DR SHAHNAZ BARAT

DEPARTMENT OF OB & GYN BABOL MEDICAL UNIVERSITY

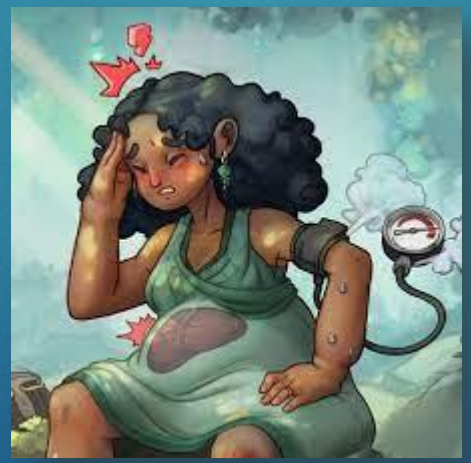
تازه های غربالگری پره اکلامپسی در بارداری

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

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.

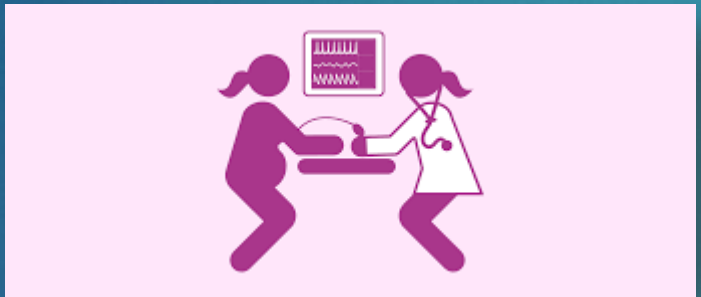
Women at high risk for developing preeclampsia may benefit from the initiation of low-dose aspirin therapy starting at the end of the first trimester, as this may reduce the frequency of preeclampsia and associated maternal and perinatal morbidity and mortality

High-risk status is based on obstetric and medical risk factors rather than laboratory and imaging tests



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 :

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.

All women : Routine blood pressure measurement in pregnancy

Although preeclampsia is not diagnosed before 20 weeks of gestation, early measurements establish the patient's baseline blood pressure

Identify women at high risk early in pregnancy

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

Multiple risk factors for development of preeclampsia have been described .

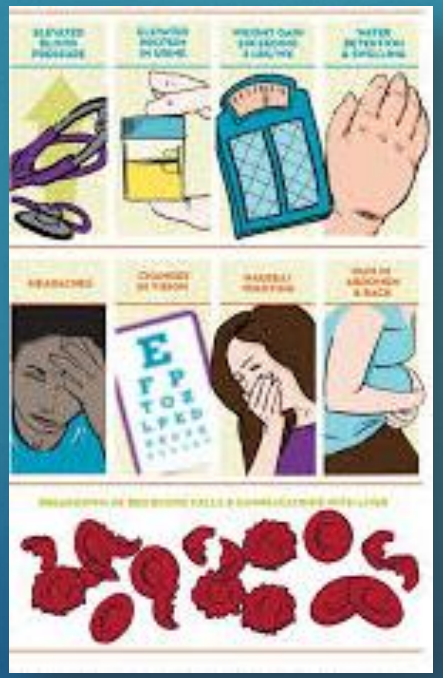
Risk criteria for high risk of development of preeclampsia are :

- **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)**

Moderate risk of development of preeclampsia are :

- Nulliparity
- Obesity (body mass index [BMI] >30 kg/m2)
- 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



Prenatal care for high-risk women

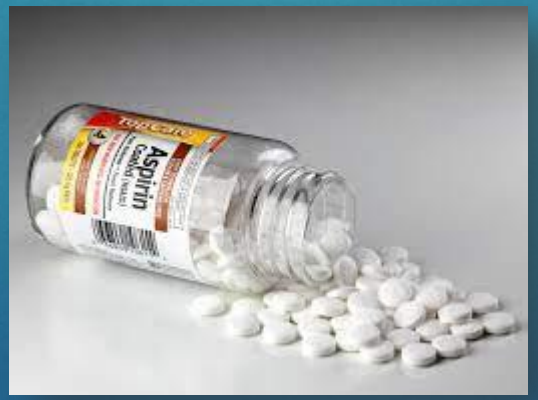
In addition to routine prenatal care, for women who are at high risk of developing preeclampsia, establishing gestational age, baseline blood pressure, and baseline laboratory values (including platelet count, creatinine concentration, liver chemistries, and urinary protein [protein:creatinine ratio 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

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.

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 .

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

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 .

INVESTIGATIONAL APPROACHES

Screening tests

We do not use blood or imaging tests to screen for preeclampsia.

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

Biomarkers

Angiogenic modulators

1- Vascular endothelial growth factor (VEGF)
2- Placental growth factor (PLGF)

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 .

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).

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

Most of the markers did not perform well in the first half of pregnancy but had better performance after 30 weeks.

Urinary PlGF :

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).

The sFlt-1 : PlGF ratio may be the best test for predicting preeclampsia, but like the above tests is not useful early in pregnancy.

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.

Unexplained abnormal maternal serum analyte concentrations (eg , 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 .

Uterine artery Doppler velocimetry :

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 in early pregnancy.

The false-positive rate of this test is quite high [51,52], leading to excessive patient anxiety and health care costs.

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.

Ophthalmic artery Doppler :

Ophthalmic artery Doppler velocimetry has also been used to predict the development of preeclampsia

operating characteristics curve [AUC] 0.68, 95% CI 0.61-0.76) [. 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.

Risk prediction models :

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.

First-trimester screening algorithms for prediction of preterm preeclampsia ranged from 75 to 92 percent at a false positive rate of 10 percent.

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.

SCREENING TESTS NOT USEFUL FOR PREDICTING

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 , roll-over test [supine pressor test] , isometric exercise test [hand-grip test]) are currently being used clinically because they are expensive, time-consuming, and, most importantly, unreliable.

Serum uric acid :

Before 25 weeks of gestation was not useful for predicting of preeclampsia .

A second systematic review concluded that serum uric acid measurement was not useful for predicting development of complications in women with preeclampsia

Screening for inherited thrombophilias :

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.

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.

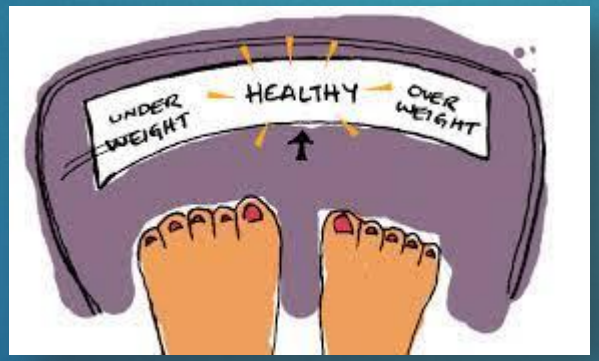
Screening the general obstetric population for antiphospholipid antibodies is not useful . Candidates for laboratory testing for antiphospholipid antibodies (aPL), such as those with an unexplained stillbirth or stillbirth related to growth restriction or severe preeclampsia or other evidence of placental insufficiency

SUMMARY AND RECOMMENDATIONS

Pregnant women should be evaluated early in pregnancy for risk factors for preeclampsia

Estimate a woman's risk of preeclampsia, educate her about this risk and its implications
and consider whether she is a candidate for prophylactic aspirin

Most risk factors for preeclampsia are not modifiable; avoiding obesity and excessive gestational weight gain are notable exceptions.



Low-dose aspirin is the only drug for which there is some evidence of benefit in reducing the risk of preeclampsia .

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

A wide variety of laboratory and imaging tests have been proposed to distinguish women who will develop preeclampsia

These tests were not sufficiently accurate for screening the general obstetric population .

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).

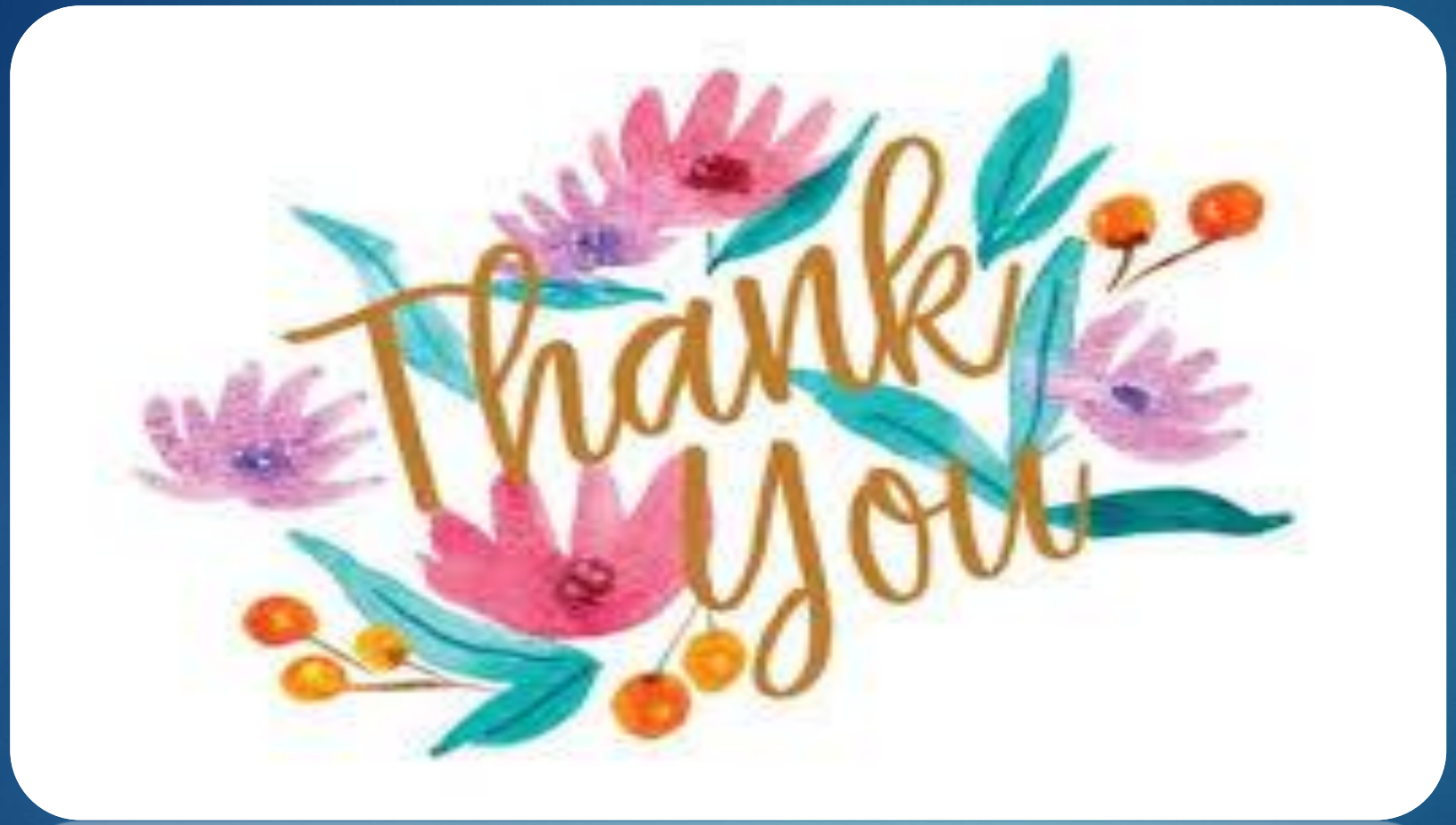
Specific maternal characteristics , Doppler ultrasound findings , and biomarkers in blood are associated with an increased risk of preeclampsia .

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.

PREECLAMPSIA

- Multi-system progressive disorder characterized by the new onset hypertension and proteinurea or hypertension + significant endorgan dysfunction with or without proteinurea in the last half of pregnant or post partum


Thank you