Early pregnancy prediction of preeclampsia

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INTRODUCTION

Preeclampsia is a multi-system progressive disorder characterized by the new onset of hypertension and proteinuria, or hypertension and significant end-organ dysfunction with or without proteinuria, in the last half of pregnancy or postpartum (table 1). The genesis of the disease is laid down in early pregnancy and is characterized anatomically by abnormal remodeling of the maternal spiral arteries at the placental site.

Women at high risk for developing preeclampsia may benefit from the initiation of low-dose aspirin therapy starting at the end of the first trimester, as this may reduce the frequency of preeclampsia and associated maternal and perinatal morbidity and mortality. High-risk status is based on obstetric and medical risk factors rather than laboratory and imaging tests because results of these tests in early pregnancy do not accurately distinguish women who will go on to develop preeclampsia from those who will not (ie, the positive predictive value is low) [1-3]. In addition to assessment of risk factors, early clinical detection of the disease is important: All pregnant women are monitored for evidence of preeclampsia at each of their prenatal visits. Early diagnosis may improve maternal and perinatal outcomes by ensuring appropriate management (eg, antenatal corticosteroids for fetal lung maturation, treatment of severe hypertension, magnesium sulfate to prevent seizures, and early delivery).

This topic will discuss available data regarding screening women in early pregnancy to identify those most likely to develop preeclampsia. Additional issues related to the diagnosis, management, and prevention of preeclampsia are discussed separately.

- (See "Preeclampsia: Clinical features and diagnosis".)
- (See "Preeclampsia: Management and prognosis".)
- (See "Preeclampsia: Prevention".)

CLINICAL APPROACH

All women: Routine blood pressure measurement in pregnancy — We agree with the assessment of the United States Preventive Services Task Force (USPSTF) that all pregnant women are at risk for preeclampsia and should be screened by measurement of blood pressure at all provider visits throughout pregnancy [4]. Although preeclampsia is not diagnosed before 20 weeks of gestation, early measurements establish the patient's baseline blood pressure.

The USPSTF assessment was based on the following principles and evidence: blood pressure can be readily and accurately measured, measurement of blood pressure is not harmful, and recognition and treatment of preeclampsia can reduce maternal and perinatal morbidity and mortality [5].

Identify women at high risk early in pregnancy — We believe that pregnant women should be evaluated early in pregnancy for risk factors for preeclampsia. By quantifying the risk of preeclampsia conferred by various individual clinical and demographic risk factors, the clinician is better equipped to estimate a woman's risk of preeclampsia and whether she is a candidate for heightened pregnancy surveillance or prophylactic measures (low-dose aspirin). Early

assessment is particularly important for women who are planning to receive pregnancy care and deliver in a low-risk setting (eg, midwifery practice, birthing center, home birth), which would be contraindicated if preeclampsia develops. These women, if identified as high risk for development of preeclampsia, should be offered consultation with a clinician with expertise in the management of the disease [6,7].

Multiple risk factors for development of preeclampsia have been described (table 2). The USPSTF risk criteria for high risk of development of preeclampsia are [8]:

- Previous pregnancy with preeclampsia, especially early onset and with an adverse outcome
- Multifetal gestation
- Chronic hypertension
- Type 1 or 2 diabetes mellitus
- Renal disease
- Autoimmune disease (antiphospholipid syndrome, systemic lupus erythematosus)

USPSTF criteria for moderate risk of development of preeclampsia are:

- Nulliparity
- Obesity (body mass index [BMI] >30 kg/m^2)
- Family history of preeclampsia in mother or sister
- Age ≥35 years
- Sociodemographic characteristics (African American, low socioeconomic level)
- Personal risk factors (eg, history of low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)

Women with multiple moderate risk factors may be considered high risk, but the evidence of the association (magnitude and consistency) between these risk factors and development of preeclampsia is variable. The National Institute for Health and Care Excellence (NICE) in the United Kingdom developed a similar checklist [9].

In a 2016 meta-analysis of cohort studies including ≥1000 patients that evaluated the risk of preeclampsia in relation to common clinical risk factors assessed at ≤16 weeks of gestation (92 studies, >25 million pregnancies), the highest rate of preeclampsia occurred in women with antiphospholipid syndrome (pooled rate 17.3 percent, pooled relative risk [RR] 2.8), and the highest relative risk of preeclampsia occurred in women with a past history of the disease (pooled rate 12 percent, pooled RR 8.4) [10]. Other prominent risk factors included chronic hypertension (pooled rate 16.0 percent, pooled RR 5.1), preexisting (pregestational) diabetes (pooled rate 11.0 percent, pooled RR 3.7), prepregnancy BMI >30 kg/m^2 (pooled rate 7.1 percent, pooled RR 2.8), multifetal pregnancy (pooled rate 6.4 percent, pooled RR 2.9), and use of assisted reproductive technology (pooled rate 6.2 percent, pooled RR 1.8).

Because historical risk factors only predict approximately 30 percent of women who will develop preeclampsia [11], use of laboratory and imaging tests in combination with historical risk factors to calculate a woman's risk of developing preeclampsia is an active area of investigation. However, current models have low positive predictive value, thus potentially worrying a large number of pregnant women about a disorder they will not develop and exposing them to tests and interventions that will not benefit them [3].

One reason for the low predictive value may be insufficiently accounting for factors that mitigate risk, such as a previous normotensive pregnancy. Another reason may involve not distinguishing between early-onset and late-onset preeclampsia, which have different risk profiles and recurrence rates. (See 'Risk prediction models' below.)

Prenatal care for high-risk women — In addition to routine prenatal care, for women who are at high risk of developing preeclampsia, establishing gestational age, baseline blood pressure, and baseline laboratory values (including platelet count, creatinine concentration, liver chemistries, and urinary protein [protein:creatinine ratio or 24-hour urine protein]) early in pregnancy can be helpful later in gestation in distinguishing preeclampsia from

underlying disorders associated with similar clinical and laboratory findings. (See "Preeclampsia: Clinical features and diagnosis", section on 'Differential diagnosis'.)

A prudent approach is to educate high-risk patients about the signs and symptoms of preeclampsia and monitor them more closely, particularly for increases in blood pressure, as women who develop high normal blood pressures are at increased risk for developing preeclampsia [12]. (See "Preeclampsia: Clinical features and diagnosis".)

Interventions to reduce risk — Most risk factors for preeclampsia are not modifiable, but avoiding prepregnancy obesity, excessive gestational weight gain, and multifetal pregnancies in the setting of treatment of infertility are notable exceptions.

- Obese women can reduce their risk of developing preeclampsia by losing weight before pregnancy. (See "Fertility and pregnancy after bariatric surgery", section on 'Preeclampsia'.)
- Both obese and nonobese women can reduce their risk of developing preeclampsia by not exceeding Institute of Medicine (now National Academy of Medicine) recommendations for gestational weight gain (table 3) [13]. (See "Gestational weight gain", section on '2009 IOM weight gain recommendations' and "Gestational weight gain", section on 'Overweight and obese women'.)
- Low-dose aspirin (60 to 150 mg daily) is the only drug for which there is proven evidence of benefit in reducing the risk of preeclampsia when administered throughout the second and third trimesters in patients at high risk. For women at low risk for development of preeclampsia, available evidence does not support use of low-dose aspirin for prevention of preeclampsia, but a modest (approximately 10 percent) reduction in the risk of preeclampsia and its sequelae (growth restriction, preterm birth) is possible for women at moderate to high risk of developing the disease. The evidence for this approach is reviewed separately. (See "Preeclampsia: Prevention", section on 'Candidates'.)
- For women undergoing infertility therapy with in vitro fertilization or ovulation induction alone, various techniques can be employed to reduce the chances of multiple gestation. (See "Strategies to control the rate of high order multiple gestation", section on 'Limiting the multiple gestation risk of assisted reproductive technology' and "Strategies to control the rate of high order multiple gestation", section on 'Limiting the multiple gestation risk of ovulation induction and superovulation'.)

Many agents other than low-dose aspirin have been studied for preeclampsia risk reduction (eg, calcium, vitamin E and C, antioxidants, omega 3 fatty acids, heparin), but the data do not show significant or consistent evidence of benefit across populations. (See "Preeclampsia: Prevention".)

INVESTIGATIONAL APPROACHES

Screening tests — We do not use blood or imaging tests to screen for preeclampsia. Based on data from patients with established preeclampsia, a wide variety of laboratory and imaging tests have been proposed to detect subgroups of women at high risk of developing the disease. Because the prevalence of preeclampsia in the general obstetric population is relatively low (1 to 7 percent), a test would need very high sensitivity and specificity to accurately predict or exclude the development of the disease. Systematic reviews of studies that evaluated clinically available tests have generally concluded that these tests are not sufficiently accurate (high sensitivity and specificity) for screening the general obstetric population and that the overall methodologic quality of available studies was generally poor [5,14-18]. For this reason, the American College of Obstetricians and Gynecologists recommends taking a detailed medical history and assessing blood pressure to assess a patient's risks for developing preeclampsia [3], as described above. (See 'Clinical approach' above.)

The utility of systematic reviews of tests for prediction of preeclampsia has been limited by several factors, including (1) variation in the definition of preeclampsia, which introduces heterogeneity in the classification of the syndrome; (2) variation in inclusion/exclusion criteria, which also increases heterogeneity; (3) variation in the criteria defining

level of risk (low versus high) of a given population (some studies of low-risk populations have had preeclampsia incidence rates higher than high-risk populations in other studies); (4) multiplicity of potential tests, test combinations, and timing of screening during pregnancy; (5) lack of inclusion of specific important information; and (6) flawed study design and/or conduct [19,20].

Biomarkers

Angiogenic modulators — 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).

Ischemic trophoblast, which is a characteristic finding in preeclampsia, increases production of anti-angiogenic proteins (sEng, sFlt1) and reduces production of angiogenic proteins (VEGF, PlGF). Alterations in absolute levels of VEGF [21-24], PlGF [21,22], sFlt-1 [21,22,25-31], and sEng [27-30,32] in maternal blood and urine precede the onset of clinical preeclampsia by several weeks to months, correlate with disease severity, and normalize after delivery. (See "Preeclampsia: Pathogenesis", section on 'sFlt-1, VEGF, PlGF' and "Preeclampsia: Pathogenesis", section on 'Soluble endoglin'.)

However, blood and urine levels of these factors have not been proven to be clinically useful for prediction of preeclampsia remote from disease onset.

- In a 2012 systematic review of 22 case-control and 12 cohort studies, serum levels of PlGF, VEGF, sFlt-1, or sEng were evaluated alone or in combination in pregnant women <30 weeks of gestation and before clinical onset of preeclampsia [33]. Test performance was too poor to recommend use of these tests for screening. The concentrations of PlGF and VEGF were lower in women who developed preeclampsia, and the concentrations of sFlt-1 and sEng were higher in these women; the summary diagnostic odds ratios (ORs) were: PlGF 9.0 (95% CI 5.6-14.5), sFlt-1 6.6 (95% CI 3.1-13.7), and sEng 4.2 (95% CI 2.4-7.2), which correspond to sensitivities of 32, 26, and 18 percent, respectively, with a 5 percent false-positive rate. When assessed by gestational age, most of the markers did not perform well in the first half of pregnancy but had better performance after 30 weeks.

- Urinary PlGF also does not perform well in early pregnancy as a screening test. A nested case-control study [34] evaluated urine PlGF to predict preeclampsia using stored urine specimens from women who had been enrolled in the Calcium for Preeclampsia Prevention trial [35], which included healthy nulliparous women with singleton pregnancies followed from between 13 and 21 weeks of gestation until 24 hours postpartum. Urine samples were collected before enrollment, at 26 to 29 weeks of gestation, at 36 weeks, and at onset of preeclampsia. Baseline urinary PlGF levels at 8 to 21 weeks of gestation were not significantly different between women who developed preeclampsia and those who remained normotensive.

  However, the test was predictive of preeclampsia late in gestation. Women who went on to develop preeclampsia had lower levels of PlGF than controls at each sampling interval from 25 weeks through onset of disease. At 21 to 32 weeks, a PlGF concentration in the lowest quartile (less than 118 pg/mL) was highly predictive of development of preterm preeclampsia (OR 22.5, 95% CI 7.4-67.8) but less predictive of term preeclampsia (OR 2.2, 95% CI 1.2-4.3). Fractional excretion modeling (ratios) may offer advantages over absolute levels of urinary angiogenic factors for identifying women at risk for developing preeclampsia since ratios account for dilutional effects [36-38].

- The sFlt-1:PlGF ratio may be the best test for predicting preeclampsia, but like the above tests is not useful early in pregnancy. In a 2018 systematic review that evaluated the sFlt-1:PlGF ratio in blood for prediction of preeclampsia (15 studies, 534 cases of preeclampsia and 19,587 controls), pooled sensitivity was 80 percent (95% CI 0.68-0.88), specificity 92 percent (95% CI 0.87-0.96), positive likelihood ratio 10.5 (95% CI 6.2-18.0), and a

negative likelihood ratio 0.22 (95% CI 0.13-0.35) [39]. However, all of these women were at least 20 weeks of gestation. The authors pointed out that previous studies demonstrated that levels of these markers in women who develop preeclampsia do not change significantly until the second half of the pregnancy and the major changes take place in the third trimester.

Other laboratory tests — Maternal serum analyte testing is an important component of Down syndrome screening programs. Increasing evidence suggests that unexplained abnormal maternal serum analyte concentrations (eg, pregnancy-associated plasma protein A [PAPP-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 [40-45]. This association is not sufficiently strong to warrant changes in routine prenatal care, but the biomarkers have been used in risk prediction models.

Uterine artery Doppler velocimetry — Although meta-analyses show that uterine artery Doppler analysis can predict women at increased risk of preeclampsia [46-48], we and most experts do not recommend these studies for screening in early pregnancy [15,49-52]. The false-positive rate of this test is quite high [51,52], leading to excessive patient anxiety and health care costs.

Impedance to flow in the uterine arteries normally decreases as pregnancy progresses. Increased impedance for gestational age is an early radiographic feature of preeclampsia and likely reflects high downstream resistance due to defective differentiation of trophoblast, which leads to defective invasion of spiral arteries and failure of these vessels to transform into low resistance vessels.

Two types of uterine artery Doppler waveform analysis techniques have emerged for prediction of preeclampsia, as well as other disorders associated with impaired placentation (eg, fetal growth restriction, pregnancy loss): (1) presence or absence of diastolic notching (unilateral, bilateral) of the uterine arcuate vessels and (2) flow waveform ratios (eg, high resistance or pulsatility index, systolic/diastolic ratio).

The use of uterine artery Doppler velocimetry for prediction of preeclampsia was best illustrated in a 2008 systematic review of 74 studies including almost 80,000 women [46]. These studies involved 15 uterine artery Doppler indices and women at either low or high risk of developing preeclampsia. The authors found that uterine artery Doppler ultrasonography was more accurate for prediction of preeclampsia when performed in the second trimester than in the first trimester. In women at high risk of developing preeclampsia, the overall risk of preeclampsia was best predicted by second-trimester elevation of pulsatility index accompanied by uterine artery notching (sensitivity 19 percent, specificity 99 percent, positive likelihood ratio [+LR] 21, negative likelihood ratio [-LR] 0.82), and the risk of severe preeclampsia was best predicted by second-trimester elevated resistance index (sensitivity 80 percent, specificity 78 percent, +LR 3.7, -LR 0.26).

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.

Ophthalmic artery Doppler — Ophthalmic artery Doppler velocimetry has also been used to predict the development of preeclampsia. In a meta-analysis of three studies involving 1119 pregnancies, a first diastolic peak velocity >23.3 cm/second showed modest sensitivity (61.0 percent, 95% CI 44.2-76.1 percent) and specificity (73.2 percent, 95% CI 66.9-78.7 percent) for the prediction of early-onset preeclampsia (area under the receiver-operating characteristics curve [AUC] 0.68, 95% CI 0.61-0.76) [53]. This is an interesting observation since, unlike the uterine artery, the change in ophthalmic artery Doppler indices cannot be the direct result of trophoblast invasion and is more likely to be related to maternal hemodynamic changes. Similar to Doppler studies of uterine arteries, ophthalmic artery Doppler velocimetry likely has little clinical utility as a standalone predictive test for either early- or late-onset preeclampsia. Although it has been described as a safe, noninvasive, inexpensive, reproducible, point-of-care test, it is unlikely that obstetric providers would become credentialed to perform this type of imaging.

Risk prediction models — As described above, specific maternal characteristics, Doppler ultrasound findings, and biomarkers in blood are associated with an increased risk of preeclampsia. Traditionally, each risk factor is treated as a separate screening test, and a higher number of risk factors is assumed to carry a higher risk for development of preeclampsia.

Multiple investigators have used these variables in logistic regression analysis to create a tool to predict an individual woman's risk of developing preeclampsia while she is still early in pregnancy (eg, Fetal Medicine Foundation [FMF] risk for preeclampsia calculator [54]). In validation studies, the detection rate of the FMF London and Fetal Medicine Barcelona combined first-trimester screening algorithms for prediction of preterm preeclampsia ranged from 75 to 92 percent at a false positive rate of 10 percent [55]. Ideally, women identified as high risk would be encouraged to address any modifiable risk factors; educated about the signs and symptoms of preeclampsia, so they will notify their provider as soon as clinical manifestations occur; and followed with more frequent office visits. Some clinicians also start these women on low-dose aspirin. (See "Preeclampsia: Prevention", section on 'Candidates'.)

The utility of prescribing aspirin based on risk determined by these tools rather than historic and demographic risk factors has not been studied extensively. Although the screen-positive rate may be lower and the positive likelihood ratio may be higher than with traditional risk factor-based models [56], these tools still have relatively low positive likelihood ratios, so many women will be made anxious and receive unnecessary treatment. They typically require determination of mean arterial pressure, a Doppler ultrasound examination at 11 to 13 weeks for uterine artery pulsatility index, specific expertise by the sonographer, additional laboratory testing (eg, serum PAPP-A and serum placental growth factor), and, in turn, additional costs. Furthermore, methodologic deficiencies are common, which limit their reliability and validity. For example, a 2015 systematic review evaluated 24 studies of 38 predictive models that included uterine artery Doppler as one of the independent variables [20]. The median number of study participants was 697, the median number of cases of preeclampsia per model was 37, and the median number of risk predictors was 5. Almost one-quarter of the models had fewer than 10 events per predictor of preeclampsia, and almost 95 percent had fewer than 10 events per predictor of early preeclampsia. Only one model adequately described treatment and handling of missing data, and only three models reported model validation.

SCREENING TESTS NOT USEFUL FOR PREDICTING PREECLAMPSIA

Provocative biophysical tests — Aberrations in vascular responsiveness have formed the basis of several screening tests for the detection of pregnant women at risk for preeclampsia. None of these tests (angiotensin II challenge test [57,58], roll-over test [supine pressor test] [58,59], isometric exercise test [hand-grip test] [60,61]) are currently being used clinically because they are expensive, time-consuming, and, most importantly, unreliable.

Serum uric acid — Although hyperuricemia is commonly seen in women with preeclampsia, a systematic review of five studies concluded that measurement of serum uric acid concentration before 25 weeks of gestation was not useful for predicting which women would develop preeclampsia [62]. One study used a rise in serum uric acid concentration above baseline level as the criterion for a positive test result, while the other four studies used threshold values above 3.5 to 4 mg/dL (0.21 to 0.24 mmol/L) as the cut-off for a positive test. Sensitivities ranged from 0 to 56 percent and specificities ranged from 77 to 95 percent. The data were not pooled because of the methodologic uncertainties and the clinical differences between studies [62].

Similarly, a second systematic review concluded that serum uric acid measurement was not useful for predicting development of complications in women with preeclampsia [63], although it may be useful in predicting the length of the latency period from diagnosis to delivery [64].

Screening for inherited thrombophilias — The weight of evidence, including data from prospective cohort studies [65,66], indicates that inherited thrombophilias (such as Factor V Leiden mutation, prothrombin gene mutation, protein C or S deficiency, and antithrombin deficiency) are not associated with preeclampsia; therefore, screening

pregnant women for inherited thrombophilias is not useful for predicting those at high risk of developing the disease. This is discussed in more detail separately. (See "Inherited thrombophilias in pregnancy", section on 'Selection of patients for screening'.)

Screening for antiphospholipid antibodies — Antiphospholipid antibody syndrome (APS) is associated with the development of severe early preeclampsia. Prophylaxis with both low-dose aspirin and prophylactic-dose heparin starting at the end of the first trimester and continuing throughout pregnancy can decrease the rate of pregnancy complications (including preeclampsia) and improve pregnancy outcome in women with APS.

Screening the general obstetric population for antiphospholipid antibodies is not useful. Candidates for laboratory testing for antiphospholipid antibodies (aPL), such as those with an unexplained stillbirth or stillbirth related to growth restriction or severe preeclampsia or other evidence of placental insufficiency, are described separately (table 4). (See "Diagnosis of antiphospholipid syndrome", section on 'When to suspect the diagnosis' and "Diagnosis of antiphospholipid syndrome", section on 'Diagnostic evaluation'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hypertensive disorders of pregnancy".)

SUMMARY AND RECOMMENDATIONS

- Pregnant women should be evaluated early in pregnancy for risk factors for preeclampsia (table 2). By quantifying the risk of preeclampsia conferred by various individual clinical risk factors, the clinician is better equipped to estimate a woman's risk of preeclampsia, educate her about this risk and its implications, determine the appropriate frequency of pregnancy surveillance, and consider whether she is a candidate for prophylactic aspirin. (See 'Identify women at high risk early in pregnancy' above.)

- Most risk factors for preeclampsia are not modifiable; avoiding obesity and excessive gestational weight gain are notable exceptions. (See 'Interventions to reduce risk' above.)

- Low-dose aspirin is the only drug for which there is some evidence of benefit in reducing the risk of preeclampsia when administered throughout the second and third trimesters to women at high risk for developing the disease. For women at low risk for development of preeclampsia, available evidence does not support use of low-dose aspirin for prevention of preeclampsia, but a modest (approximately 10 percent) reduction in the risk of preeclampsia and its sequelae (growth restriction, preterm birth) is possible for women at moderate to high risk of developing the disease. (See 'Interventions to reduce risk' above.)

- For women who are at high risk of developing preeclampsia, establishing gestational age, baseline blood pressure, and baseline laboratory values including platelet count, creatinine concentration, liver function tests, and urinary protein estimation early in pregnancy can be helpful later in gestation in distinguishing preeclampsia from underlying disorders associated with similar clinical and laboratory findings. (See 'Prenatal care for high-risk women' above.)

- A wide variety of laboratory and imaging tests have been proposed to distinguish women who will develop preeclampsia from those who will not. Systematic reviews of studies that evaluated clinically available tests have generally concluded that these tests were not sufficiently accurate for screening the general obstetric population and that the overall methodologic quality of available studies was generally poor. For this reason, we agree with American College of Obstetricians and Gynecologists recommendations for taking a detailed medical history to assess a patient's risks for developing preeclampsia but not using laboratory and imaging screening

tests (including uterine artery Doppler velocimetry and serum biomarkers such as pro- and anti-angiogenic factors). (See 'Screening tests' above.)

- Specific maternal characteristics, Doppler ultrasound findings, and biomarkers in blood are associated with an increased risk of preeclampsia. Multiple investigators have used these variables in logistic regression analysis to create tools to predict an individual woman's risk of developing preeclampsia while she is still early in pregnancy. We do not use these tools because they have low positive predictive values, so many women will be made anxious and treated unnecessarily, and methodologic deficiencies are common, which limit their reliability and validity. (See 'Risk prediction models' above.)

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Topic 6750 Version 47.0

GRAPHICS

Criteria for the diagnosis of preeclampsia

Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of 1 or more of the following*:
▪ Proteinuria ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (mg/mg) (30 mg/mmol) in a random urine specimen or dipstick ≥2+ if a quantitative measurement is unavailable
▪ Platelet count <100,000/microL
▪ Serum creatinine >1.1 mg/dL (97.2 micromol/L) or doubling of the creatinine concentration in the absence of other renal disease
▪ Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
▪ Pulmonary edema
▪ New-onset and persistent headache not accounted for by alternative diagnoses and not responding to usual doses of analgesics¶
▪ Visual symptoms (eg, blurred vision, flashing lights or sparks, scotomata)

Preeclampsia is considered superimposed when it occurs in a woman with chronic hypertension. It is characterized by worsening or resistant hypertension (especially acutely), the new onset of proteinuria or a sudden increase in proteinuria, and/or significant new end-organ dysfunction after 20 weeks of gestation in a woman with chronic hypertension.

* If systolic blood pressure is ≥160 mmHg or diastolic blood pressure is ≥110 mmHg, confirmation within minutes is sufficient.
¶ Response to analgesia does not exclude the possibility of preeclampsia.

Adapted from: American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 222: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2020; 135:e237.

Graphic 79977 Version 36.0

Clinical factors that have been associated with an increased risk of developing preeclampsia

Nulliparity
Preeclampsia in a previous pregnancy
Age >40 years or <18 years
Family history of preeclampsia
Chronic hypertension
Chronic renal disease
Autoimmune disease (eg, antiphospholipid syndrome, systemic lupus erythematosus)
Vascular disease
Diabetes mellitus (pregestational and gestational)
Multifetal gestation
Obesity
Black race
Hydrops fetalis
Poorly controlled hyperthyroidism
Woman herself was small for gestational age
Fetal growth restriction, abruptio placentae, or fetal demise in a previous pregnancy
Prolonged interpregnancy interval if the previous pregnancy was normotensive; if the previous pregnancy was preeclamptic, a short interpregnancy interval increases the risk of recurrence
Partner-related factors (new partner, limited sperm exposure [eg, previous use of barrier contraception])
In vitro fertilization
Obstructive sleep apnea
Elevated blood lead level
Posttraumatic stress disorder

By comparison, smoking decreases the risk of preeclampsia, and Asian and Hispanic women have a lower risk of preeclampsia than white women and a much lower risk than black women.

Graphic 61266 Version 11.0

Recommendations for total and rate of weight gain for singleton pregnancies by prepregnancy BMI

	Total weight gain		Rates of weight gain* second and third trimester	
Prepregnancy BMI	**Range in kg**	**Range in lb**	**Mean (range) in kg/week**	**Mean (range) in lb/week**
Underweight (<18.5 kg/m^2)	12.5 to 18	28 to 40	0.51 (0.44 to 0.58)	1 (1 to 1.3)
Normal weight (18.5 to 24.9 kg/m^2)	11.5 to 16	25 to 35	0.42 (0.35 to 0.50)	1 (0.8 to 1)
Overweight (25.0 to 29.9 kg/m^2)	7 to 11.5	15 to 25	0.28 (0.23 to 0.33)	0.6 (0.5 to 0.7)
Obese (≥30.0 kg/m^2)	5 to 9	11 to 20	0.22 (0.17 to 0.27)	0.5 (0.4 to 0.6)

Recommended weight gain is higher for women with multiple gestations.

BMI: body mass index.
* Calculations assume a 0.5 to 2 kg (1.1 to 4.4 lb) weight gain in the first trimester.

Weight Gain During Pregnancy: Reexamining the Guidelines. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines, Rasmussen KM, Yaktine AL (Eds), National Academies Press (US), The National Academies Collection: Reports funded by National Institutes of Health, Washington (DC) 2009. Reprinted with permission from the National Academies Press, Copyright © 2009 National Academy of Sciences.

Graphic 75820 Version 18.0

Revised classification criteria for the antiphospholipid syndrome

Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*
Clinical criteria
1. Vascular thrombosis¶ One or more clinical episodes[Δ] of arterial, venous, or small vessel thrombosis[◊], in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency[§]; or c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
Laboratory criteria[¥]
1. LA present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-beta-2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

LA: lupus anticoagulant; aCL: anticardiolipin antibody; Ig: immunoglobulin; ELISA: enzyme-linked immunosorbent assay; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GFR: glomerular filtration rate.

* Classification of APS should be avoided if less than 12 weeks or more than five years separate the positive aPL test and the clinical manifestation.

¶ Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the presence; and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) cases include: age (>55 in men and >65 in women) and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg m^{-2}, microalbuminuria, estimated GFR <60 mL $minute^{-1}$), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis.

Δ A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

◊ Superficial venous thrombosis is not included in the clinical criteria.

§ Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), eg, a non-reactive non-stress test, suggestive of fetal hypoxemia; (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, eg, absent end-diastolic flow in the umbilical artery; (iii) oligohydramnios, eg, an amniotic fluid index of 5 cm or less; or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

¥ Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-beta-2 glycoprotein-I antibody present alone.

Graphic 104569 Version 3.0

Contributor Disclosures

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Conflict of interest policy

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