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

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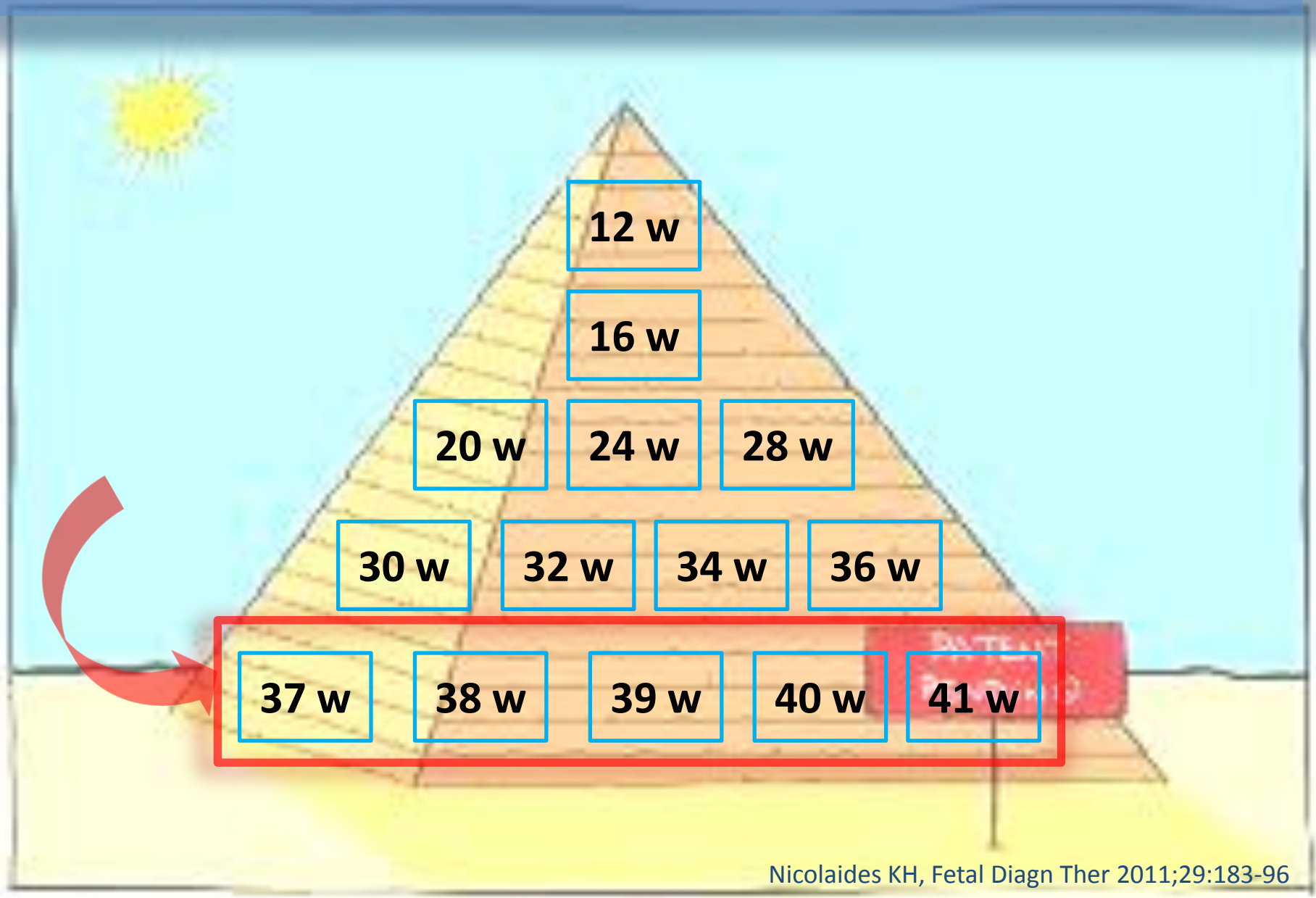
Prenatal Care



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

Prenatal Care

The Fetal Medicine Foundation

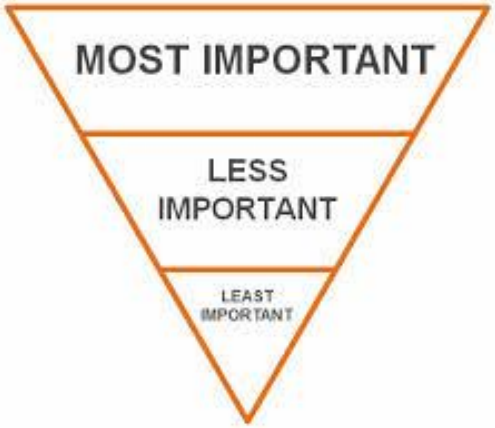
12 w

12-34 w Specialist

22 w

32 or 37 w

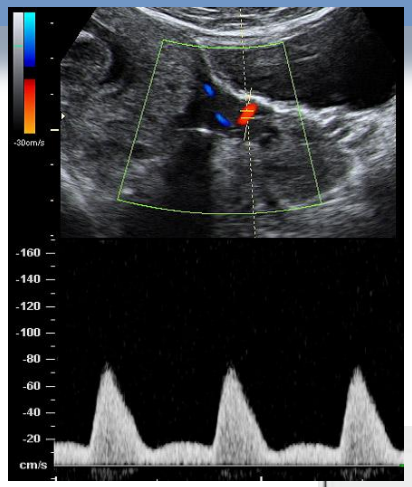
41 w

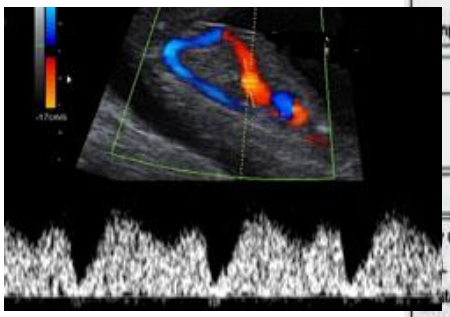


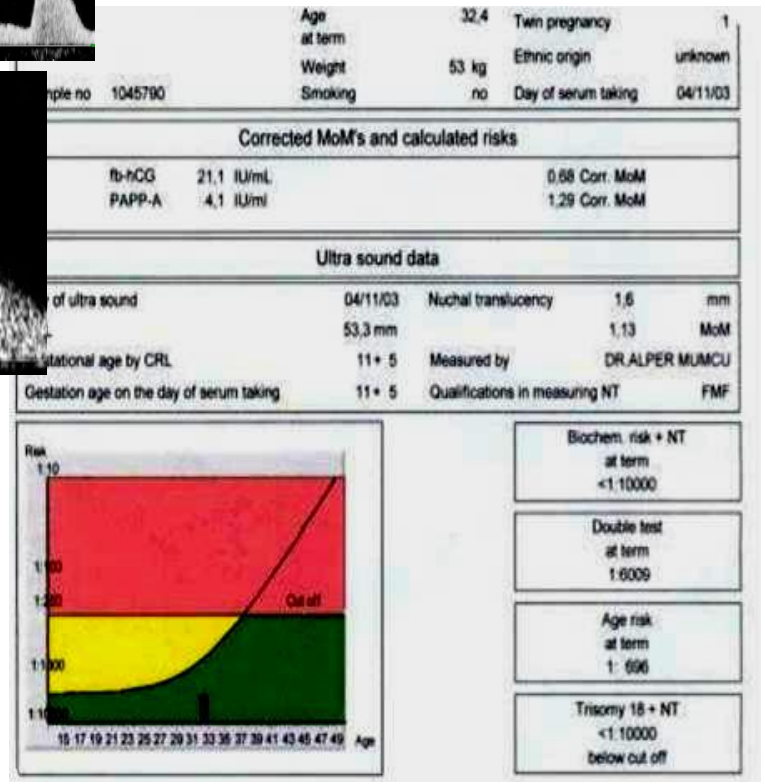
Nicolaides KH, Fetal Diagn Ther 2011;29:183-96

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)

-IUGR

-Stillbirth

- Miscarriage

f β-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
Plasencia W, Ultrasound Obstet Gynecol 2007;30:742-9

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 aneuplodies ~ **90%**

false (+) 5%

12^{th} w

1) 9-10 w biochemistry → 12 w US → **93-94%**

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

NT  + Maternal charac.-history + PAPP-A + fβ-hCG

	DR	FPR
fβ-hCG+PAPP-A	62%	4.7%
fβ-hCG+PAPP-A+PlGF	69%	4.3%
Biochem.+NT	89%	4.8%
Biochem.+NT+PlGF	88%	2.6%

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

US 11-13 w

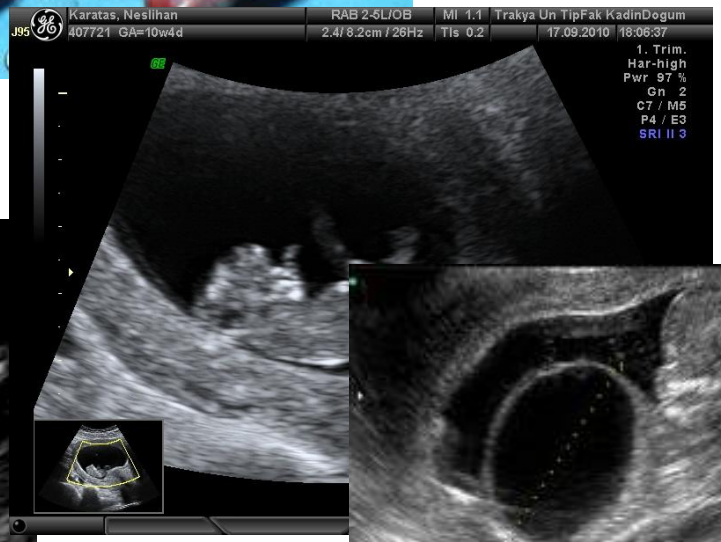
	Aneuploidi	Normal
Absent nasal bone	60%	2.5%
DV reverse “a”	66%	3%
Tricuspid regurgitation	55%	1%

- 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

11-13 week US Scan

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
Syngelaki A, Prenat Diagn 2011;31:90-102

11-13 week US Scan

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)

  Detection rate of major anomaly → similar

12 w		18 w
38%		47%

Saltvedt S, BJOG 2006;113:664-74

- 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

Syngelaki A, Prenat Diagn 2011;31:90-102

11-13 w Scan → Goals

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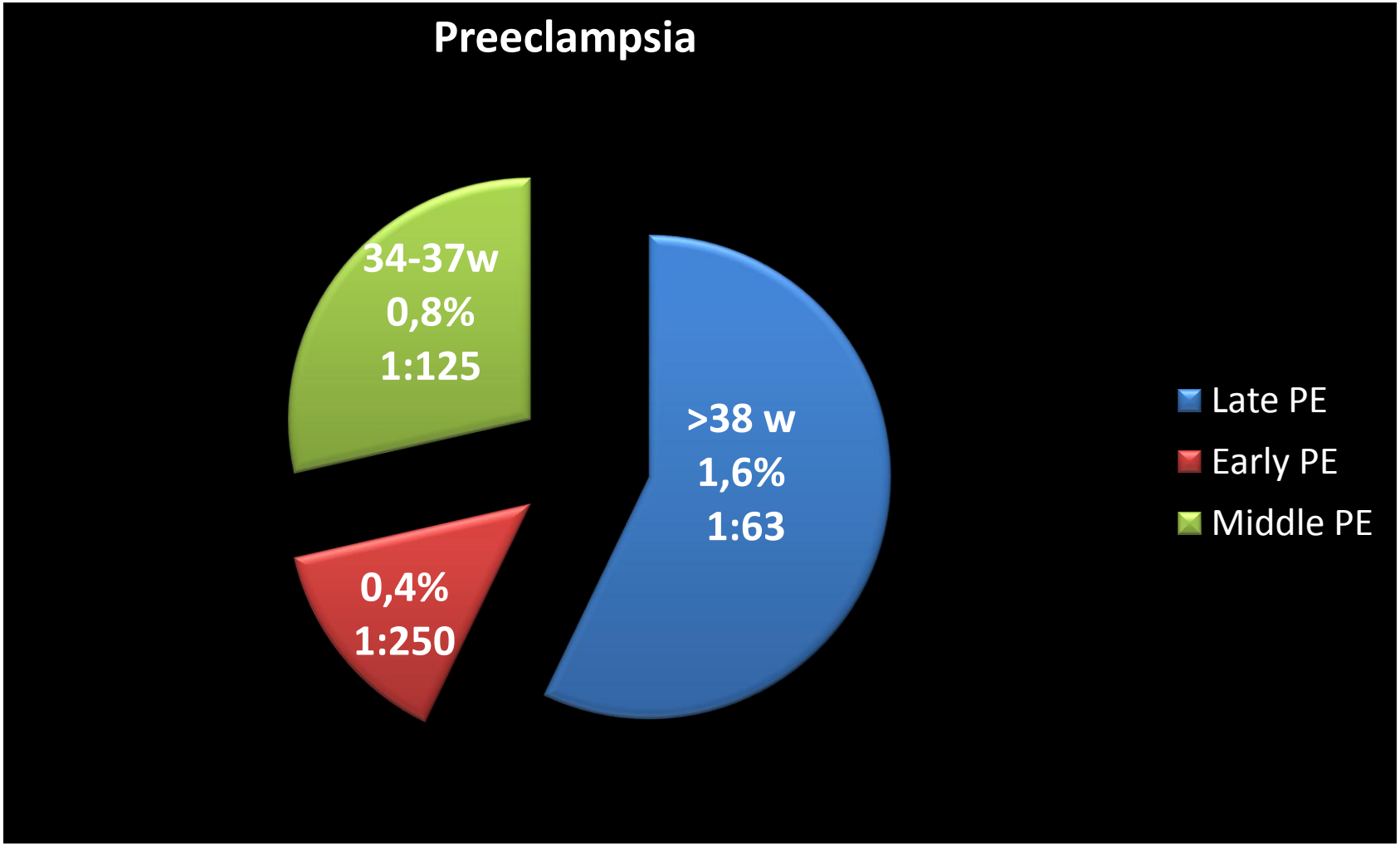
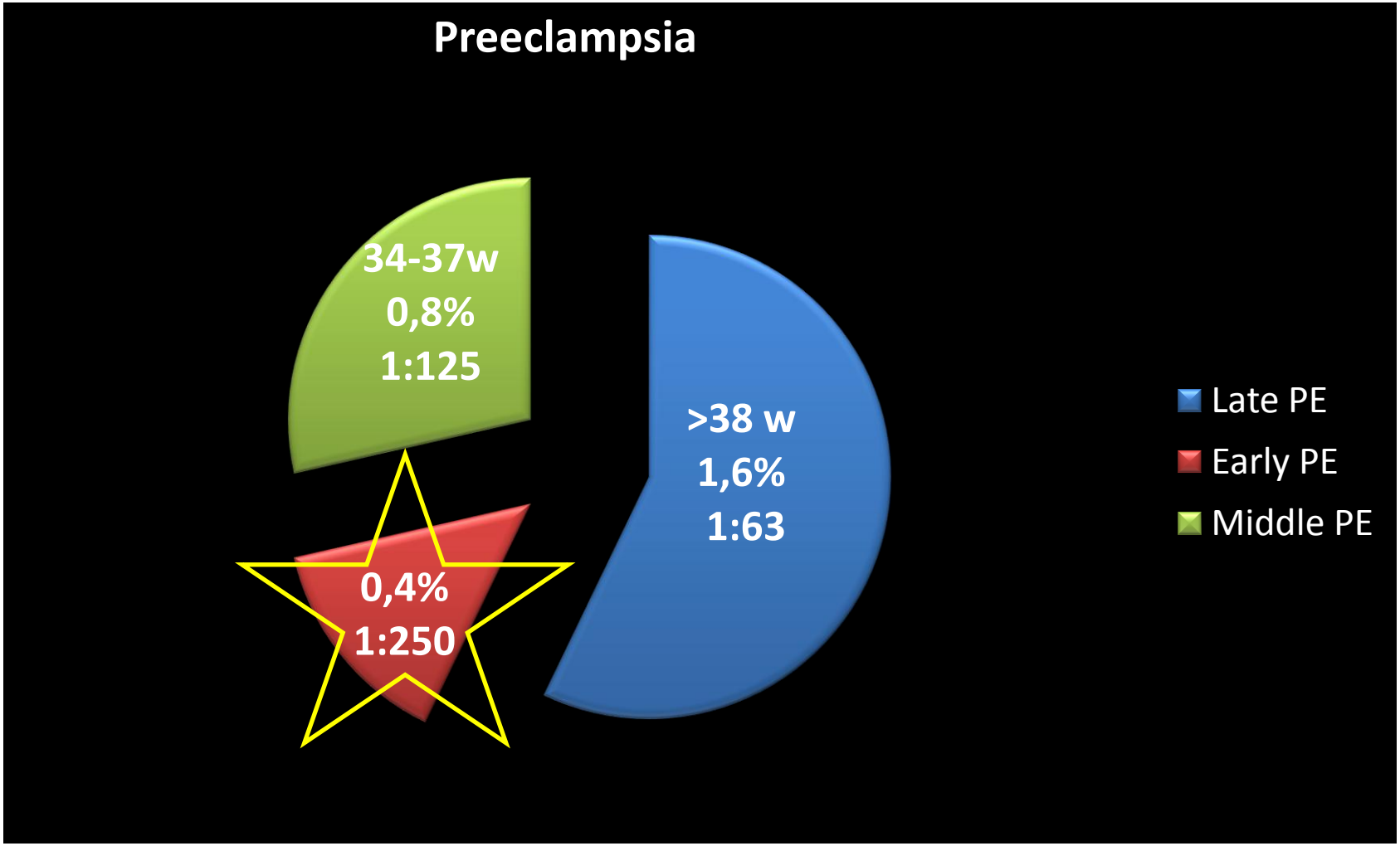
- Gestational DM
- Macrosomia

Preeclampsia



Preeclampsia



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

- PlGF
- 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)
- ….

Telang MA, Placenta 2013;34:2-8

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

Preeclampsia

- **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

Ultrasound Obstet Gynecol 2010; **35**: 662–670
Published online 15 March 2010 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.7628

Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11–13 weeks

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Table 1 Maternal characteristics in the four outcome groups

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

Table 2 Data for each marker in the four outcome groups

	Control	*Early pre-eclampsia*	*Late pre-eclampsia*	*Gestational hypertension*
Mean arterial pressure				
MoM	0.99 (0.95–1.05)	1.16 (1.08–1.25)*	1.09 (1.02–1.13)*	1.08 (1.02–1.14)*
mmHg	84.2 (80.5–89.5)	98.0 (91.8–106.5)	93.8 (87.0–98.7)	93.3 (86.5–98.3)
Lowest uterine artery PI				
MoM	1.05 (0.85–1.31)	1.65 (1.31–1.82)*	1.26 (0.92–1.55)†	1.12 (0.87–1.38)
Unit	1.43 (1.18–1.84)	2.29 (1.87–2.45)	1.73 (1.26–2.18)	1.53 (1.19–1.87)
PAPP-A				
MoM	1.00 (0.69–1.45)	0.62 (0.42–1.11)†	0.96 (0.61–1.33)	0.86 (0.62–1.39)
mU/L	2.79 (1.78–4.57)	2.63 (0.95–3.36)	2.79 (1.57–4.32)	2.01 (1.52–3.45)
Placental growth factor				
MoM	0.96 (0.75–1.31)	0.59 (0.49–0.78)*	0.85 (0.55–1.03)*	0.93 (0.69–1.18)
pg/mL	34.2 (26.2–50.0)	23.0 (15.04–33.5)	30.1 (21.5–37.2)	29.6 (23.8–42.4)
Inhibin-A				
MoM	0.98 (0.73–1.41)	1.54 (0.94–2.03)‡	1.23 (0.88–1.66)†	1.07 (0.82–1.40)
pg/mL	245.9 (175.1–340.7)	378.8 (243.6–530.0)	317.2 (217.8–433.3)	254.3 (199.5–333.7)
Activin-A				
MoM	1.02 (0.77–1.29)	1.12 (0.93–1.61)	1.30 (0.94–1.73)*	1.11 (0.90–1.48)
pg/mL	1.80 (1.43–2.43)	2.42 (1.80–2.94)	2.29 (1.82–3.02)	2.00 (1.49–2.66)
TNF-R1				
MoM	1.00 (0.87–1.13)	1.10 (0.91–1.32)	1.08 (0.94–1.19)‡	1.03 (0.95–1.15)
pg/mL	1178.2 (1012.4–1299.0)	1293.0 (1096.3–1457.6)	1260.1 (1083.1–1403.9)	1204.3 (1104.7–1408.0)
Matrix metalloproteinase-9				
MoM	1.03 (0.71–1.41)	1.23 (0.92–1.71)	1.20 (0.96–1.62)‡	1.09 (0.82–1.37)
pg/mL	454.9 (325.6–658.9)	530.2 (387.6–768.1)	536.1 (417.1–699.9)	495.4 (380.8–641.0)
Pentraxin-3				
MoM	0.97 (0.74–1.21)	1.39 (0.82–2.01)	1.12 (0.78–1.62)	1.11 (0.82–1.55)
ng/mL	0.48 (0.38–0.61)	0.57 (0.42–0.87)	0.48 (0.37–0.78)	0.50 (0.39–0.69)
P-selectin				
MoM	1.02 (0.83–1.24)	1.25 (0.87–1.51)	1.24 (1.00–1.46)*	1.11 (0.95–1.30)‡
ng/mL	29.7 (22.9–35.0)	35.0 (25.1–40.1)	35.3 (27.0–40.4)	32.7 (27.1–38.7)

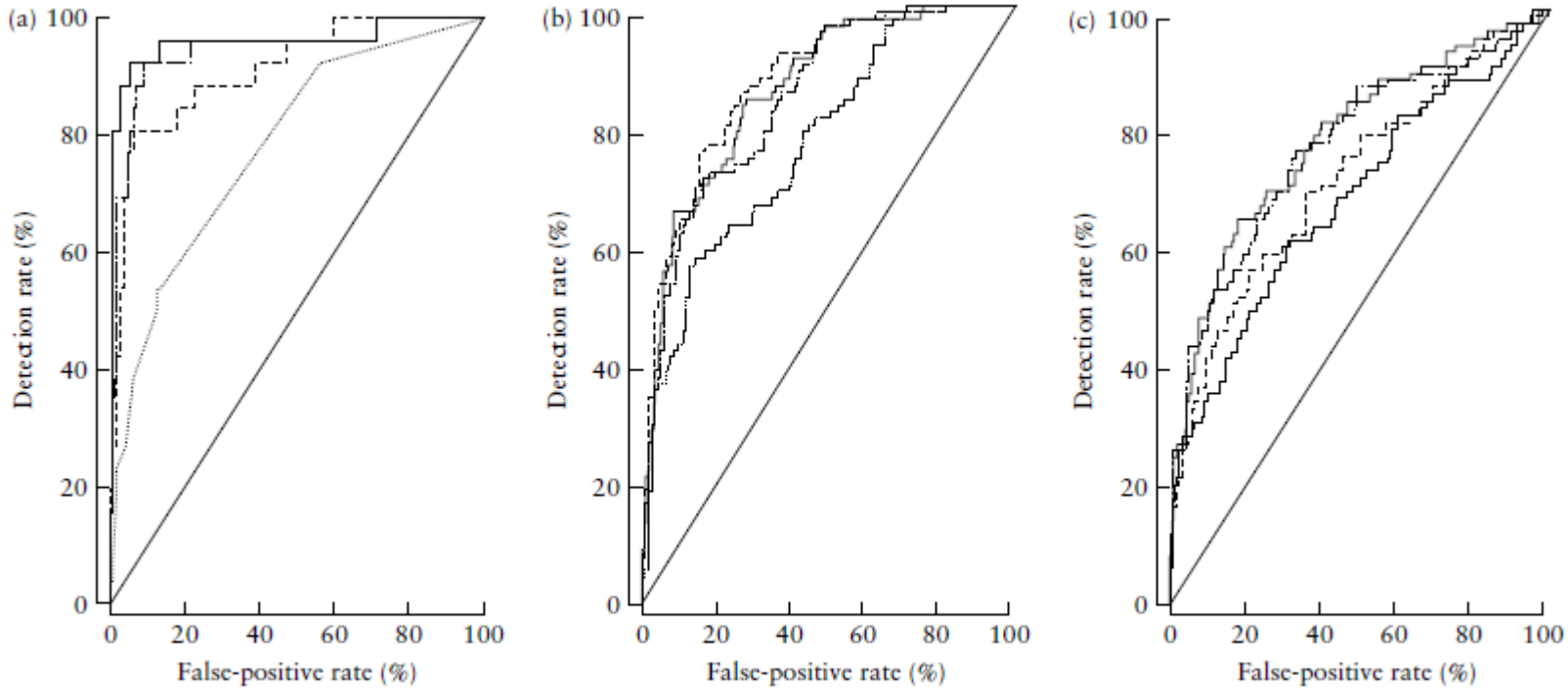

(a)
(b)
(c)
Detection rate (%)
False-positive rate (%)
0
20
40
60
80
100

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

	Area under ROC curve (95% CI)		
Screening test	*Early pre-eclampsia*	*Late pre-eclampsia*	*Gestational hypertension*
Maternal factors	0.715 (0.652–0.773)	0.778 (0.726–0.824)	0.677 (0.619–0.731)
Maternal factors plus:			
Biochemistry	0.908 (0.863–0.942)	0.876 (0.833–0.912)	0.715 (0.659–0.767)
Uterine artery L-PI, MAP	0.933 (0.892–0.962)	0.835 (0.787–0.876)	0.759 (0.705–0.807)
Uterine artery L-PI, MAP, biochemistry	0.959 (0.925–0.981)	0.862 (0.817–0.900)	0.782 (0.730–0.829)

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)

	Detection rate (% (95% CI)) for fixed FPR					
	Early pre-eclampsia		*Late pre-eclampsia*		*Gestational hypertension*	
	FPR 5%	*FPR 10%*	*FPR 5%*	*FPR 10%*	*FPR 5%*	*FPR 10%*
Maternal factors	39.5 (5.0–69.0)	47.0 (12.5–79.0)	36.7 (26.8–47.5)	47.5 (24.0–67.5)	28.2 (19.0–39.0)	35.0 (17.0–56.0)
Maternal factors plus:						
Biochemistry	76.9 (56.3–91.0)	80.8 (60.6–93.4)	53.3 (42.5–63.9)	64.4 (53.7–74.3)	27.1 (18.0–37.8)	38.8 (28.4–50.0)
Uterine artery L-PI, MAP	77.5 (40.0–96.0)	87.5 (54.0–99.5)	40.0 (10.0–67.5)	57.0 (27.5–80.0)	37.0 (12.5–62.0)	48.2 (37.3–59.3)
Uterine artery L-PI, MAP, biochemistry	88.5 (69.8–97.4)	92.3 (74.8–98.8)	46.7 (36.1–57.5)	65.6 (54.8–75.3)	35.3 (25.2–46.4)	49.4 (38.4–60.5)

Preeclampsia

- Maternal characteristics → PE

  Early PE - 30%

  Late PE - 20%

Yu CK, Am J Obstet Gynecol 2005;193:429-36

- PAPP-A → PE

  10-20%

Goetzinger KR, Prenat Diagn 2010;30:1138-42
Poon LC, Ultrasound Obstet Gynecol 2009;33:23-33
Spencer K, Prenat Diagn 2008;28:7-10

- Algorithm (11-13 w): Biochem. (PAPP-A, fβ-hCG, PP13, PlGF, ADAM12)

  PE prediction **44%** - false (+) 5%

  - Clinical utility is not successful, for an adequate screening test additional characteristics are necessary

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)
    - **PlGF** (0.83 *vs* 1.04 MoM; P<.001)

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

- Clinical utility of the model is <u>not</u> successful

Myatt L, Obstet Gynecol 2012;119:1234-42

Preeclampsia

- Algorithm (11-13 w): Maternal characteristics **+** Ut A PI

  Early PE - **81%**

  Late PE - **61%**

Plasencia W, Ultrasound Obstet Gynecol 2007;30:742-9

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

  - PAPP-A+Inhibin-A+PlGF + clinical chrc. → early onset PE **75%**

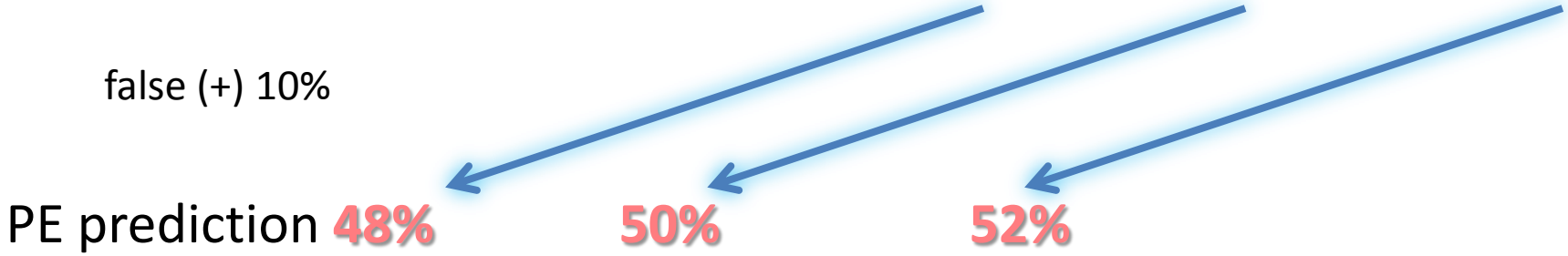
    false (+) 10%

  - 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



  - Are not sufficient (either alone or in combinations)

Goetzinger KR, J Ultrasound Med 2013;32:1593-600

Preeclampsia

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

PAPP-A, fβHCG, PlGF, PP13

PlGF + fβ-hCG + Maternal Ch.HT → <34 w PE **75%**

false (+) 10%

PlGF + UtA PI + Maternal Ch.HT → PE **60%**

false (+) 20%

Di Lorenzo, Placenta 2012;33:495-501

Preeclampsia

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

PAPP-A, PlGF, endoglin, Activin-A, inhibin-A

PE <34 w **90%**

34-37 w **80%**

>37 w **60%**

false (+) 5%

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

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

PE <34 w **90%**

PE Total **57%**

false (+) 10%

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%**

Abdelaziz A, Ultrasound Obstet Gynecol 2012;40:398-405

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

Poon LC, Hypertension 2009;53:812-8

Preeclampsia

- Algorithm (11-13 w): Maternal charac. + MAP + UtA PI + PlGF + 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

+ PlGF

+ 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

Study	Parameters	Detection rate for 5% FPR	Detection rate for 10% FPR
Poon *et al.*[61]	MC, UtA Dopp, MAP, PlGF, PAPP-A	93%	
Poon *et al.*[62]	MC, UtA Dopp, MAP, PAPP-A	84%	95%
Akolekar *et al.*[72]	MC, UtA Dopp, MAP, PlGF, PAPP-A, PP-13, sEng, inhibin A, activin A, PTX3, P-selectin	91%	95%
Akolekar *et al.*[65]	MC, UtA Dopp, MAP, PlGF, PAPP-A	93%	96%
Scazzocchio *et al.*[63]	MC, UtA Dopp, MAP, PAPP-A	69%	81%

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%

Park FJ, Aus N Z J Obstet Gynaecol 2013;53:532-9

Kane SC, Aus N Z J Obstet Gynaecol 2014;54:101-7

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 metalloprotease-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

FGR

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

→ **35%** false (+) 10%

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

Maternal charac. → 34%

+ NT**+** PAPP-A → **37%**

False (+) 10%

Poon LC, Prenat Diagn 2011;31:58-65

FGR

Maternal charac. → 37%

+ NT+ PAPP-A + fβ-hCG → **55%**

FGR → 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%

Papastefanou I, Acta Obstet Gynecol Scand 2012;91:104-11

FGR

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

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

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

False (+) 10%

Karagiannis G, Fetal Diagn Ther 2011;29:148-54

FGR

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

FGR

Metaanalysis

- Angiogenic factors: prediction *minimal*

  (+) LR= 1.7, (-) LR=0.8

  2 case-control study: PlGF and angiopoetin-2 successful

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

- Maternal charac.+ PAPP-A + fβ-HCG + UtA Doppler

  + Umb.A + DV Doppler → ★ Overall prediction is low

  ★ Not improved by the incorporation of **fetal** Doppler

Seravalli V, Am J Obstet Gynecol 2014 Mar 12

FGR

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

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- **Miscarriage**
- **Stillbirth**
- Preterm delivery
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Miscarriage - Stillbirth

- After demonstration of a live fetus at 11-13 w
  - Miscarriage **1%**
  - Stillbirth **0.4%**
- PAPP-A ≤ 0.4 MoM

Miscarriage	2.7
Stillbirth	2.4

Karim JN, J Obstet Gynecol 2013;33:351-4

- 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%**

  [30% false (+)]

  \+ US → **85.7%**

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

- Algorithm: Maternal charac. + NT + DV reverse "a" + low PAPP-A

  Abort. → maternal char. **34%**

  \+ 1.trim markers **37%**

  False (+) 10%

  Identify stillbirth → <34w **45%**, >34 w 25%

Akolekar R, Prenatal Diagn 2011;31:38-45

11-13 w Scan → Goals

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

Preterm Delivery

- Algorithm (11-13 w): Low Maternal age, PAPP-A, fβ-hCG

  → Low prediction rate **6%** (AUC %56)

  → Clinical practice?

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

Preterm Delivery

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

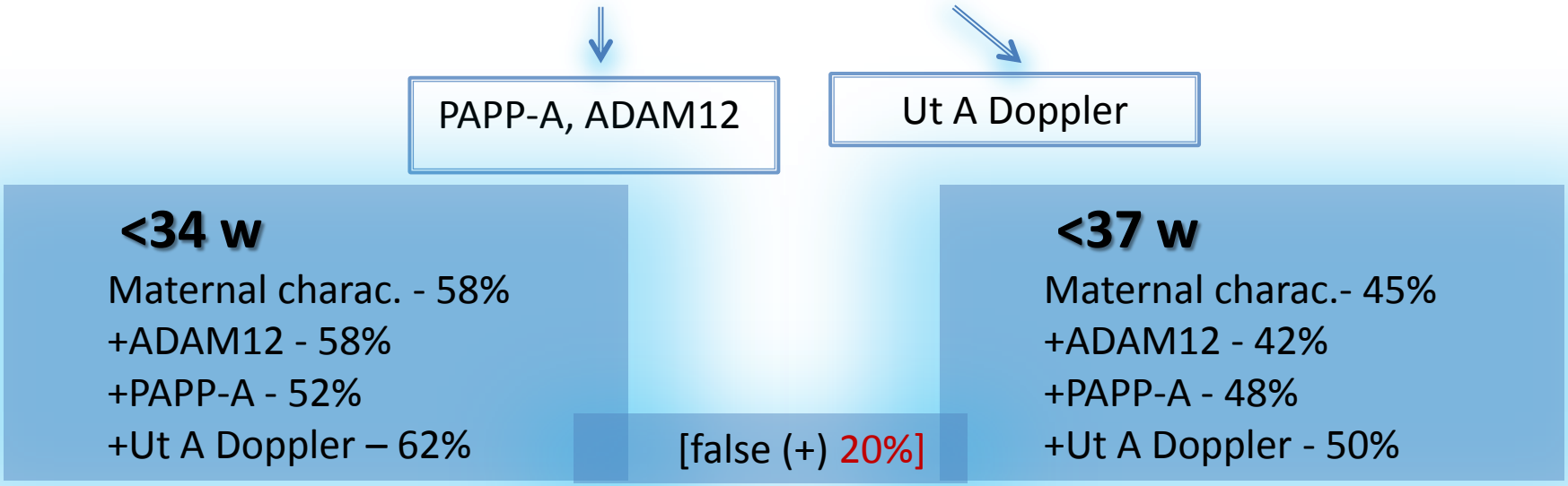
- Ut A PI, **PAPP-A**, f β-hCG, PlGF, PP13, ADAM12, Inhibin-A or Activin-A – did <u>not</u> improve test performance

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. + biophsysical



- 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

Goetzinger KR, Prenat Diagn 2012;32:1002-7

Preterm Delivery

- Algorithm: 11-13 w: (Spontaneous + induced) preterm

maternal charac.+ biochem. + Ut A Doppler

↓PP13, PAPP-A

↑Ut A PI

<37w	**<33 w**
72-75% [5% false (+)]	75-77% [5% false (+)]
74-80% [10% false (+)]	77-85% [10% false (+)]
77-81% [20% 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

Sananes N, Eur J Obstet Gynecol Reprod Biol 2013;171:18-22

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 lenght (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

Preterm Delivery

- 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)

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

- Algorithm (11-13 w):
  - Smoking + previous preterm birth → <34 w preterm birth detection 26% [false (+) 10%]
  - SL and Ut A Doppler → no contribution

Parra-Cordero M, Ultrasound Obstet Gynecol 2013 Mar 21.

Preterm Delivery

- 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

11-13 w Scan → Goals

- Fetal abnormalities
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- Fetal growth restriction
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- 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%**]

Waugh N, Health Technol Assess 2007;11:1-125
Scott DA, Health Technol Assess 202;6:1-172

Gestational DM

11 – 13 w

- NT -→ similar
  - GDM=1.56 mm *vs* controls=1.54 mm

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

Gestational DM

11 – 13 w

- GDM (↓ *insulin*)
  - PAPP-A
  - f β-hCG

similar

Husslein H, J Matern Fetal Neonatal Med 2012;25:2230-3

Gestational DM

11 – 13 w

Algorithm: Maternal charac. → 61.6%

false (+) 20%

+ *adiponectin* + ***SHBG*** → **74%**

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 → **130 gr/dl**

- OGTT
  - 1st hour 190 mg → **161 mg/dl** (18%)
  - 2nd hour 165 mg → **128 mg/dl** (29%)
  - 3rd hour 145 mg → **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**

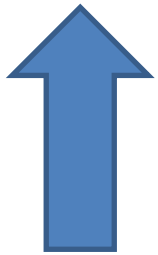
Macrosomia

- 11-13 w:

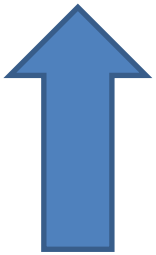
  Maternal BMI

  PAPP-A

  NT



Macrosomia



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

- 11-13 w

  Maternal charac.+ PAPP-A + Ut-A PI → 30.2 %

  + fetal biometric variables in the <u>second trimester</u> → 41.2%

  False (+) 10%

González González NL, J Matern Fetal Neonatal Med 2013;26:1635-40

Macrosomia

- Algorithm (11-13 w):

  Maternal charac. → 32.1%

  + NT+ biochem. → **34.4%**

  PAPP-A, f β-hCG ↑

  False (+) 10%

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

- Maternal charac. → 34.6%

  + serum adiponectin → **38.2%**

  False (+) 10%

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

Macrosomia

Maternal charac. → 30%

+ NT+ biochemistry → **48%**

false (+) 20%

Papastefanou I, Acta Obstet Gynecol Scand 2012;91:104-11

- Algorithm (11-13 w):

Maternal charac. → 32.5%

+ NT+ biochemistry **+Ut A PI** → **34.4%**

false (+) 10%

PAPP-A , f β-hCG ⇧

fβ-hCG → no contribution to the model

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

Conclusions

- P… *rnal … PAPP-A +*
  P… help…
- F… …2 (55-72%)
- M…
- Pre…
  pra…
- GD…
- Ma… …d
  dat…
  pat…
- Mc…
  pro…
- Other potential variables … …sts and well known variables should also be standardized