A New Concept of Prenatal Care: Turning The Pyramid Upside Down

Prof. Dr. N. Cenk SAYIN
Trakya University, Faculty of Medicine
Obstetrics & Gynecology
Perinatology
Edirne
Prenatal Care

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
Prenatal Care

12 w

12-34 w Specialist

22 w

32 or 37 w

41 w

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
11-13 w Scan

- Patient specific risk
  - Fetal abnormalities
  - Preeclampsia
  - Fetal growth restriction
  - Miscarriage
  - Stillbirth
  - Preterm delivery
  - Gestational DM
  - Macrosomia
Prenatal Care

Table 1 WHO principles of screening

| Condition | The condition sought should be an important health problem. There should be a recognisable latent or early symptomatic stage. The natural history of the condition, including development from latent to declared disease, should be adequately understood. |
| Test | There should be a suitable test or examination. The test should be acceptable to the population. |
| Treatment | There should be an accepted treatment for patients with recognised disease. |
| Screening program | Facilities for diagnosis and treatment should be available. There should be an agreed policy on whom to treat as patients. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. Case finding should be a continuing process and not a ‘once and for all’ project. |

- Preeclampsia
- Fetal growth restriction
- Miscarriage
- Stillbirth
- Preterm birth
- Gestational DM
- Macrosomia

Prediction → Mathematical models
Prenatal Care

• Smoking
  – Low birth weight
  – Preterm birth
  – Stillbirth

• Advanced maternal age
  – Miscarriage
  – Preterm birth
  – Low birth weight

• High BMI
  – Preterm birth
  – Stillbirth
  – Macrosomia

• Gender

• Parity

• Familial risk factors
  – PE
  – DM

• Conception

• Medical history
Prenatal Care

PAPP-A

- Low birth weight
- Preterm birth
- Pregnancy induced HT
- Preeclampsia (early preeclampsia)

fβ-hCG

- Miscarriage
- Hypertensive disorders of pregnancy

D'Antonio F, Prenat Diagn 2013;33:839-47
Anderson UD, Placenta 2012;33:S42-7
Van Ravenswaaij R, Prenatal Diagn 2011;31:50-7
Huang T, Prenatal Diagn 2010;30:471-7
Ong CY, BJOG 2000;107:1265-70
11-13 w Scan ➔ Goals

- **Fetal abnormalities**
  - Preeclampsia
  - Fetal growth restriction
  - Miscarriage
  - Stillbirth
  - Preterm delivery
  - Gestational DM
  - Macrosomia
Fetal Aneuploidy Scanning

1970
Maternal age

1980
Serum biochemistry + Detailed US

1990
1st trimester

Nicolaides KH, Fetal Diagn Ther 2011;31:3-6
Fetal Aneuploidy Scanning

Combined test- Tri 21 and other major aneuploidies ~ **90%**
false (+) 5%

12\textsuperscript{th} w

1) 9-10 w biochemistry $\rightarrow$ 12 w US $\rightarrow$ **93-94%**

2) PAPP-A 9. w $\rightarrow$ 12. w US $\rightarrow$ fβ-hCG ≥12. w $\rightarrow$ **95%**

<table>
<thead>
<tr>
<th></th>
<th>DR</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>fβ-hCG+PAPP-A</td>
<td>62%</td>
<td>4.7%</td>
</tr>
<tr>
<td>fβ-hCG+PAPP-A+PlGF</td>
<td>69%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Biochem.+NT</td>
<td>89%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Biochem.+NT+PlGF</td>
<td>88%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

46% reduction

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
Nicolaides KH, Fetal Diagn Ther 2011;31:7-15
Nicolaides KH, Fetal Diagn Ther 2011;31:3-6
# Fetal Aneuploidy Scanning

<table>
<thead>
<tr>
<th></th>
<th>Aneuploidi</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent nasal bone</td>
<td>60%</td>
<td>2.5%</td>
</tr>
<tr>
<td>DV reverse “a”</td>
<td>66%</td>
<td>3%</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>55%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Detection rate **93-96%** — false (+) **2.5%**
11-13 week US Scan

1. Detectable
   - Body-stalk anomaly
   - Anencephaly
   - Alobar holoprosencephaly
   - Omphalocele, gastroschisis
   - Megacystis

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
Nicolaides KH, Prenat Diagn 2011;31:3-6
Syngelaki A, Prenat Diagn 2011;31:90-102
2. Potentially detectable

- Diaphragmatic hernia
- Major cardiac defects
- Lethal skeletal dysplasias
- Facial cleft
- Renal agenesis, multicystic kidney

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
Nicolaides KH, Prenat Diagn 2011;31:3-6
Sygelaki A, Prenat Diagn 2011;31:90-102
3. Undetectable

- Microcephaly
- Corpus callosum agenesis
- Semilobar holoprocencephaly
- Hypoplasia of the cerebellum or vermis
- CCAM, pulmonary sequestration
- Bowel obstruction

- Hydrocephaly
- Achondroplasia
- Renal anomalies
- Fetal tm (nasopharynx, cardiac, teratoma)

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
Nicolaides KH, Prenat Diagn 2011;31:3-6
Syngelaki A, Prenat Diagn 2011;31:90-102
11-13 week US Scan

11-13 w US non-chromosomal anomaly?
Rand. study: screening by “check-list” (n=35 792)

<table>
<thead>
<tr>
<th>12 w</th>
<th>18 w</th>
</tr>
</thead>
<tbody>
<tr>
<td>38%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Detection rate of major anomaly → similar

Cardiac anomaly (11-13 w)
- 1/2 – DORV, hypoplastic left heart, TGA
- 1/3 – AVSD, coarctation of aorta, TOF, pulmonary atresia
- None – VSD, Ebstein, AS, PS, Tricuspid atresia, cardiac tm

Saltvedt S, BJOG 2006;113:664-74
Syngelaki A, Prenat Diagn 2011;31:90-102
11-13 w Scan ➔ Goals

- Fetal abnormalities

- **Preeclampsia**
  - Fetal growth restriction
  - Miscarriage
  - Stillbirth
  - Preterm delivery
  - Gestational DM
  - Macrosomia
Preeclampsia

- Early PE: 0.4%, 1:250
- Middle PE: 0.8%, 1:125
- Late PE: 1.6%, 1:63

- >38 w: 1.6%, 1:63
Preeclampsia

- Late PE
  - >38 w
  - 1,6%
  - 1:63

- Early PE
  - 34-37w
  - 0,8%
  - 1:125

- Middle PE
  - 0,4%
  - 1:250
Preeclampsia

Biochemical tests for the detection and prediction of PE

- Renal dysfunction
- Endothelial dysfunction
- Metabolic status
- Oxidative stress
- Placenta-derived factors
- Hemolysis and inflammatory markers

Telang MA, Placenta 2013;34:2-8
**Preeclampsia**

**Angiogenic factors and receptors**

- PIGF
- VEGF
- sVEGF-1
- Soluble fms-like tyrosine kinase-1 (sFlt-1)
- PP13
- PAPP-A
- hCG
- Soluble endoglin (sEng)
- Inhibin-A
- Activin-A
- AFP
- CRF, CRF-BP
- Leptin
- IGF-1, IGFBP-1
- Homosistein
- Asymmetric dimethylarginin (ADMA)
- Maternal serum fetal erythroblast, cell-free fetal DNA
- Fetal hemoglobin (HbF)
- Alfa-1 microglobulin (A1M)
- Fibronectin
- TGF-3, TGF-receptors
- Hyperglycosylated human chorionic gonadotrophin (hCG-h)
- ...
Preeclampsia

Other markers

- Marinobufagenin
- Neurokinin B
- Porphyrin
- P-type inositolphosphoglycans
- Uric acid metabolites
- Angiopoietin-2
- ADAM 12
- Thrombocyte activation index
- Anti-protease-activated receptor antibody
- miRNAs in maternal serum
- Adenosine diphosphatase
- Fetal 2,3-biphosphoglycerate mutase
- Calcineurin
- Glucoroniated dihydroxyeicosatrienoic acids
- Histidine and its methyl derivative
- High temperature requirement A (HtrA) polymorphisms
- HIF-1a
- Human adrenomedullin peptides

Today no diagnostic test in clinical practice

Telang MA, Placenta 2013;34:2-8
Low-dose aspirin (75 mg/d) initiated in early pregnancy (<16th week) halves the incidence of preeclampsia, preterm birth and IUGR.

Roberge S, Ultrasound Obstet Gynecol 2013;41:491-9
Bujold E, Obstet Gynecol 2010; 116: 402-14
National Collaborating Centre for Women’s and Children’s Health. NICE clinical guideline 2010;vol.107
Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks

L. C. Y. POON, R. AKOLEKAR, R. LACHMANN, J. BETA and K. H. NICOLAIDES

Harris Birthright Research Centre for Fetal Medicine, King’s College Hospital, London, UK

Table 1 Maternal characteristics in the four outcome groups

<table>
<thead>
<tr>
<th>Maternal variable</th>
<th>Unaffected (n = 201)</th>
<th>Early pre-eclampsia (n = 26)</th>
<th>Late pre-eclampsia (n = 90)</th>
<th>Gestational hypertension (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>32.1 (28.7–35.5)</td>
<td>32.7 (27.4–38.7)</td>
<td>31.5 (26.3–36.3)</td>
<td>33.4 (30.1–35.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1 (22.9–28.7)</td>
<td>27.2 (23.7–32.0)</td>
<td>27.1 (23.8–33.4)</td>
<td>26.7 (24.2–31.4)</td>
</tr>
<tr>
<td>Racial origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>139 (69.2)</td>
<td>11 (42.3)*</td>
<td>40 (44.4)†</td>
<td>63 (74.1)</td>
</tr>
<tr>
<td>Black</td>
<td>40 (19.9)</td>
<td>11 (42.3)†</td>
<td>38 (42.2)‡</td>
<td>17 (20.0)</td>
</tr>
<tr>
<td>Indian or Pakistani</td>
<td>15 (7.5)</td>
<td>2 (7.7)</td>
<td>7 (7.8)</td>
<td>0</td>
</tr>
<tr>
<td>Chinese or Japanese</td>
<td>2 (1.0)</td>
<td>0</td>
<td>1 (1.1)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Mixed</td>
<td>5 (2.5)</td>
<td>2 (7.7)</td>
<td>4 (4.4)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>60 (29.9)</td>
<td>9 (34.6)</td>
<td>39 (43.3)</td>
<td>31 (36.5)</td>
</tr>
<tr>
<td>Miscarriage/termination before 24 weeks</td>
<td>19 (9.5)</td>
<td>4 (15.4)</td>
<td>20 (22.2)*</td>
<td>16 (18.8)</td>
</tr>
<tr>
<td>Parous—no previous PE</td>
<td>115 (57.2)</td>
<td>6 (23.1)†</td>
<td>22 (24.4)‡</td>
<td>29 (34.1)†</td>
</tr>
<tr>
<td>Parous—previous PE</td>
<td>7 (3.5)</td>
<td>7 (26.9)†</td>
<td>9 (10.0)</td>
<td>9 (10.6)*</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>16 (8.0)</td>
<td>0</td>
<td>6 (6.7)</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td>Family history of PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>6 (3.0)</td>
<td>3 (11.5)</td>
<td>11 (12.2)*</td>
<td>8 (9.4)</td>
</tr>
<tr>
<td>Sister</td>
<td>3 (1.5)</td>
<td>3 (11.5)</td>
<td>1 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Conception</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>193 (96.0)</td>
<td>23 (88.5)</td>
<td>86 (95.6)</td>
<td>82 (96.5)</td>
</tr>
<tr>
<td>Ovulation induction</td>
<td>7 (3.5)</td>
<td>2 (7.7)</td>
<td>3 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>In-vitro fertilization</td>
<td>1 (0.5)</td>
<td>1 (3.8)</td>
<td>1 (1.1)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>194 (96.5)</td>
<td>21 (80.8)*</td>
<td>85 (94.4)</td>
<td>82 (96.5)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>1 (0.5)</td>
<td>4 (15.4)†</td>
<td>4 (4.4)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (1.0)</td>
<td>0</td>
<td>0</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Anti-phospholipid syndrome/thrombophilia</td>
<td>3 (1.5)</td>
<td>1 (3.8)</td>
<td>1 (1.1)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Medication during pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>181 (90.0)</td>
<td>22 (84.6)</td>
<td>83 (92.2)</td>
<td>73 (85.9)</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>2 (1.0)</td>
<td>2 (7.7)*</td>
<td>2 (2.2)</td>
<td>0</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3 (1.5)</td>
<td>1 (3.8)</td>
<td>0</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (7.0)</td>
<td>1 (3.8)</td>
<td>5 (5.6)</td>
<td>7 (8.2)</td>
</tr>
</tbody>
</table>
Table 2  Data for each marker in the four outcome groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Early pre-eclampsia</th>
<th>Late pre-eclampsia</th>
<th>Gestational hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoM (mmHg)</td>
<td>0.99 (0.95–1.05)</td>
<td>1.16 (1.08–1.25)*</td>
<td>1.09 (1.02–1.13)*</td>
<td>1.08 (1.02–1.14)*</td>
</tr>
<tr>
<td>Lowest uterine artery PI</td>
<td>84.2 (80.5–89.5)</td>
<td>98.0 (91.8–106.5)</td>
<td>93.8 (87.0–98.7)</td>
<td>93.3 (86.5–98.3)</td>
</tr>
<tr>
<td>MoM (Unit)</td>
<td>1.05 (0.85–1.31)</td>
<td>1.65 (1.31–1.82)*</td>
<td>1.26 (0.92–1.55)†</td>
<td>1.12 (0.87–1.38)</td>
</tr>
<tr>
<td>PAPP-A (MoM)</td>
<td>1.00 (0.69–1.45)</td>
<td>0.62 (0.42–1.11)†</td>
<td>0.96 (0.61–1.33)</td>
<td>0.86 (0.62–1.39)</td>
</tr>
<tr>
<td>PAPP-A (mU/L)</td>
<td>2.79 (1.78–4.57)</td>
<td>2.63 (0.95–3.36)</td>
<td>2.79 (1.57–4.32)</td>
<td>2.01 (1.52–3.45)</td>
</tr>
<tr>
<td>Placental growth factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoM (pg/mL)</td>
<td>0.96 (0.75–1.31)</td>
<td>0.59 (0.49–0.78)*</td>
<td>0.85 (0.55–1.03)*</td>
<td>0.93 (0.69–1.18)</td>
</tr>
<tr>
<td>Inhibin-A (MoM)</td>
<td>0.98 (0.73–1.41)</td>
<td>1.54 (0.94–2.03)†</td>
<td>1.23 (0.88–1.66)†</td>
<td>1.07 (0.82–1.40)</td>
</tr>
<tr>
<td>Inhibin-A (pg/mL)</td>
<td>245.9 (175.1–340.7)</td>
<td>378.8 (243.6–530.0)</td>
<td>317.2 (217.8–433.3)</td>
<td>254.3 (199.5–333.7)</td>
</tr>
<tr>
<td>Activin-A (MoM)</td>
<td>1.02 (0.77–1.29)</td>
<td>1.12 (0.93–1.61)</td>
<td>1.30 (0.94–1.73)*</td>
<td>1.11 (0.90–1.48)</td>
</tr>
<tr>
<td>Activin-A (pg/mL)</td>
<td>1.80 (1.43–2.43)</td>
<td>2.42 (1.80–2.94)</td>
<td>2.29 (1.82–3.02)</td>
<td>2.00 (1.49–2.66)</td>
</tr>
<tr>
<td>TNF-R1 (MoM)</td>
<td>1.00 (0.87–1.13)</td>
<td>1.10 (0.91–1.32)</td>
<td>1.08 (0.94–1.19)†</td>
<td>1.03 (0.95–1.15)</td>
</tr>
<tr>
<td>TNF-R1 (pg/mL)</td>
<td>1178.2 (1012.4–1299.0)</td>
<td>1293.0 (1096.3–1457.6)</td>
<td>1260.1 (1083.1–1403.9)</td>
<td>1204.3 (1104.7–1408.0)</td>
</tr>
<tr>
<td>Matrix metalloproteinase-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoM (pg/mL)</td>
<td>1.03 (0.71–1.41)</td>
<td>1.23 (0.92–1.71)</td>
<td>1.20 (0.96–1.62)†</td>
<td>1.09 (0.82–1.37)</td>
</tr>
<tr>
<td>Pentraxin-3 (MoM)</td>
<td>0.97 (0.74–1.21)</td>
<td>1.39 (0.82–2.01)</td>
<td>1.12 (0.78–1.62)</td>
<td>1.11 (0.82–1.55)</td>
</tr>
<tr>
<td>Pentraxin-3 (ng/mL)</td>
<td>0.48 (0.38–0.61)</td>
<td>0.57 (0.42–0.87)</td>
<td>0.48 (0.37–0.78)</td>
<td>0.50 (0.39–0.69)</td>
</tr>
<tr>
<td>P-selectin (MoM)</td>
<td>1.02 (0.83–1.24)</td>
<td>1.25 (0.87–1.51)</td>
<td>1.24 (1.00–1.46)*</td>
<td>1.11 (0.95–1.30)†</td>
</tr>
<tr>
<td>P-selectin (ng/mL)</td>
<td>29.7 (22.9–35.0)</td>
<td>35.0 (25.1–40.1)</td>
<td>35.3 (27.0–40.4)</td>
<td>32.7 (27.1–38.7)</td>
</tr>
</tbody>
</table>
Table 3  Performance of screening for pre-eclampsia and gestational hypertension by maternal factors only, a combination of maternal factors with biochemistry, a combination of maternal factors, lowest uterine artery pulsatility index (L-PI) and mean arterial pressure (MAP) and a combination of maternal factors, uterine artery L-PI, MAP and biochemistry as shown by area under receiver–operating characteristics (ROC) curve

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Area under ROC curve (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early pre-eclampsia</td>
</tr>
<tr>
<td>Maternal factors</td>
<td>0.715 (0.652–0.773)</td>
</tr>
<tr>
<td>Maternal factors plus:</td>
<td></td>
</tr>
<tr>
<td>Biochemistry</td>
<td>0.908 (0.863–0.942)</td>
</tr>
<tr>
<td>Uterine artery L-PI, MAP</td>
<td>0.933 (0.892–0.962)</td>
</tr>
<tr>
<td>Uterine artery L-PI, MAP, biochemistry</td>
<td>0.959 (0.925–0.981)</td>
</tr>
</tbody>
</table>

Table 4  Performance of screening for pre-eclampsia and gestational hypertension by maternal factors only, a combination of maternal factors with biochemistry, a combination of maternal factors, lowest uterine artery pulsatility index (L-PI) and mean arterial pressure (MAP) and a combination of maternal factors, uterine artery L-PI, MAP and biochemistry as shown by detection rate for a fixed false-positive rate (FPR)

<table>
<thead>
<tr>
<th>Detection rate (% (95% CI)) for fixed FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pre-eclampsia</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>FPR 5%</td>
</tr>
<tr>
<td>Maternal factors</td>
</tr>
<tr>
<td>Maternal factors plus:</td>
</tr>
<tr>
<td>Biochemistry</td>
</tr>
<tr>
<td>Uterine artery L-PI, MAP</td>
</tr>
<tr>
<td>Uterine artery L-PI, MAP, biochemistry</td>
</tr>
</tbody>
</table>
Preeclampsia

- Maternal characteristics → PE
  - Early PE - 30%
  - Late PE - 20%

- PAPP-A → PE
  - 10-20%

- Algorithm (11-13 w): Biochem. (PAPP-A, fβ-hCG, PP13, PI GF, ADAM12)
  - PE prediction 44% - false (+) 5%
  - Clinical utility is *not* successful, for an adequate screening test additional characteristics are necessary


Poon LC, Ultrasound Obstet Gynecol 2009;33:23-33
Spencer K, Prenat Diagn 2008;28:7-10

Wortelboer EJ, BJOG 2010;117:1384-9
Preeclampsia

• Low risk nullipar 9-13 w
  – ADAM-12, PAPP-A, PP 13, PlGF, sfms-like tyrosine kinase-1, endoglin

  ➤ Preeclamptic women vs controls
    ➤ **ADAM-12** (1.14 vs 1.04 MoM; P=.003)
    ➤ **PAPP-A** (0.94 vs 0.98 MoM; P=.04)
    ➤ **PIGF** (0.83 vs 1.04 MoM; P<.001)

**Model:** Maternal charac.+ADAM-12+PAPP-A+PIGF → sens. 46.1%

➤ Clinical utility of the model is **not** successful

Myatt L, Obstet Gynecol 2012;119:1234-42
Algorithm (11-13 w): Maternal characteristics + Ut A PI
- Early PE - 81%
- Late PE - 61%

Algorithm (11-13 w): PAPP-A, fβ-hCG, PP13, PIGF, ADAM 12, Inhibin-A + Ut A

- PAPP-A+Inhibin-A+PIGF + clinical chrc. ➔ early onset PE 75%
- Adding Ut A Doppler, PP13, ADAM12 did not contributed to the model

Audibert F, Am J Obstet Gynecol 2010;203:e1-8
Preeclampsia

- Algorithm (11-13 w): Biochemistry (PAPP-A, ADAM12)+Ut A PI

false (+) 10%

PE prediction 48% 50% 52%

- Are not sufficient (either alone or in combinations)

Preeclampsia

Algorithm: Maternal charac.+Ut A PI + Biochem.

PIGF + fβ-hCG + Maternal Ch.HT $\rightarrow$ <34 w PE 75%
false (+) 10%

PIGF + UtA PI + Maternal Ch.HT $\rightarrow$ PE 60%
false (+) 20%

Di Lorenzo, Placenta 2012;33:495-501
# Preeclampsia

**Algorithm:** Maternal charac. + Ut.A PI + MAP + Biochem.

<table>
<thead>
<tr>
<th></th>
<th>&lt;34 w</th>
<th>34-37 w</th>
<th>&gt;37 w</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>90%</td>
<td>80%</td>
<td>60%</td>
<td>57%</td>
</tr>
<tr>
<td>false (+)</td>
<td>5%</td>
<td>false (+) 5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- PAPP-A, PIGF, endoglin, Activin-A, inhibin-A

---

Akolekar R, Prenatal Diagn 2011;31:66-74

Wright D, Fetal Diagn Ther 2012;32(3):171-8
Preeclampsia

- Algorithm (11-13 w): Maternal charac. + MAP + sEndoglin
  - Early PE – **84%**
  - Late PE – **80%**

- Algorithm (11-13 w): Maternal charac. + MAP + UtA PI + PAPP-A + PIgF
  - Early PE – **93%**
  - Late PE – **35%**

Poon LC, Hypertension 2009;53:812-8
Preeclampsia

- Algorithm (11-13 w): Maternal charac. + MAP + UtA PI + PIGF + TNF-R1+ MMP-9 +pentraxin-3 + Activin-A+ P-selectin ➔ PE

  - Early PE – **88%**
  - Late PE – **46%**
  - Gest HT – **35%**

  False (+) 5%

Poon LCY, Ultrasound Obstet Gynecol 2010;35:662-70
Preeclampsia

Algorithm (11-13 w):
Maternal charac.

+ MAP

+ UtA PI

+ PIGF

+ PAPP-A → PE

Early PE – 95.3%

Late PE – 45.6%

False (+) 10%

Poon LCY, Fetal Diagn Ther 2013;33:16-27
**Preeclampsia**

- **Algorithm (11-13 w):**
  - PE < 34 w

<table>
<thead>
<tr>
<th>Study</th>
<th>Parameters</th>
<th>Detection rate for 5% FPR</th>
<th>Detection rate for 10% FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poon et al.⁶¹</td>
<td>MC, UtA Dopp, MAP, PIGF, PAPP-A</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>Poon et al.⁶²</td>
<td>MC, UtA Dopp, MAP, PAPP-A</td>
<td>84%</td>
<td>95%</td>
</tr>
<tr>
<td>Akolekar et al.⁷²</td>
<td>MC, UtA Dopp, MAP, PIGF, PAPP-A, PP-13, sEng, inhibin A, activin A, PTX3, P-selectin</td>
<td>91%</td>
<td>95%</td>
</tr>
<tr>
<td>Akolekar et al.⁶⁵</td>
<td>MC, UtA Dopp, MAP, PIGF, PAPP-A</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>Scazzochio et al.⁶³</td>
<td>MC, UtA Dopp, MAP, PAPP-A</td>
<td>69%</td>
<td>81%</td>
</tr>
</tbody>
</table>

MC, maternal characteristics; UtA Dopp, uterine artery Doppler (usually PI); MAP, mean arterial pressure.

Park et al, MC, UtA Dopp, MAP, PAPP-A 41.7% 91.7%

11-13 w Scan ➔ Goals

- Fetal abnormalities
- Preeclampsia
- **Fetal growth restriction**
- Miscarriage
- Stillbirth
- Preterm delivery
- Gestational DM
- Macrosomia
**FGR**

**Novel biomarkers for predicting IUGR**

1. **Angiogenesis-related biomarkers**
   - Placental growth factor
   - Soluble fms-like tyrosine kinase-1
   - Soluble endoglin
   - Vascular endothelial growth factor
   - Angiopoietin

2. **Endothelial function/oxidative stress-related biomarkers**
   - Homocysteine
   - Leptin
   - Asymmetric dimethylarginine
   - Soluble vascular cell adhesion molecule-1
   - Soluble intercellular adhesion molecule-1
   - Isoprostanes
   - 8-oxo-7,8-dihydro-2′-deoxyguanosine
   - Fibronectin
   - Lactate dehydrogenase
   - Pentraxin 3
   - Interferon-γ
   - Interleukin-1 receptor antagonist
   - Interleukin-12
   - Eotaxin
   - Regulated on activation, normal T-cell expressed and secreted (RANTES)
   - C-reactive protein
   - Folate

3. **Placental proteins/hormone-related biomarkers**
   - Insulin-like growth factor binding protein-1 and -3
   - A disintegrin and metalloproteinase-12
   - Placental protein-13
   - Activin A
   - Placental growth hormone
   - Pregnancy-specific β-1-glycoprotein
   - Annexin A5
   - Hepatocyte growth factor

4. **Others**
   - Urinary albumin:creatinine ratio
   - Vitamin D
   - Thyroid function tests (thyroid-stimulating hormone, free thyroxine, free triiodothyronine)
   - Metabolomics
   - Genetic biomarkers

---

Conde-Agudelo A, BJOG 2013;120:681-94
Algorithm (11-13 w): Maternal charac. + obstetric history

$\Rightarrow 35\%$ false (+) 10%

Maternal charac. $\Rightarrow 34\%$

$\Rightarrow NT+, PAPP-A \Rightarrow 37\%$

False (+) 10%

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96

Poon LC, Prenat Diagn 2011;31:58-65
Maternal charac. $\rightarrow$ 37%

+ NT+ PAPP-A + fβ-hCG $\rightarrow$ 55%

FGR $\rightarrow$ PAPP-A  ↓  fβ-hCG??

0.1 MoM increase in PAPP-A decrease FGR risk by 4.3%
0.1 MoM increase in fβ-hCG increase FGR risk by 4.02%

FGR

- Algorithm (11-13 w): Maternal charac. + Ut.A PI + MAP + biochem.+ obstetric history

- <37 w FGR **73%**
- Term FGR **46%**

- NT, PAPP-A, f β-hCG, PLGF, PP13, ADAM12 decreased

- False (+) 10%

Karagiannis G, Fetal Diagn Ther 2011;29:148-54
Serum biochem. + blood pressure + Ut A Doppler

Detection rate → early SGA (<34 w) 73%
False (+) 15%
First-trimester screening predicts early SGA mainly because of its strong association with preeclampsia

Crovetto F, Ultrasound Obstet Gynecol 2014;43:34-40
Metaanalysis

- **Angiogenic factors**: prediction *minimal*
  
  (+) LR = 1.7, (-) LR = 0.8
  
  2 case-control study: PIGF and angiopoietin-2 successful

- Maternal charac. + PAPP-A + fβ-HCG + UtA Doppler
  
  + Umb.A + DV Doppler ➤ ★ Overall prediction is low
  
  ★ Not improved by the incorporation of fetal Doppler

Conde-Agudelo A, BJOG 2013;120:681-94

Maternal charac. + Ut A PI + MAP + PAPP-A + PlGF

preterm-FGR 55.5%
term-FGR 44.3%
false (+) 10.9%

Poon LC, Fetal Diagn Ther 2013;33:16-27
11-13 w Scan ➔ Goals

- Fetal abnormalities
- Preeclampsia
- Fetal growth restriction
- Miscarriage
- Stillbirth
- Preterm delivery
- Gestational DM
- Macrosomia
**Miscarriage - Stillbirth**

- After demonstration of a live fetus at 11-13 w:
  - Miscarriage **1%**
  - Stillbirth **0.4%**

- PAPP-A ≤ 0.4 MoM

- Algorithm (11-13 w): Low PAPP-A, fβ-hCG, maternal age
  - Low prediction rate **28%**
  - Clinical practice?

---

*Van Ravenswaaij R, Prenatal Diagn 2011;31:50-7*
**Miscarriage - Stillbirth**

- Algorithm (11-13 w) → early abortion
  - Vaginal bleeding → 45%
  - Maternal factors → 53%
  - US → 85.7%

- Algorithm: Maternal charac. + NT + DV reverse “a” + low PAPP-A
  - Abort. → maternal char. 34%
  - 1.trim markers 37%
  - Identify stillbirth <34w 45%, >34 w 25%

[30% false (+)]

Papaioannou GI, Hum Reprod 2011;26:1685–1692

False (+) 10%

Akolekar R, Prenatal Diagn 2011;31:38-45
11-13 w Scan ➔ Goals

- Fetal abnormalities
- Preeclampsia
- Fetal growth restriction
- Miscarriage
- Stillbirth

- Preterm delivery
- Gestational DM
- Macrosomia
Algorithm (11-13 w): Low Maternal age, PAPP-A, fβ-hCG

- Low prediction rate 6% (AUC %56)
- Clinical practice?
Preterm Delivery

Algorithm (11-13 w): Maternal charac. + obstetrical history
- Preterm prediction=Nullipar 18%, multipar 38%  [false (+) 10%]

Ut A PI, PAPP-A, f β-hCG, PlGF, PP13, ADAM12, Inhibin-A or Activin-A – did not improve test performance

Beta J, Prenat Diagn 2011;31:75-83
Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
**Preterm Delivery**

**Algorithm (11-13 w):** (spontaneous+induced) Maternal charac. + biochem. + biophysical

- PAPP-A, ADAM12
- Ut A Doppler

**<34 w**
- Maternal charac. - 58%
- +ADAM12 - 58%
- +PAPP-A - 52%
- +Ut A Doppler – 62%

**<37 w**
- Maternal charac. - 45%
- +ADAM12 - 42%
- +PAPP-A - 48%
- +Ut A Doppler - 50%

- For the prediction of preterm delivery UtA PI, PAPP-A or ADAM12 either individually or in combination do not further improve their screening efficiency → poor clinical performance

Preterm Delivery

- Algorithm: 11-13 w: (Spontaneous + induced) preterm maternal charac.+ biochem. + Ut A Doppler

- PP13, PAPP-A

- Ut A PI

- <37w
  - 72-75% [5% false (+)]
  - 74-80% [10% false (+)]
  - 77-81% [20% false (+)]

- <33 w
  - 75-77% [5% false (+)]
  - 77-85% [10% false (+)]
  - 82-90% [20% false (+)]

Single marker or combinations are not superior to each other

Stout MJ, Placenta 2013;34:14-9
Preterm Delivery

Algorithm (11-13 w): Maternal charac. + SL

- Maternal charac.
  - <37 w preterm delivery 23% [false (+) 10%]
- SL, PAPP-A → no contribution

SL: Endocervix* and cervicoisthmic complex

- 11-13 w: 32.4 mm – 45.3 mm
- 20-24 w: 32.2 mm – 40.4 mm

Preterm birth:
- endocervical length (27.5 vs 32.5 mm, p < 0.0001)
- cervicoisthmic complex (41.4 vs 45.4 mm, p = 0.054)

Matern charac.+SL→ successful
- <34 w preterm birth detection rate 55% [false (+) 10%]


Greco E, Fetal Diagn Ther 2012;31:154-61
Greco E, Fetal Diagn Ther 2012;31:84-9
11-13 w SL

- Preterm birth prediction
  - <34 hf (OR, 0.746; 95% CI, 0.649-0.869)
  - <32 hf (OR, 0.734; 95% CI, 0.637-0.912)

Algorithm (11-13 w):

- Smoking + previous preterm birth $\Rightarrow$ <34 w preterm birth detection 26% [false (+) 10%]
- SL and Ut A Doppler $\Rightarrow$ no contribution

Souka AP, J Ultrasound Med 2011;30:997-1002

Metaanalysis – different gestational weeks

72 studies, 89,786 pregnant women and 30 different biomarkers

*None predicted preterm birth*

Conde-Agudelo A, 2011;118:1042-54
Fetal abnormalities

Preeclampsia

Fetal growth restriction

Miscarriage

Stillbirth

Preterm delivery

Gestational DM

Macrosomia
Gestational DM

High risk → OGTT

- BMI > 30
- Previous GDM – macrosomic infant
- Family history of DM
- Gender (African, South Asia, Middle East)

Detection rate by this model 60% – [false (+) 30-40%]

Scott DA, Health Technol Assess 202;6:1-172
Gestational DM

11 – 13 w

NT \(\rightarrow\) similar

- GDM = 1.56 mm vs controls = 1.54 mm

Luchi C, Gynecol Endocrinol 2011;27:782-4
Gestational DM

11 – 13 w

- GDM ($\Upsilon$ insulin)
  - PAPP-A  similar
  - f $\beta$-hCG

Gestational DM

Algorithm: Maternal charac. $\rightarrow$ 61.6%

+ adiponectin + SHBG $\rightarrow$ 74%

false (+) 20%

Nanda S, Prenat Diagn 2011;31:135-41
Thadhani R, Diabetes Care 2010;33:664-9
Gestational DM

11 – 13 w

- 50 gr challenge test
  - Limit 140 mg/dl $\rightarrow$ **130 gr/dl**

- OGTT
  - 1\textsuperscript{st} hour 190 mg $\rightarrow$ **161 mg/dl** (18%)
  - 2\textsuperscript{nd} hour 165 mg $\rightarrow$ **128 mg/dl** (29%)
  - 3\textsuperscript{rd} hour 145 mg $\rightarrow$ **107 mg/dl** (35%)

Nicolaides KH, Fetal Diagn Ther 2011;29:183-96
Plasencia W, Fetal Diagn Ther 2011;30:108-15
11-13 w Scan ➔ Goals

- Fetal abnormalities
- Preeclampsia
- Fetal growth restriction
- Miscarriage
- Stillbirth
- Preterm delivery
- Gestational DM
- Macrosomia
11-13 w:
- Maternal BMI
- PAPP-A
- NT

Macrosomia

11-13 w
- Maternal characteristics + PAPP-A + Ut-A PI $\rightarrow$ 30.2%
- Fetal biometric variables in the second trimester $\rightarrow$ 41.2%
- False (+) 10%

Timmerman E, Prenat Diagn 2014; 34:103-8

Macrosomia

- Algorithm (11-13 w):
  - Maternal charac. → 32.1%
  - + NT+ biochem. → 34.4%
  - PAPP-A, f β-hCG

- Maternal charac. → 34.6%
  - + serum adiponectin → 38.2%

False (+) 10%

Poon LCY, Fetal Diagn Ther 2011;29:137-47

Nanda S, Prenat Diagn 2011;31:479-83
Macrosomia

Maternal charac. → 30%
+ NT+ biochemistry → 48%


Algorithm (11-13 w):
Maternal charac. → 32.5%
+ NT+ biochemistry + Ut A PI → 34.4%

false (+) 10%
fβ-hCG → no contribution to the model

Plasencia W, Ultrasound Obstet Gynecol 2012;39:389-95
Conclusions

Preeclampsia: "Maternal characteristics + MAP + UtrA + PI + PAPP-A + PlGF" model seems helpful (90-96%).

FGR: Maternal characteristics + MAP + UtA + PI + PAPP-A (??) (55-73%).

Miscarriage and stillbirth: (?) (30-40%).

Preterm birth: no useful model that can be used in clinical practice yet. Maternal characteristics + SL + biochemistry (?) (23-55%).

GDM: Maternal characteristics + adiponectin + SHBG (74%).

Macrosomia: (35-45%) Suggested strategies by already acquired data can predict an important part of patients without increasing the costs.

More effective tests must be developed, validated and other prognostic models are needed.

Other potential variables must be added to the tests and well-known variables should also be standardized.