CANDIDATE BIOCHEMICAL MARKERS FOR EARLY PREGNANCY SCREENING OF PREECLAMPSIA

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Pregnancy Related Disorders:
Present Perspectives and Emerging Challenges
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PREECLAMPSIA AND OTHER HYPERTENSIVE DISORDERS OF PREGNANCY

• What is preeclampsia ?
• What is known about its pathophysiology ?
• What can be done for prevention/treatment ?
• What are the tools for detection ?
  – Maternal risk factors
  – Biochemical markers
  – Ultrasonographic markers

PERSPECTIVES

• What are the screening strategies (why and when)?
• Criteria for effective predictive algorithms
• Benefits and risks
### Terms and Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDP</td>
<td>Hypertensive Disorders of Pregnancy</td>
</tr>
<tr>
<td>PE</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>GH</td>
<td>Gestational Hypertension</td>
</tr>
<tr>
<td>HELLP</td>
<td>Hemolysis Elevated Liver enzymes Low Platelet</td>
</tr>
<tr>
<td>CH</td>
<td>Chronic Hypertension</td>
</tr>
<tr>
<td>BP</td>
<td>Blood Pressure (SBP: systolic; DBP: diastolic)</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean Arterial Blood Pressure</td>
</tr>
<tr>
<td>PI</td>
<td>Pulsatility Index (Doppler)</td>
</tr>
<tr>
<td>UtA</td>
<td>Uterine Artery</td>
</tr>
<tr>
<td>PTB</td>
<td>Premature Birth</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intra Uterine Growth Restriction</td>
</tr>
<tr>
<td>SGA</td>
<td>Small-for-Gestational Age</td>
</tr>
<tr>
<td>GDM</td>
<td>Gestational Diabetes</td>
</tr>
<tr>
<td>T21, T18, T13</td>
<td>Trisomies 21, 18, 13</td>
</tr>
<tr>
<td>FL</td>
<td>Fetal Loss</td>
</tr>
<tr>
<td>AFP</td>
<td>Alpha-Fetoprotein</td>
</tr>
<tr>
<td>hCG</td>
<td>human Chorionic Gonadotropin</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>Pregnancy-Associated Plasma Protein-A</td>
</tr>
<tr>
<td>InhA</td>
<td>Inhibin A</td>
</tr>
<tr>
<td>PI GF</td>
<td>Placental Growth Factor</td>
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<tr>
<td>sEndog</td>
<td>soluble Endoglin</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
<tr>
<td>VEGFR1</td>
<td>soluble Vascular Endothelial Growth Factor Receptor-1 (soluble fms-like tyrosine kinase-1)</td>
</tr>
<tr>
<td>PP-13</td>
<td>Placental Protein 13</td>
</tr>
<tr>
<td>IGF</td>
<td>Insulin-like Growth Factor</td>
</tr>
</tbody>
</table>

### A Definition of Preeclampsia

(National High Blood Pressure Education Program Working Group USA 2000)

- **Hypertension after the 20th week of pregnancy, remit after delivery**
  - Systolic BP $\geq$ 140 mmHg
  - Diastolic BP $\geq$ 90 mmHg
- **Normal BP prior**
- **With proteinuria**
- **Early onset:** $\leq$ 34 wks; **late onset:** $>$ 34 wks
Proteinuria

- Quantitative measurement of total protein excretion over 24h period
  - Proteinuria: ≥ 300 mg protein / 24h
    - supersedes all dipstick values

- If 24-h urine data not available:
  - Spot concentration of 0.3 g/L on single random urine specimen
  - Proteinuria on dipsticks in at least 2 random mid-stream samples at least 4h apart (2+ = 1 g/L)

---

**Hypertensive Disorders of Pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>Chronic Hypertension</th>
<th>Normal Pre-Pregnancy BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP before pregnancy</td>
<td>DBP ≥ 90 mmHg</td>
<td>Normal</td>
</tr>
<tr>
<td>BP during pregnancy</td>
<td>DBP ≥ 90 mmHg</td>
<td>SBP ≥ 160 mmHg or DBP ≥ 110 mmHg</td>
</tr>
<tr>
<td></td>
<td>DBP ≥ 90 mmHg</td>
<td>DBP ≥ 90 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBP ≥ 90 mmHg</td>
</tr>
<tr>
<td>Onset</td>
<td>before</td>
<td>≥ 20 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onset of PE before 34 wks but may happen later</td>
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<td></td>
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<td>≥ 20 wks</td>
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<td></td>
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<td>BP after pregnancy</td>
<td>DBP ≥ 90 mmHg</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Adapted from Magee et al. (2008) JOGC 30 (suppl1):1-52
### Hypertensive Disorders of Pregnancy

**Chronic Hypertension Normal Pre-Pregnancy BP**

<table>
<thead>
<tr>
<th></th>
<th>CH</th>
<th>PE</th>
<th>Severe PE</th>
<th>GH</th>
<th>PE</th>
<th>Severe PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>None</td>
<td>≥ 2+ dipstick ≥ 300 mg/d ≥ 30 mg/ mmol creatinine</td>
<td>3-5 g/d</td>
<td>None</td>
<td>≥ 2+ dipstick ≥ 300 mg/d ≥ 30 mg/ mmol creatinine</td>
<td>3-5 g/d</td>
</tr>
<tr>
<td>Onset before</td>
<td>≥ 20 wks</td>
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<th>PE</th>
<th>Severe PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other adverse conditions (variable extent)</td>
<td>Maternal symptoms • Vision, Headache • Dyspnea • Maternal signs of end-organ dysfunction • Edema, eclampsia • Abnormal maternal laboratory testing • HELLP: Liver (ALT, AST, LDH) + Platelet Count • Fetal Morbidity</td>
<td>Maternal symptoms • Vision, Headache • Dyspnea • Maternal signs of end-organ dysfunction • Edema, eclampsia • Abnormal maternal laboratory testing • HELLP: Liver (ALT, AST, LDH) + Platelet Count • Fetal Morbidity</td>
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Epidemiology of Preeclampsia

- Worldwide, hypertensive disorders of pregnancy affect up to 15% of pregnancies (specific reports of > 20%).
- Preeclampsia affects between 2 and 8% of pregnancies in developed countries.
  - Wide geographical variation
  - Severe PE: 10–20% of all PE
  - Early-onset PE (≤ 34 weeks): 10-20% of all PE
- Is largely a disease of the first pregnancy.
- Is a major cause of maternal and perinatal morbidity and mortality (5-fold increase)
  - Is a cause of iatrogenic prematurity (15% of preterm births are secondary to delivery for preeclampsia)
  - Is a cause of intra uterine growth restriction (IUGR)

Pathophysiology of Preeclampsia

- Maternal constitutional factors
  - Genetic predisposition
  - Immunological maladaptation
  - Pre-existing vascular disease
- Environmental factors
  - Defective placentation
  - Placental ischemia
  - Oxidative stress
  - Cytotoxic factors
- Systemic maternal endothelial dysfunction
  - Vasospasm
  - Hypertension
  - Hypovolemia
  - Abnormal coagulation
  - Thrombosis
  - Endothelial damage
  - Increased permeability
  - Oedema
  - Proteinuria
Some Risk Factors of Preeclampsia

- Couple-related risk factors
  - Limited sperm exposure
  - Primiparity / Primipaternity
  - In vitro fertilization

- Maternal risk factors
  - Extremes of maternal age
  - Women’s own birth weight
  - Previous PE (or family history of PE)
  - Chronic hypertension or renal disease
  - Inflammatory diseases
  - Obesity and insulin resistance

- Pregnancy-associated risk factors
  - Multiple pregnancy
  - Gestational diabetes
  - Hydrops fetalis / Hydatiform mole
  - Chromosomal anomalies (trisomy 13,...)
  - Various infections (urinary tract, gingivitis, ...)

Adapted from Sibai et al. (2005) Lancet 365: 785.

Normal Placentation

- Invasion of the decidua and the myometrium by the cytotrophoblastic cells occurs early in pregnancy.
- Transformation of the walls of the uterine spiral arteries: replacement of endothelial cells by cytotrophoblastic cells, creation of high-flow, low-resistance arteriolar system, and lost of maternal vasomotor control.
Endovascular Trophoblast Invasion

Anatomopathology of Preeclampsia

Abnormal uterine vascular remodelling during early pregnancy reduces blood flow from uterus to placenta
Impaired trophoblast invasion of the myometrium (limited at the decidua);

30 to 50% of the placental bed’s spiral arteries escape entirely from endovascular trophoblastic invasion;

Myometrial segments remain anatomically intact and adrenergic nerve supply to the spiral arteries remains also intact;

Increased responsiveness of spiral arteries to vasoconstrictor mediators results in...

- placental hypoperfusion,
- local hypoxia,
- overproduction of various mediators,
- oxidative stress.
Pathogenesis of Preeclampsia
The “Angiogenic Imbalance” Theory

Initial mechanisms
- Inflammatory challenges (disorders);
- Alterations in the regulation and signalling of angiogenesis pathways contribute to inadequate cytotrophoblastic invasion;
- Up-regulation of anti-angiogenic factors (sFlt-1, s-Endog);
- Down-regulation of circulating angiogenic factors (VEGF, PIGF).


Pathophysiology of Preeclampsia

Genetic Susceptibility

Abnormal Uterine Vascular Remodelling during early Pregnancy
Placental Hypotrophy, Infarctus
Reduced Placental Perfusion
Hypoxia (Oxidative Stress)
Placental Dysfunction

Release of Placental Mediators in Maternal Circulation

Systemic Maternal Endothelial Dysfunction
Hypertension
Proteinuria
HELLP syndrome
Eclampsia

Adapted from Giguère et al (2011) submitted
Abnormal Uterine Vascular Remodelling during early Pregnancy

Abnormal profile of adhesion molecules (Δ VE-cadherin, VCAM-1, PECAM-1)
Decrease of plasminogen activation (Δ urokinase, MMP-9, PAI-1)
Modification of uterine angiogenesis (Δ sFlt-1, sEndog, PIGF, VEGF, hCG)

Placental Dysfunction

AFP, hCG, PAPP-A, inhibin A, activin A, PP-13

Release of Placental Mediators in Maternal Circulation

Growth Factors : EGF, IGF-II, TGF α/β, VEGF, PIGF, sFlt-1, sEndog;
Cytokines : TNFa; Interleukins 1, 6, 10; LIF; Interferon; Prostaglandins;
Enzymes : PAI 1, PAI 2, MMP-2, MMP-9;
Others : Peroxylated Lipids, Endothelins, Apoptotic/Necrotic debris,
Cell-free foetal nucleic acids

Systemic Maternal Endothelial Dysfunction

Adapted from Giguère et al (2011) submitted

Altered Parameters before Occurrence of Clinical Symptoms of PE

- Clinical (maternal history and characteristics, BMI, MAP, ...)
- Blood and Urine Parameters
- Doppler Uterine Artery Blood Flow Velocity Measurements
- 3-Dimensional Doppler Ultrasonography (placental volume)
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– PERSPECTIVES

• What are the screening strategies (why and when)?
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Early Prediction of PE

Objectives:
• To identify women at high risk of developing preeclampsia later in pregnancy, and to offer specific preventive measures;
• To apply prophylactic interventions at optimal time;
• To propose closer follow-up.
Interventions for the Prevention of Preeclampsia

- Improved socio-economic conditions (perinatal policy)
- Structured prenatal counselling and follow-up
- Potential prophylactic therapies
  - Antiplatelet agents (aspirin)
    - Inhibit thromboxane-mediated vasoconstriction and pathological blood coagulation in the placenta
  - Low-molecular weight heparin

Clinical Intervention and Treatment

Early recognition, key to prevention and treatment.

- The objective is to prolong pregnancy whenever possible to permit fetal lung maturity while preventing progression to severe disease;
- Antiplatelet prophylactic therapy (aspirin);
- Antihypertensive therapy (>160/100 mmHg: methyldopa, labetalol, nifedipine);
- The definitive treatment is delivery;
- Eclampsia: emergency; High-risk morbidity/mortality.
PE can be Prevented by ASA

Prevention of Preeclampsia and Intrauterine Growth Restriction With Aspirin Started in Early Pregnancy
A Meta-Analysis


Trials using ASA before 16 weeks RR: 0.47

Trials using ASA after 16 weeks RR: 0.81

- 27 trials including 11,348 women

"... current evidence indicates that low-dose aspirin started in early pregnancy may reduce the incidence of PE, IUGR and PTB in women identified at moderate or high risk for PE."


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Clinical Maternal Risk Factors

Recommendations for determination of HDP risk at 1st visit

- **Intensity of monitoring**
  - Ex.: Maternal age > 40 yrs; nulliparity, woman’s own birth weight, pre-existing chronic hypertension, diabetes, previous PE, BMI > 30.

- **Very few published data of performance**
  - In one recent study by Poon et al. (J Hum Hypert (2010) 24 : 104-10), logistic regression analysis of maternal characteristics shows:
    - At a false positive rate of 5 %, detection rates:
      - for early PE: 37%; late PE: 29 %; GH: 20%.
    - Screening suggested by NICE (Natl. Inst. for Clinical Excellence): (essentially treats each factor as a separate screening test) false positive rate of 64 %; detection rate of 89, 93 and 85 % , respectively.

Maternal Risk Factors for HDP as *a priori* Risk

- Elements from maternal history may serve to determine *a priori* risk using a multivariate approach.
  - Ethnicity, maternal age, woman’s own birth weight, prior PE, BMI...

- As for screening for Trisomy 21, patient specific risk may be derived by multiplying *a priori* risk by the likelihood ratio associated with selected biochemical and biophysical parameters.

  Cuckle (2011) Placenta 32: S42-S48
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Potential Biomarkers for PE – Summary

<table>
<thead>
<tr>
<th>Marker</th>
<th>Altered levels during</th>
<th>Assessed in combination with</th>
<th>Associated with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before onset of PE</td>
<td>After onset of PE</td>
<td>Ultrasound markers Maternal characteristics</td>
</tr>
<tr>
<td></td>
<td>(1st /2nd trim.)</td>
<td>(3rd trim.)</td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>↓</td>
<td>↓</td>
<td>UA PI</td>
</tr>
<tr>
<td>PIGF</td>
<td>↓</td>
<td>↓</td>
<td>sFlt-1;PIGF; PAPP-A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ethnicity, MAP, weight, history CH, smoking, Conception</td>
</tr>
<tr>
<td>aFlt-1</td>
<td>↑</td>
<td>↑</td>
<td>PIGF; aEng;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GH, GDM, HELLP, FD, IUGR, stillbirth, T13</td>
</tr>
<tr>
<td>sEndog</td>
<td>↑</td>
<td>↑</td>
<td>PIGF; aFlt-1; PAPP-A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>weight</td>
</tr>
<tr>
<td>AFP</td>
<td>↑</td>
<td>↑</td>
<td>hCG</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>GH, HELLP, FD, IUGR, SGA,</td>
</tr>
<tr>
<td>hCG</td>
<td>↓</td>
<td>↑</td>
<td>AFP, PAPP-A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GH, GDM, HELLP, PTB, FL, SGA, T21, Neural tube defects</td>
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<tr>
<td>Inhibin A</td>
<td>↑</td>
<td>↑</td>
<td>PAPP-A, activin A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ethnicity, parity, BMI</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>↓</td>
<td>↑</td>
<td>sEng, PIGF, PP-13, inhibin A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight, BMI, MAP, ethnicity, CH, parity, age conception, fetal CRL, smoking</td>
</tr>
</tbody>
</table>

From Giguère et al. 2011 submitted
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<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before onset of PE (1st/2nd trim.)</td>
<td>After onset of PE (3rd trim.)</td>
<td>Other biochem. markers</td>
</tr>
<tr>
<td>Cell free fetal DNA</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Cell free fetal RNA</td>
<td>↑</td>
<td>↑</td>
<td></td>
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<tr>
<td>P-selectin</td>
<td>↑</td>
<td>↑</td>
<td>UtA PI</td>
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<tr>
<td>VCAM</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>PP-13</td>
<td>↓</td>
<td>↓</td>
<td>PAPP-A UtA PI</td>
</tr>
<tr>
<td>ADAM-12</td>
<td>↓</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Visfatin</td>
<td>↑</td>
<td>↑</td>
<td></td>
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<tr>
<td>PTX3</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

From Giguère et al. 2011 submitted

### Challenges with Measurement of Biochemical Markers to Predict PE Early in Pregnancy

- Concentration of marker changes during pregnancy;
  - Necessity to express results in Multiple of Median – MoM
- Lack of standardized methods and reference materials, commercial availability and automation, CE label;
- Overlap of results between normal pregnancy and HDP.
Potential Biomarkers for PE

Which of the putative biomarkers
– Are predictive of preeclampsia and other adverse pregnancy outcomes?
– Have demonstrated clinical utility?

Summary of Criteria for Screening

- **Condition**
  - Important health problem;
  - Natural history understood;
  - Recognizable latent or early symptomatic stage;

- **Diagnosis**
  - Suitable diagnostic test available, safe and acceptable to the population concerned;
  - Agreed policy, based on respectable test findings and national standards, as to whom to regard as patients;
  - Whole process, continuing;

- **Treatment**
  - Accepted and established treatment / intervention for individuals identified as having the disease or pre-disease condition;
  - Facilities for treatment should be available;

- **Cost**
  - Cost of case-finding (including diagnosis and treatment) should be economically balanced in relation to possible expenditure on medical care.
### Summary of Criteria for Evaluation of Screening Tests

(Holland et al. WHO (2006))

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplicity</td>
<td>The test should be simple to perform, easy to interpret and, where possible, capable of use by paramedics and other personnel.</td>
</tr>
<tr>
<td>Acceptability</td>
<td>Since participation in screening is voluntary, the test must be acceptable to those undergoing it.</td>
</tr>
<tr>
<td>Accuracy</td>
<td>The test must give a true measurement of the condition or symptom under investigation.</td>
</tr>
<tr>
<td>Cost</td>
<td>The expense of the test must be considered in relation to the benefits of early detection of the disease.</td>
</tr>
<tr>
<td>Repeatability</td>
<td>The test should give consistent results in repeated trials.</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>The test should be capable of giving a positive finding when the individual being screened has the condition being sought.</td>
</tr>
<tr>
<td>Specificity</td>
<td>The test should be capable of giving a negative finding when the individual being screened does not have the condition being sought.</td>
</tr>
</tbody>
</table>

### Systematic Reviews of Combinations of Biomarkers

- Until now, numerous systematic reviews have been unable to demonstrate a single biochemical marker capable of detecting, early in pregnancy, those women susceptible to develop PE.
  
  

- Because of the heterogeneous nature of PE, a combination of independent biomarkers, each reflecting a different pathophysiological process, should increase the likelihood to derive suitable predictive algorithms.

- Indeed, combinations of biochemical and ultrasonographic markers into algorithms derived by multivariate analysis improve the performance of early prediction of PE.

- From the perspective of integrative medicine, there is a clear need for prospective large-scale studies with rigorous study design criteria to determine the clinical usefulness of combinations of biomarkers in different geographic and healthcare environments.


Clinical Screening Strategies for PE

Existing Clinical Investigations

- Dating, Nuchal translucency
- Trisomy screening
- Trisomy screening (Ultrasound)
- Fetal Development (Ultrasound)
- Screening for Gestational Diabetes
- Trisomy screening (Biochemistry)
- Fetal Development (Ultrasound)

Development of Preeclampsia

Screening Strategies

1st trimester:
- Prediction of HDP / PE
- (Preventive treatment for high-risk women)

2nd trimester:
- Late identification of imminent HDP / PE
- (Closer follow-up of high-risk women)

PREGNANCY

0 40

(1st trim.)

(2nd trim.)

(3rd trim.)

10 -13
14 -17
20
24 -28
30, 32, 36
(depending)

Clinical screening strategies for PE

Benefits

- To develop an approach using biomarkers to detect, as early as possible, women at risk of developing preeclampsia with a greater performance than that of conventional methods in order to offer, in a targeted manner, prophylactic interventions, specific surveillance and / or closer management.

Risks

- False positive results creating anxiety and possibly unnecessary interventions
- False negative results causing false reassurance or reduction of surveillance.
Challenges

• What should be the expected performance to reach clinical utility?

• Will the same factors for calculation of *a priori* risk and biomarkers (biochemical / biophysical) perform uniformly in different environments?

• Commercial availability of best performing markers?
• Cost-effectiveness studies?
• Optimal time to screen?

In Summary

• No individual biochemical or biophysical markers have met the criteria for a screening test.

• Maternal history & risk factors, have as a whole poor predictive value; with some guidelines, 2/3 of the patients would be falsely classified as high risk.

• A growing body of evidence suggests that the combination of maternal factors (BMI, age, parity, ethnicity, past history,...) with serum markers and UtA Doppler indices may identify early in pregnancy women at risk of developing preeclampsia.
In Summary

There is a need for large-scale prospective studies to determine the usefulness of multivariate risk-prediction algorithms early in pregnancy, in different populations.

This may lead to the implementation of an efficient screening procedure to identify women at risk for PE who would benefit from early targeted interventions.

References

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