First Trimester Screening for Early Onset Preeclampsia

Terrence W. Hallahan, Ph.D.
Laboratory Director
PerkinElmer Labs | NTD
Early Onset Preeclampsia – Less Common – More Severe

- All Preeclampsia
- Perinatal Death
- Severe Morbidity

- Early Onset
- Late Onset
First of its kind serum screening test for **early onset preeclampsia**

Quantitates demographic and historical factors in a risk algorithm
- Body mass index (BMI)
- Ethnicity
- Patient history, including
  - Previous delivery >=24 weeks
  - Maternal and personal history of preeclampsia
  - History of chronic hypertension

Measures three biochemical markers in maternal serum
- PAPP-A (pregnancy-associated plasma protein-A)
- PIGF (placental growth factor)
- AFP (alpha fetoprotein)

Two biophysical markers
- MAP
- UtAD-PI
Nonpregnancy

- Rapid rise and fall in uterine artery flow velocity during systole and a “notch” in the descending waveform in early diastole

(UtAD) Helps Demonstrate Vascular Resistance in Uterine Arteries in Women With Preeclampsia

Evolving UtAD in Nonpregnant and Pregnant Women

Nonpregnant Patient

Normal First Trimester

Normal Second Trimester

Abnormal UtAD Demonstrating High Resistance

The blood pressure (BP) should be measured in both arms simultaneously.

Series of recordings at 1-minute intervals should be taken until readings become stable.

The measurement from the arm with the higher final pressure should be used for risk assessment.

Mean Arterial Pressure

There is evidence that in a high proportion of pregnancies predisposed to develop pre-eclampsia the maternal mean arterial pressure (MAP) is increased at 11 to 13 weeks.

MAP = Diastolic BP + (Systolic BP – Diastolic BP) / 3

Figure 1: Squares are observed medians. Solid lines show regressed values by GA.

Regression Formula Coefficients

<table>
<thead>
<tr>
<th></th>
<th>PIGF</th>
<th>PAPP-A</th>
<th>AFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>In-linear</td>
<td>In-In</td>
<td>In-linear</td>
</tr>
<tr>
<td>Slope</td>
<td>0.2144</td>
<td>4.9164</td>
<td>0.3096</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.2236</td>
<td>-4.7076</td>
<td>-1.2407</td>
</tr>
</tbody>
</table>
Biomarker MoM Values Found in PerkinElmer Labs/NTD Validation Studies for Early Onset Preeclampsia

Markers

MoM Values:
- PIGF: 0.83
- PAPP-A: 0.60
- AFP: 1.39
- MAP: 1.14
- UtAD-PI: 1.60

Number of EOPE Cases: 31
Quantitative Risk Assessment of Early Onset Preeclampsia:
Combined Biochemical and Biophysical Markers
<table>
<thead>
<tr>
<th></th>
<th>Biochemistry + History</th>
<th>Biochemistry + History + MAP</th>
<th>Biochemistry + History + UtAD-PI</th>
<th>Biochemistry + History + MAP + UtAD-PI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers</strong></td>
<td>PIGF, PAPP-A, AFP</td>
<td>PIGF, PAPP-A, AFP, MAP</td>
<td>PIGF, PAPP-A, AFP, MAP, UtAD-PI</td>
<td>PIGF, PAPP-A, AFP, MAP, UtAD-PI</td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td>10 weeks, 0 days – 13 weeks, 6 days</td>
<td>11 weeks, 1 day – 13 weeks, 6 days</td>
<td>11 weeks, 1 day – 13 weeks, 6 days</td>
<td>11 weeks, 1 day – 13 weeks, 6 days</td>
</tr>
<tr>
<td><strong>Detection rate</strong></td>
<td>60%</td>
<td>77%</td>
<td>82%</td>
<td>91%</td>
</tr>
<tr>
<td><strong>Requirements</strong></td>
<td>• 5 ml maternal serum in SST (red/grey speckled or gold) tube or red top tube</td>
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<td>• 5 ml maternal serum in SST tube, or red top tube</td>
</tr>
</tbody>
</table>
Early Preeclampsia Screening Improves Clinical Focus

Women with early onset preeclampsia

Before Testing: 1/200

Biochemistry Only: 1/14

Biochemistry + MAP: 1/11

Biochemistry + UtAD-PI: 1/10.5

Biochemistry + MAP + UtAD-PI: 1/9.5
Positive Predictive Value and Negative Predictive Value of PreeclampsiaScreen™ | T1

<table>
<thead>
<tr>
<th>Protocol</th>
<th>PPV (1 in...)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry only</td>
<td>14</td>
<td>7.0</td>
<td>99.73</td>
</tr>
<tr>
<td>Biochemistry + MAP</td>
<td>11</td>
<td>9.0</td>
<td>99.84</td>
</tr>
<tr>
<td>Biochemistry + UtAD-PI</td>
<td>10.5</td>
<td>9.5</td>
<td>99.88</td>
</tr>
<tr>
<td>Biochemistry + MAP + UtAD-PI</td>
<td>9.5</td>
<td>10.5</td>
<td>99.94</td>
</tr>
</tbody>
</table>
### Sample Report: Increased Risk for Early Onset Preeclampsia

**Identifying Information**

#### PerkinElmer Labs
- **NTD**
- **Physician ID #: 24328**
- **Physician Tel #: (000) 000-0000**
- **OB SPECIALISTS**
- **100 ANYWHERE ST**
- **MELVILLE, NY 11747**

#### Preeclampsia Screen™ | T1 Report

**Patient Name:** INCRIK, MAPPI
**Patient ID #:** 13PE0001084
**U/S Date:** 02/04/13
**GA @ U/S:** 11w4d
**Client ID #:**
**Draw Date:** 02/04/13
**GA @ Draw:** 11w4d (CRL)
**Date of Birth:** 06/10/83 (age at EDC: 30)
**CRL (mm):** 50
**Multi. Preg:** No
**GA @ MAP:** 11w4d
**Smoker:** No
**MAP Date:** 02/04/13
**Date Received:** 02/06/13
**Report Date:** 02/07/13

<table>
<thead>
<tr>
<th>Mean Anterior Pressure (MAP)</th>
<th>110 mm Hg</th>
<th>1.24</th>
<th>99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine Artery Doppler PI (UAAD-PI)</td>
<td>3.2</td>
<td>1.09</td>
<td>60</td>
</tr>
</tbody>
</table>

**Risk Table**

<table>
<thead>
<tr>
<th>Prior Risk Factors</th>
<th>1 in 10</th>
<th>1 in 97</th>
<th>1 in 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Risk Factors</td>
<td><strong>INCREAS ED RISK</strong></td>
<td>---------</td>
<td>---------</td>
</tr>
</tbody>
</table>

**Early Onset Preeclampsia Risk**

**Before**

- **Decreased Risk Zone**
- **Increased Risk Zone**

**After**

- **Risk:** 1

**Caution:**

- **Recommend immediate follow-up with increased monitoring.**

**Comments:**

- **Jonathan B. Carmichael, Ph.D.**
- **Laboratory Director**
- **PerkinElmer Labs NTD**

- **Terrence W. Mallehe, Ph.D.**
- **Laboratory Director**
- **PerkinElmer Labs NTD**

_**CAUTION:** This test was developed and its performance characteristics determined by PerkinElmer Labs NTD. It has not been cleared or approved by the U.S. Food and Drug Administration. The methods and performance characteristics have been reviewed and approved by the New York State Department of Health. These results do not indicate the possibility that the pregnancy may be associated with birth defects or pregnancy complications including preeclampsia, pre-term delivery and low birth weight. The report contains increased risk information. The recipient shall not disclose the information unless required to provide appropriate medical care without the permission of the patient._

- _The outcome of the test and the results provided in this report are dependent on the accuracy of the demographic and ultrasound information provided. The referring physician should refer to the ultrasound information obtained from a properly trained sonographer, including verification of the gestational age._
Sample Report: Increased Risk for Early Onset Preeclampsia

Prior Risk Factors

- Ethnicity: Afr. Amer./Carib.
- Previous delivery >24 weeks: No
- Fam Hx Preeclampsia: No
- Previous Preeclampsia: No
- Chronic Hypertension: No
- Weight: 138 lbs
- Height: 5' 2''
- BMI: 25.24
**Sample Report: Increased Risk for Early Onset Preeclampsia**

### Test Parameters

#### Serum Markers

<table>
<thead>
<tr>
<th>Serum Markers</th>
<th>Value</th>
<th>MoM</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIGF</td>
<td>30.2 pg/ml</td>
<td>0.62</td>
<td>10</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>2649 mU/l</td>
<td>1.19</td>
<td>60</td>
</tr>
<tr>
<td>AFP</td>
<td>10.12 U/ml</td>
<td>0.95</td>
<td>50</td>
</tr>
</tbody>
</table>

#### Physical Markers

<table>
<thead>
<tr>
<th>Physical Markers</th>
<th>Value</th>
<th>MoM</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Pressure (MAP)</td>
<td>110 mm Hg</td>
<td>1.24</td>
<td>90</td>
</tr>
<tr>
<td>Uterine Artery Doppler PI (UtAD-PI)</td>
<td>3.2</td>
<td>1.09</td>
<td>60</td>
</tr>
</tbody>
</table>

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**Interpretation:** **INCREASED RISK FOR EARLY ONSET PREECLAMPSIA**

**Risk Table:**

- Early Onset Preeclampsia: 1 in 10
  - Before: 1 in 10
  - After: 1 in 24

**Comments:**

- Recommend immediate follow-up with increased monitoring.

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Sample Report: Increased Risk for Early Onset Preeclampsia

**Increased Risk for Early Onset Preeclampsia**

Risk Table

<table>
<thead>
<tr>
<th>Risk Before Screening</th>
<th>Risk After Screening</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 87</td>
<td>1 in 18</td>
<td><strong>INCREASED RISK</strong></td>
</tr>
</tbody>
</table>

Early Onset Preeclampsia Risk

Before

Risk: 1 in 10,000

After

Risk: 1 in 100
What Do You Do With Patients Identified As Increased Risk for Early Onset Preeclampsia?
Severe Preeclampsia - severe hypertension (BP of at least 160 mmHg systolic or 110 mmHg diastolic or 105 mmHg diastolic), severe proteinuria (at least 2, 3, or 5 g of protein in 24 h or 3 on dipstick), reduced urinary volume (less than 400 to 500 mL in 24 h), neurologic disturbances such as headache and visual perturbations, upper abdominal pain, pulmonary edema, impaired liver function tests, high serum creatinine, low platelet count.
Low-dose aspirin was defined as 50–150 mg of acetylsalicylic acid (ASA) daily, alone or in combination with < 300 mg of dipyridamole, another antiplatelet agent. Preterm preeclampsia is defined by delivery of women with preeclampsia before 37 completed weeks of gestation.
For asymptomatic pregnant women who are at high risk for preeclampsia prescribe low-dose (81 mg/d) aspirin after 12 weeks gestation

TABLE 2. CLINICAL RISK ASSESSMENT FOR PREECLAMPSIA*

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Factors</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High†</td>
<td>History of preeclampsia, especially when accompanied by an adverse outcome Multifetal gestation Chronic hypertension Type 1 or 2 diabetes Renal disease Autoimmune disease (i.e., systemic lupus erythematosus, antiphospholipid syndrome)</td>
<td>Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors</td>
</tr>
<tr>
<td>Moderate‡</td>
<td>Nulliparity Obesity (body mass index &gt;30 kg/m²) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (African American race, low socioeconomic status) Age ≥35 y Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, &gt;10 y pregnancy interval)</td>
<td>Consider low-dose aspirin if the patient has several of these moderate-risk factors§</td>
</tr>
<tr>
<td>Low</td>
<td>Previous uncomplicated full-term delivery</td>
<td>Do not recommend low-dose aspirin</td>
</tr>
</tbody>
</table>

* Includes only risk factors that can be obtained from the patient medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.
† Single risk factors that are consistently associated with the greatest risk for preeclampsia. The preeclampsia incidence rate would be approximately 8% in a pregnant woman with 1 of these risk factors (1, 5).
‡ A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk for preeclampsia. These risk factors are independently associated with moderate risk for preeclampsia, some more consistently than others (1).
§ Moderate-risk factors vary in their association with increased risk for preeclampsia.

Screening/Treatment Parameters based on NICE Parameters

- 0.5% Incidence of EOPE
- 44% Screen Positive Rate
- 77% Detection Rate
- 90% Reduction in EOPE w/ LDA

69% Theoretical Reduction in Incidence of EOPE

347/500 EOPE cases prevented
Screening for Early Onset Preeclampsia in 100,000 Patients

 EOPE Screening/Treatment Parameters

- 0.5% Incidence of EOPE
- 5% Screen Positive Rate
- 91% Detection Rate
- 90% Reduction in EOPE w/ LDA

82% Theoretical Reduction in Incidence of EOPE

410/500 EOPE cases prevented
Prediction and prevention of early onset pre-eclampsia: The impact of aspirin after first trimester screening

<table>
<thead>
<tr>
<th>Early Onset Preeclampsia Screening</th>
<th>Observational</th>
<th>Interventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>3066</td>
<td>2717</td>
</tr>
<tr>
<td>Testing</td>
<td>Map, U1AD, PAPP-A, Demographics</td>
<td>Map, U1AD, PAPP-A, Demographics</td>
</tr>
<tr>
<td>Screening Results</td>
<td>2760 Screen (-)</td>
<td>306 Screen (+)</td>
</tr>
<tr>
<td>Treatment</td>
<td>1 EOPE</td>
<td>11 EOPE</td>
</tr>
<tr>
<td>Outcomes</td>
<td>92% Detection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seqential Cohorts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Early onset preeclampsia is a serious complication of pregnancy</td>
</tr>
<tr>
<td>• Associated with significant morbidity and mortality</td>
</tr>
<tr>
<td>• Number of therapeutic options for prevention of preeclampsia in high-risk women under investigation</td>
</tr>
<tr>
<td>• A variety of risk factors for preeclampsia are recognized</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>• Opportunity to change treatment paradigms with an effective screening protocol for early onset PE</td>
</tr>
</tbody>
</table>
First Trimester Screening for Early Onset Preeclampsia

Thank You
Why Not Just Give Aspirin to All Pregnant Women?

- 90% Reduction in EOPE
- However, although aspirin is considered generally safe during pregnancy potentials risks include;
- Aspirin has not been formally assigned to pregnancy category by the FDA. However, aspirin is considered to be in pregnancy category D by the FDA if full dose aspirin is taken in the third trimester.