall test performance was summarized using summary receiver operating characteristic (SROC) curve analysis. A total of 6 articles were included in this meta-analysis. The overall estimates of IMA in detecting PE were pooled sensitivity; 0.80 (95 % CI: 0.73 to 0.86), pooled specificity; 0.76 (95 % CI: 0.70 to 0.81), DOR; 14.32 (95 % CI: 5.06 to 40.57), and area under curve (AUC); 0.860. There was no between-study heterogeneity due to threshold effect. The authors concluded that the findings of this meta-analysis showed that IMA could be useful as a biomarker for PE with good accuracy (AUC = 0.860). However, these investigators stated that further research is needed for re-evaluation and clinical validation of these promising findings of this meta-analysis.

Preeclampsia Screen|T1

Preeclampsia Screen|T1 is a screening test to measure 3 biochemical markers in the mother's serum associated with PE: alpha-fetoprotein (AFP), pregnancy associated plasma protein-A (PAPPA), and placental growth factor (PIGF). Together, these 3 biochemical markers are intended to contribute to accurate prediction of risk for early onset preeclampsia.

Duan and colleagues (2017) noted that identifying women at risk of PE by maternal serum screening is conducive to prompt gestational management and thereby improve both maternal and perinatal outcomes. These researchers examined the association between the concentrations of maternal serum PLGF, PAPPA, free beta-hCG, and AFP and the development of PE early in the second trimester. A total of 40 pregnant women subsequently developed mild PE, 21 pregnant women subsequently developed severe PE, and 61 cases of normotensive controls were included. Maternal serum concentrations of PLGF, PAPPA, β-hCG, and AFP were measured at 15 to 20 weeks of gestation. Serum PLGF level was lower in women who subsequently developed PE than in normotensive controls. However, the significant difference was only found between the severe PE and control groups (p = 0.015). Serum PAPPA, β-hCG, and AFP levels were not significantly different between the PE and control groups. The authors concluded that serum PLGF level was lower in women who subsequently developed severe PE early in the second trimester, suggesting its role in prediction of PE.

In a prospective, first-trimester study, Allen and Aquilina (2018) examined the efficacy of biomarkers, arteriography and uterine artery Dopplers for predicting hypertensive disease of pregnancy, SGA and stillbirth. Ultrasound was used to assess uterine artery Doppler. Maternal arteriography was performed and serum was taken for the measurement of AFP, beta-hCG, PlGF, and PAPP-A levels. Logistic regression with step-wise selection was carried out to determine multi-variate models. A total of 145 women were left for analysis after exclusions; 14 developed PE, 23 pregnancy-induced hypertension (PIH), 64 SGA of less than fifth centile, 118 SGA of less than 10th centile and 3 stillbirth. Systolic blood pressure (SBP) in the aorta (SBPAO) (p = 0.002) was significantly associated with PE. Detection rate (DR) was 72 % for a false-positive rate (FPR) of 15 %, an area under the curve (AUC) of 0.81 (95 % CI: 0.69 to 0.93). Mean arterial pressure (MAP) and maternal weight (p =0 .001) were significantly associated with PIH (DR 48 %, AUC 0.76, 95 % CI: 0.65 to 0.86). Low PAPP-A and PlGF were significantly associated with SGA of less than 10th centile (p = 0.007 and 0.004, respectively; DR 30 %, AUC 0.60 8, 95 % CI: 0.54 to 0.68). SGA of less than fifth centile was significantly associated with low PlGF (p < 0.001; DR 57 %, AUC 0.73, 95 % CI: 0.65 to 0.80). The authors concluded that no association was found between first-trimester biomarkers and PE / PIH. There was a significant association between low PlGF and PAPP-A and SGA.

Furthermore, an UpToDate review on "Early pregnancy prediction of preeclampsia" (Norwitz and Bellussi, 2019) states that "Data from both human and animal models suggest that aberrant expression of angiogenic modulators is important in the pathogenesis of diffuse endothelial injury and increased capillary permeability, which are the pathophysiologic hallmarks of preeclampsia. The angiogenic factors of interest include vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), as well as two anti-angiogenic proteins, soluble endoglin (sEng) and the truncated form of the full-length VEGF receptor type-1 (Flt-1), known as soluble fms-like tyrosine kinase 1 (sFlt-1) … However, blood and urine levels of these factors have not been proven to be clinically useful for prediction of preeclampsia remote from disease onset … Maternal serum analyte testing is an important component of Down syndrome screening programs. Increasing evidence suggests that unexplained abnormal maternal serum analyte concentrations (e.g., pregnancy-associated plasma protein A), as well as abnormalities in cell-free DNA levels, in the first and second trimesters are also predictive of adverse pregnancy outcomes, including preeclampsia. This association is not sufficiently strong to warrant changes in routine prenatal care, but the biomarkers have been used in risk prediction models". Moreover, this review does not mention AFP.

PlGF Preeclampsia Screen

Youssef et al (2011) examined the performance of screening for late PE by maternal characteristics, uterine artery (UtA) Doppler and a set of biochemical markers in prospectively enrolled women at 11 + 0 to 13 + 6 weeks. Maternal characteristics, highest UtA pulsatility index and serum placental biomarkers including PAPP-A, PlGF, soluble fms-like tyrosine kinase 1 (sFlt-1), P-selectin and neutrophil gelatinase-associated lipocalin were recorded. The rate of PE was 2.5 % (13/528); 4 (0.8 %) had severe PE. A combined screening model that included PlGF, sFlt-1 and neutrophil gelatinase-associated lipocalin could detect 77 % of PE at a 10 % false-positive rate. Mean risk for mild PE was 8.8 % ± 6.4, mean risk for severe PE was 38.6 % ± 4.3. Mean risk for controls was 2 % ± 4.1. The authors concluded that this combination of maternal biochemical variables in the 1st trimester could detect a consistent number of late PE. Moreover, these researchers stated that further studies on a new and independent series of data could confirm the presented results.

Park et al (2014) attempted to establish a cut-off value for the sFlt-1/PlGF ratio measured using the Elecsys assay to predict late-onset PE in low-risk pregnancies. The secondary objective was to examine the ability of combination models using Elecsys data, 2nd trimester UtA Doppler US measurements, and the serum fetoplacental protein levels used for Down's syndrome screening, to predict PE. This prospective cohort study included 262 pregnant women with a low risk of PE. Plasma levels of PAPP-A and serum levels of alpha-fetoprotein, unconjugated estriol, human chorionic gonadotropin, and inhibin-A were measured, and sFlt-1/PlGF ratios were calculated. All women underwent UtA Doppler US at 20 to 24 weeks of gestation; 8 of the 262 women (3.0 %) developed late-onset PE. Receiver operating characteristic curve analysis showed that the 3rd trimester sFlt-1/PlGF ratio yielded the best detection rate (DR) for PE at a fixed false-positive rate (FPR) of 10 %, followed by the 2nd trimester sFlt-1/PlGF ratio, sFlt-1 level, and PlGF level. Binary logistic regression analysis was used to determine the 5 best combination models for early detection of late-onset PE. The combination of the PAPP-A level and the 2nd trimester sFlt-1/PlGF ratio yielded a DR of 87.5 % at a fixed FPR of 5 %, the combination of 2nd and 3rd trimester sFlt-1/PlGF ratios yielded a DR of 87.5 % at a fixed FPR of 10 %, the combination of BMI and the 2nd trimester sFlt-1 level yielded a DR of 87.5 % at a fixed FPR of 10 %, the combination of the PAPP-A and inhibin-A levels yielded a DR of 50 % at a fixed FPR of 10 %, and the combination of the PAPP-A level and the 3rd trimester sFlt-1/PlGF ratio yielded a DR of 62.5 % at a fixed FPR of 10 %. The authors concluded that the combination of the PAPP-A level and the 2nd trimester sFlt-1/PlGF ratio, and the combination of the 2nd trimester sFlt-1 level with BMI, were better predictors of late-onset PE than any individual marker. Moreover, these researchers stated that further studies are needed to evaluate the usefulness of the combined screening test in low-risk populations.

The authors stated that a drawback of this study was the different risk estimation results obtained when different combinations of markers were used in the same subject. This was probably due to the low number of patients with PE, and the fact that PE results from various pathophysiologic mechanisms that may alter the markers in different ways. However, 3 of the 8 cases were detected by all the models used, and all the cases were detected by at least 2 of the models. A larger number of patients may have resulted in different accuracy rates for the combinations evaluated in this study; however, there was a steep increase in the sFlt-1/PlGF ratio in patients with PE, which was consistent with previously reported results, and these investigators expected that the main conclusions would not change with a larger study population. Although the slope of the sFlt-1/PlGF ratio was not used in their algorithms, this value may be useful for enhancing predictive accuracy in a future larger scale study.

von See et al (2016) noted that the angiogenic factors sFlt-1 and PlGF are significantly altered in PE with elevated sFlt-1 levels and low PlGF in the continuation of pregnancies. Furthermore, patients with PE showed significantly low PlGF levels in the 1st trimester. These researchers carried out a retrospective study including 161 patients during the 1st trimester screening between 11+0 and 13+6 weeks of gestation. Furthermore, they analyzed sFlt-1 und PlGF in maternal serum with a Roche Elecsys System. The mean values for sFlt-1 were 1 247,11 ± 545,84 pg/ml and 47,00 ± 22,62 pg/ml for PlGF. There was a positive correlation between sFlt-1 and PAPP-A MoM ($rS = 0.681$, $p < 0.001$), and PlGF and PAPP-A MoM ($rS = 0.465$, $p < 0.001$), respectively. There was a negative correlation between sFlt-1 and maternal BMI ($rS = -0.225$, $p = 0.005$). Over-weight patients had significantly lower sFlt-1 values than patients with normal weight ($p = 0.003$). PlGF and the crown-rump-length of the fetus showed a positive correlation ($rS = 0.27$, $p < 0.001$), whereas PlGF and the Pulsatility Index of the UtA were negatively correlated ($rS = -0.235$; $p = 0.012$). Patients with a pre-existent diabetes mellitus had significantly low sFlt-1 and PlGF ($p < 0.05$) values. Smokers had significantly elevated PlGF-values ($p < 0.001$). The authors concluded that sFlt-1 and PlGF were influenced by various factors during the 1st trimester of pregnancy, which can be relevant for correct interpretation. These researchers stated that further prospective studies are needed to validate these findings. The objective should be to establish sFlt-1 and PlGF MoM values to allow for integration into a screening for PE in the 1st trimester.

Mayer-Pickel et al (2018) stated that an imbalance of angiogenic placental factors such as endoglin, sFlt-1 and PlGF has been implicated in the pathophysiology of PE. These investigators examined serum levels of sFlt-1, PlGF and endoglin in women with primary and secondary anti-phospholipid Syndrome (APS) and systemic lupus erythematosus (SLE) longitudinally through pregnancy. Serum levels of sFlt-1, PlGF and endoglin were measured prospectively at 4-week intervals (from gestational weeks 12 to 36) in 17 women with primary APS (PAPS), 18 women with secondary APS (SAPS), and 23 women with SLE. A total of 6/17 (35 %) of women with PAPS, 3/18 (17 %) of women with SAPS, and 2/23 (9 %) of women with SLE developed early-onset PE. Women who developed PE had significantly higher mean sFlt-1 and endoglin levels, higher sFlt-1/PlGF ratios, and lower mean PlGF levels than women who did not. These changes became statistically significant at 12 weeks for sFlt-1, PlGF and endoglin. The authors concluded that endoglin, sFlt-1 and PlGF are potential early screening parameters for the development of PE in pregnant women with autoimmune diseases like APS and SLE.

Townsend et al (2019) noted that primary studies and systematic reviews provided estimates of varying accuracy for different factors in the prediction of PE. These investigators reviewed published systematic reviews to collate evidence on the ability of available tests to predict PE, to identify high-value avenues for future research and to minimize future research waste in this field. Medline, Embase and the Cochrane Library including DARE (Database of Abstracts of Reviews of Effects) databases, from database inception to March 2017, and bibliographies of relevant articles were searched, without language restrictions, for systematic reviews and meta-analyses on the prediction of PE. The quality of the included reviews was examined using the AMSTAR tool and a modified version of the QUIPS tool. These researchers examined the comprehensiveness of search, sample size, tests and outcomes evaluated, data synthesis methods, predictive ability estimates, risk of bias related to the population studied, measurement of predictors and outcomes, study attrition and adjustment for confounding. From a total of 2,444 citations identified, 126 reviews were included, reporting on over 90 predictors and 52 prediction models for PE. Approximately 1/3 (n = 37 (29.4 %)) of all reviews examined solely biochemical markers for predicting PE, 31 (24.6 %) examined genetic associations with PE, 46 (36.5 %) reported on clinical characteristics, 4 (3.2 %) examined only US markers,

and 6 (4.8 %) evaluated a combination of tests; 2 (1.6 %) additional reviews examined primary studies investigating any screening test for PE. Reviews included between 2 and 265 primary studies, including up to 25,356,688 women in the largest review. Only approximately half (n = 67 (53.2 %)) of the reviews evaluated the quality of the included studies. There was a high risk of bias in many of the included reviews, especially in relation to population representativeness and study attrition. Over 80 % (n = 106 (84.1 %)) summarized the findings using meta-analysis; 32 (25.4 %) studies lacked a formal statement on funding. The predictors with the best test performance were BMI greater than 35 kg/m2 , with a specificity of 92 % (95 % CI: 89 to 95 %) and a sensitivity of 21 % (95 % CI: 12 to 31 %); BMI greater than 25 kg/m2 , with a specificity of 73 % (95 % CI: 64 to 83 %) and a sensitivity of 47 % (95 % CI: 33 to 61 %); 1st-trimester UtA pulsatility index or resistance index of greater than 90th centile (specificity 93 % (95 % CI: 90 to 96 %) and sensitivity 26 % (95 % CI: 23 to 31 %)); PlGF (specificity 89 % (95 % CI: 89 to 89 %) and sensitivity 65 % (95 % CI: 63 to 67 %)); and placental protein 13 (specificity 88 % (95 % CI: 87 to 89 %) and sensitivity 37 % (95 % CI: 33 to 41 %)). No single marker had a test performance suitable for routine clinical use. Models combining markers showed promise, but none had undergone external validation. The authors concluded that this review of reviews called into question the need for further aggregate meta-analysis in this area given the large number of published reviews subject to the common limitations of primary predictive studies. These researchers stated that prospective, well-designed studies of predictive markers, preferably randomized intervention studies, and combined through individual-patient data meta-analysis are needed to develop and validate new prediction models to facilitate the prediction of PE and minimize further research waste in this field.

Perry et al (2020) examined the prognostic value of angiogenic markers and maternal risk factors in pregnant women with hypertension. This was a prospective study of pregnancies complicated by PE, gestational hypertension, or chronic hypertension presenting to 1 of 2 tertiary referral hospitals between May 2013 and May 2018. Maternal characteristics along with blood samples for angiogenic marker analysis were obtained from participants. The primary outcome was delivery related to PE within 1 and 2 weeks. A total of 302 women with hypertension were included in the study cohort. The baseline model included maternal BMI, MAP, and clinical diagnosis at the time of assessment. The use of sFlt-1/PlGF ratio combined with the baseline model significantly improved the area under the curve values for predicting delivery within a week (0.83 versus 0.88; p = 0.025) or in 2 weeks (0.86 versus 0.93; p = 0.001) due to PE-related events in gestational ages of less than 35 weeks. The magnitude of increase in accuracy was 7.9 % (-0.5 % to 16.4 %, posterior probability of increase: 96.7 %) for sFlt-1/PlGF ratio. The authors concluded that these findings emphasized the additive value of angiogenic biomarkers and the superior performance of a continuous scale of sFlt-1/PlGF ratio in the model. The added utility of angiogenic markers diminished after 35 weeks' gestation.

The authors stated that this study had several drawbacks. First, these researchers were yet to validate their findings in an external cohort; thus, they could not be certain that their model would perform as well in other populations. Second, these investigators only had a small number of pregnancies complicated by chronic hypertension in the study cohort; thus, they could not derive strong conclusions in this subgroup. Moreover, PlGF levels were affected by smoking, ethnicity, body weight, and maternal age. These researchers did not adjust for smoking, maternal age, or ethnicity while calculating the MoM values due to small number of smokers in the reference population (smoking) and insignificant differences in maternal age or ethnicity between the cases and controls. While both sites followed a very similar protocol with regards to timing of delivery, the decision was at the discretion of the individual clinicians, and not standardized to the study. Last, the number of recruited patients was limited by the low incidence of PE and smaller number of births in 1 of the study centers, availability of the research team for recruitment and participation in other multi-center trials with overlapping inclusion criteria. These factors may have contributed to the relatively small number of patients enrolled in this study.

Furthermore, an UpToDate review on “Preeclampsia: Clinical features and diagnosis” (August and Sibai, 2021) does not recommend screening of placental growth factor (PlGF) as a management tool. "Tests for measurement of angiogenic factors are commercially available in some countries (not the United States) but are generally still considered investigational. However, in the United Kingdom, the National Institute for Health and Care Excellence suggests offering PlGF-based testing to help rule out (but not rule in) preeclampsia in women presenting with suspected preeclampsia up to 35 weeks of gestation [citing NICE, 2019]. . . . The clinical utility of these tests remains unclear. Although some prospective studies and trials demonstrated that angiogenic markers have a high negative predictive value and thus can be useful in ruling out preeclampsia and reducing the time to diagnosis, the value of early accurate diagnosis alone without a concomitant improvement in maternal and/or neonatal outcome is questionable. In a meta-analysis of studies examining the performance of sFlT-1, PlGF, or the sFlT-1/PlGF ratio in predicting adverse outcomes in patients with suspected or confirmed preeclampsia, both PlGF and the sFlt-1/PlGF ratio demonstrated pooled area under the summary receiver operating characteristic curve values from 0.68 to 0.87 for predicting composite adverse maternal and perinatal outcomes, preterm birth, and fetal growth restriction, but very high heterogeneity of the population sampled coupled with differences in study methodology, study quality, and the outcomes measured limited conclusions regarding the prognostic value of these biomarkers in clinical practice [citing Lim, et al., 2021]".

Measurement of Preeclampsia sFlt-1/PlGF Ratio (PERA)

Karge et al (2021) noted that an elevated sFlt-1/PlGF ratio is associated with adverse perinatal outcome (APO) and the mean time until delivery (MTUD) in singleton pregnancies complicated by PE. Data on APO and MTUD prediction in twin pregnancies using sFlt-1/PlGF ratio are scarce. In a retrospective, single-center study, these researchers examined the predictive value of the sFlt-1/PlGF ratio regarding APO and MTUD in twin pregnancies with suspected PE and/or HELLP syndrome. All twin pregnancies with suspected PE/HELLP and determined sFlt-1/PlGF were included. Composite APO (CAPO) was defined as the presence of at least 1 of the following outcomes: respiratory distress syndrome (RDS), intubation, admission to neonatal

intensive care unit (NICU), and arterial umbilical cord pH value of less than 7.10. Selective fetal growth restriction (s-FGR) was analyzed separately. For final analysis, 49 twin pregnancies were included. Median sFlt-1/PlGF ratio was not significantly different in patients with CAPO compared to those without (89.45 versus 62.00, p = 0.669). MTUD was significantly negative correlated with sFlt-1/PlGF ratio (r = -0.409, p < 0.001). For the whole study cohort, ROC analysis revealed no predictive value for sFlt-1/PlGF and CAPO (AUC = 0.618, 95 % CI: 0.387 to 0.849, p = 0.254). However, sFlt-1/PlGF ratio showed a predictive value for s-FGR (AUC = 0.755, 95 % CI: 0.545 to 0.965, p = 0.032). The authors concluded that in twin pregnancies with PE and/or HELLP, sFlt-1/PlGF ratio may be helpful for s-FGR prediction and decision-making regarding close monitoring of high-risk patients.

Binder et al (2022) noted that although the most recent guidance from the International Society for the Study of Hypertension in Pregnancy (ISSHP) has highlighted the role of angiogenic marker assessment in the diagnosis of PE in women with chronic hypertension, the ISSHP has withheld recommending its implementation due to the limited available evidence in this group of women. In a retrospective study, these investigators examined the value of sFlt-1 and PlGF assessment in women with chronic hypertension and suspected superimposed PE. This analysis entailed prospectively collected data recorded in an electronic database between January 2013 and October 2019. Women with chronic hypertension and singleton pregnancy who had suspected superimposed PE were included. Superimposed PE was suspected in women presenting with worsening hypertension, epigastric pain, new-onset edema, dyspnea, or neurological symptoms. The exclusion criteria were delivery within 1 week after assessment for reasons other than PE, chronic kidney disease, history of cardiac disease, fetal aneuploidy, genetic syndrome, or major structural anomaly and missing pregnancy outcome. Maternal serum angiogenic markers (sFlt-1, PlGF and sFlt-1/PlGF ratio) were measured. The primary outcome was the use of angiogenic markers in the prediction of superimposed PE. Predictive accuracy was assessed for superimposed PE diagnosed at different time-points, including within 1 week after assessment and any time before birth. The secondary outcome was comparison of adverse maternal and perinatal outcomes between women with superimposed PE diagnosed according to the traditional ISSHP criteria and those diagnosed according to extended criteria including angiogenic markers. The predictive accuracy of each angiogenic marker was assessed using ROC analysis; and AUC values were compared using De Long's test. A sensitivity analysis was planned for gestational age at assessment. The association of various variables with composite adverse maternal and perinatal outcomes was assessed using binomial regression. The study included 142 pregnant women with chronic hypertension and suspected superimposed PE, of whom 25 (17.6 %) developed PE within 1 week after assessment, 52 (36.6 %) developed PE at any time-point before birth, and 90 (63.4 %) delivered without PE. Maternal serum angiogenic imbalance was associated significantly with superimposed PE diagnosed according to the ISSHP criteria within 1 week or at any time after assessment (p < 0.001 for both). The predictive accuracy of maternal serum sFlt-1/PlGF ratio for superimposed PE diagnosed within 1 week after assessment was superior to that of maternal serum PlGF level (AUC, 0.91 versus 0.86; p = 0.032). The addition of angiogenic imbalance to the traditional ISSHP diagnostic criteria was associated with an increase in the detection rate (35.1 % increase; 95 % CI: 16.6 % to 53.6 %) and positive (9.6 % increase; 95 % CI: 0.0 % to 20.6 %) and negative (3.1 % increase; 95 % CI: 1.3 % to 4.9 %) predictive values for composite adverse maternal outcome, with high posterior probabilities of an increase in each predictive accuracy parameter (greater than 99.9 %, 95.6 % and greater than 99.9 %, respectively), without a meaningful decrease in specificity. The addition of angiogenic imbalance improved the detection rate for composite adverse perinatal outcome (20.6 % increase; 95 % CI: 0.0 % to 42.2 %), with a high posterior probability (96.9 %). There was a corresponding drop in specificity (5.7 % decrease; 95 % CI: -2.3 % to 13.6 %), with a posterior probability of 91.8 %. The authors concluded that in women with chronic hypertension and suspected superimposed PE, addition of maternal serum angiogenic markers to the traditional diagnostic criteria for superimposed PE improved significantly the sensitivity for the prediction of both maternal and perinatal adverse outcomes. Thus, these investigators stated that implementation of angiogenic marker assessment in the evaluation of pregnant women with chronic hypertension should be considered.

Stepan et al (2023) stated that PE is characterized by placental and maternal endothelial dysfunction, and associated with FGR, placental abruption, preterm delivery (PTD) and still-birth. The angiogenic factors sFlt-1 and PlGF are altered in pregnancies complicated by placenta-related disorders. In this review, these investigators examined the available evidence, assessing the performance of maternal PlGF, sFlt-1 and the sFlt-1/PlGF ratio for screening PE, predicting development of PE in the short-term, diagnosing PE, monitoring established PE, and predicting other placenta-related disorders in singleton pregnancy. In addition, they discussed the performance of PlGF and the sFlt-1/PlGF ratio for predicting PE in twin pregnancy. For 1st-trimester screening in singleton pregnancy, a more accurate way of identifying high-risk women than current practice is to combine maternal PlGF levels with clinical risk factors and US markers. Later in pregnancy, the sFlt-1/PlGF ratio has advantages over PlGF because it has a higher pooled sensitivity and specificity for diagnosing and monitoring PE. It has clinical value because it can rule out the development of PE in the 1- to 4-week period after the test. Once a diagnosis of PE is established, repeat measurement of sFlt-1 and PlGF could aid in monitoring progression of the condition and may inform clinical decision-making regarding the optimal time for delivery. The sFlt-1/PlGF ratio is useful for predicting FGR and PTD; however, the association between still-birth and the angiogenic factors is unclear. The sFlt-1/PlGF ratio can be used to predict PE in twin pregnancy, although different sFlt-1/PlGF ratio cut-offs from those for singleton pregnancy should be applied for optimal performance. The authors concluded that PlGF, sFlt-1 as well as the sFlt-1/PlGF ratio are useful for screening, diagnosing, predicting, and monitoring placenta-related disorders in singleton and twin pregnancy.

Chirila et al (2023) noted that regarding the hypertensive disorders of pregnancy, PE remains one of the leading causes of severe and life-threatening maternal and fetal complications. Screening of early-onset PE (less than 34 weeks of pregnancy), as well as late-onset PE (34 weeks or greater), showed poor performance if based solely on clinical features. In recent years, biochemical markers from maternal blood -- the pro-angiogenic protein PlGF and the anti-angiogenic protein sFlt-1, and Doppler

velocimetry indices -- primarily the mean uterine pulsatility index (PI), but also the uterine resistivity index (RI), the uterine systolic/diastolic ratio (S/D), uterine and umbilical peak systolic velocity (PSV), end-diastolic velocity (EDV), as well as uterine notching -- have all shown improved screening performance. In this review, these researchers examined the scientific literature on the role of biochemical markers and Doppler velocimetry indices in early prediction of the onset and severity of PE and other placenta-related disorders, as well as their role in monitoring established PE and facilitating improved obstetrical surveillance of patients categorized as high-risk in order to prevent adverse outcomes. A sFlt-1/PlGF ratio of 33 or less ruled out early-onset PE with 95 % sensitivity and 94 % specificity, whereas a sFlt-1/PlGF of 88 or higher predicted early-onset PE with 88.0 % sensitivity and 99.5 % specificity. Concerning the condition's late-onset form, sFlt-1/PlGF of 33 or less displayed 89.6 % sensitivity and 73.1 % specificity in ruling out the condition, whereas sFlt-1/PlGF of 110 or higher predicted the condition with 58.2 % sensitivity and 95.5 % specificity. The cut-off values of the sFlt-1/PlGF ratio for the screening of PE were established in the PROGNOSIS study: a sFlt-1/PlGF ratio of equal to or lower than 38 ruled out the onset of PE within 1 week, regardless of the pregnancy's gestational age. The NPV in this study was 99.3 %. Furthermore, sFlt-1/PlGF of higher than 38 showed 66.2 % sensitivity and 83.1 % specificity in predicting the occurrence of PE within 4 weeks. In addition, 2018 International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Practice Guidelines stated that a 2nd-trimester mean uterine artery PI of 1.44 or higher increased the risk of later PE development. The authors concluded that the implementation of a standard screening procedure based on the sFlt-1/PlGF ratio and uterine Doppler velocimetry may improve early detection of PE and other placenta-related disorders.

Palmrich et al (2024) stated that pregnancies with FGR are at increased risk for PE. Angiogenic markers including sFlt-1 and PlGF are altered in pregnancies complicated by FGR; however, their use for predicting PE in growth-restricted pregnancies is uncertain. In a retrospective study, these investigators examined the prognostic value of angiogenic markers for predicting the development of PE in pregnancies with FGR and suspected PE. This trial included singleton pregnancies with FGR, defined according to Delphi consensus criteria, which underwent sampling of sFlt-1 and PlGF for suspicion of PE at the Medical University of Vienna, Vienna, Austria, between 2013 and 2020. Women with an established diagnosis of PE at sampling were excluded. Cox regression analysis and logistic regression analysis were carried out to examine the association of angiogenic markers with the development of PE at various time-points. In this cohort of 93 women, PE was diagnosed in 14 (15.1 %) women within 1 week after sampling, 21 (22.6 %) within 2 weeks after sampling, and 38 (40.9 %) at any time after assessment. The sFlt-1/PlGF ratio consistently showed a stronger association with the development of PE compared to sFlt-1 or PlGF alone (pre-eclampsia within 1 week: AUC, 0.87 versus 0.82 versus 0.72). Models including the sFlt-1/PlGF ratio were associated more strongly with PE hazard compared to models including sFlt-1 or PlGF alone (concordance index, 0.790 versus 0.759 versus 0.755). The risk classification capability of the sFlt-1/PlGF ratio decreased after the 2-week time-point. The established cut-off value for the sFlt-1/PlGF ratio of less than 38 was effective for ruling out PE within 2 weeks, with a NPV of 0.933 and sensitivity of 0.952. The authors concluded that the use of the sFlt-1/PlGF ratio is preferable to the use of PlGF alone for the prediction of PE in pregnancies with FGR. Established cut-offs for ruling out the development of PE in the short-term appeared to be effective in these patients.

Furthermore, an UpToDate review on “Preeclampsia: Antepartum management and timing of delivery” (Norwitz, 2024) states that “Laboratory tests that measure urinary or plasma anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), and pro-angiogenic factors, such as placental growth factor (PlGF), or their ratios can be used for predicting risk of progression to preeclampsia with severe features and those who are most likely to have adverse maternal and neonatal outcomes. This information can help plan management and facilitate decision-making around such issues as inpatient versus outpatient care and timing of delivery … the sFlt-1:PlGF test was approved by the US Food and Drug Administration (FDA) in May 2023 for use in pregnant patients with singleton pregnancies hospitalized for hypertensive disorders of pregnancy. The test should be used in conjunction with other laboratory tests and clinical assessments to aid in the risk assessment for progression to preeclampsia with severe features within two weeks of presentation. The American College of Obstetricians and Gynecologists subsequently stated that the sFlt-1:PlGF ratio should only be used for patients who met inclusion criteria for the PRAECIS trial (e.g., hospitalized patients with a hypertensive disorder of pregnancy at 23+0 to 34+6 weeks of gestation)”.

Ghidini et al (2024) stated that in 2019 the ACOG issued specific recommendations for performance of antepartum fetal surveillance (AFS) based on individual risk factors. As similar recommendations were already in place at the authors’ institution, they examined the impact of AFS on stillbirth (SB) occurrence in a 5-year cohort. These investigators carried out a retrospective review of all deliveries between July 1, 2013 and June 30, 2018. Excluded were multiples, anomalous fetuses or newborns, and deliveries before 32 0/7 weeks' gestation. AFS was performed from 32 weeks with a modified biophysical profile, with a complete biophysical profile as back-up for non-reactive, non-stress tests. All cases of SB were prospectively identified and individually reviewed to verify the presence of risk factors, the results of fetal testing if performed, and calculate the interval between last fetal test and delivery. The electronic medical records during the study period were queried to identify women who underwent AFS and those who did not. Chi-square was used to compare the rates of SB between the 2 groups. A total of 16,827 women fulfilled the study inclusion and exclusion criteria, 5,711 (34 %) had risk factors that prompted AFS; 37 % had 2 or more risk factors. SB occurred in 1.8 %, of them (10/5,711) (3 had 1 risk factor, 5 had 2, and 2 had 3 risk factors). Rates of SB at 32.0 weeks or greater were similar between women who had AFS and those who did not (1.8 % versus 2.3 %, p = 0.51, OR = 0.75, 95 % CI: 0.36 to 1.55). The false-negative rate at less than 7 days of a reassuring AFS among compliant women was 1.4 % (8/5,711). Rates of pre-term delivery were similar in the tested versus untested population (6.5 % versus 6.0 %, p = 0.22). The authors concluded that implementation of AFS in women with risk factors similar to those recommended by the ACOG may lower the risk of SB from 32 weeks to that of low-risk pregnancies.

Glossary of Terms

Term	Definition
Fetal growth restriction, formerly called Intra-uterine growth restriction (IUGR)	A fetus whose estimated fetal weight or abdominal circumference is less than the 10th percentile for its gestational age (ACOG, 2021; Chew and Verma, 2023)
Oligohydramnios	Can be isolated or associated with maternal or fetal conditions. Defined as no ultrasonographically measurable vertical pocket of amniotic fluid greater than 2 cm or an amniotic fluid index (AFI) of 5 cm or less (Preboth, 2000) Note: The deepest (maximal) vertical pocket depth is considered a reliable method for assessing amniotic fluid volume on ultrasound. It is performed by assessing a pocket of a maximal depth of amniotic fluid which is free of an umbilical cord and fetal parts (Haouimi, 2023).
Oligohydramnios (isolated)	Single deepest vertical pocket less than 2 cm (ACOG, 2021)
Polyhydramnios	Frequently categorized as mild, moderate, or severe, based on a deepest vertical pocket of 8–11 cm, 12–15 cm, or 16 cm or greater, or an amniotic fluid index of 24.0–29.9 cm, 30.0–34.9 cm, and 35 cm or greater, respectively (ACOG, 2021).
Polyhydramnios (moderate or severe)	Deepest vertical pocket equal to or greater than 12 cm or amniotic fluid index equal to or greater than 30 cm (ACOG, 2021).
Twin growth discordance	A term used in obstetric imaging to describe a significant size or weight difference between the two fetuses of a twin pregnancy (Foster, 2019).

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Policy History

- Last Review 03/10/2025

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  Next Review: 01/08/2026

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes