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Prediction and prevention of preeclampsia

Methods for prediction of preeclampsia:

- Risk scoring
- Logistic regression models
- Competing risks approach

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Risk scoring

NICE guidelines 2010

High risk factors
• Previous preeclampsia
• Chronic renal disease
• Chronic hypertension
• Diabetes mellitus
• SLE or APS
Moderate risk factors
• First pregnancy
• Age ≥ 40 yrs
• Body mass index ≥ 35 kg/m^2
• Inter-pregnancy interval > 10 yrs
• Family history of preeclampsia

ACOG guidelines 2018

High risk factors
• Previous preeclampsia
• Chronic renal disease
• Chronic hypertension
• Diabetes mellitus
• SLE or APS
Moderate risk factors
• First pregnancy
• Age ≥ 35 yrs
• Body mass index > 30 kg/m^2
• Inter-pregnancy interval > 10 yrs
• Family history of preeclampsia
• Black or poor

Simple, but:

- DR 40% SPR 10%
- No personalized risk

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Logistic regression models

Maternal factors
- Previous preeclampsia
- Chronic renal disease
- Chronic hypertension
- Diabetes mellitus
- SLE or APS
- First pregnancy
- Maternal age
- Body mass index
- Inter-pregnancy interval
- Family history of PE

Biomarkers
- Uterine artery PI
- Mean arterial pressure
- PAPP-A, PLGF, sFLT-1

Risk for early, preterm, late PE

- Plasencia et al: **Uterine artery Doppler**. UOG 2007
- Akolekar et al: **Placental growth factor**. UOG 2008
- Poon et al: **Mean arterial pressure.** Hypertension 2008
- Poon et al: **Maternal risk factors** J Hum Hypertens 2010
- Akolekar et al: **Early, intermediate, late PE**. Prenat Diagn 2011
- Scazzocchio et al: **Early and late PE** by maternal factors, PAPP-A, UtA-PI and BP. Am J Obstet Gynecol 2013
- Baschat et al: **Early and all PE** by maternal factors, MAP and PAPP-A. Am J Obstet Gynecol 2014.

Gives personalized risk, but:
- **Fixed GA cut-off for PE**
- **Cannot be easily expanded to include additional biomarkers**
- **Do not take into account the increasing effect of biomarkers with severity of PE**

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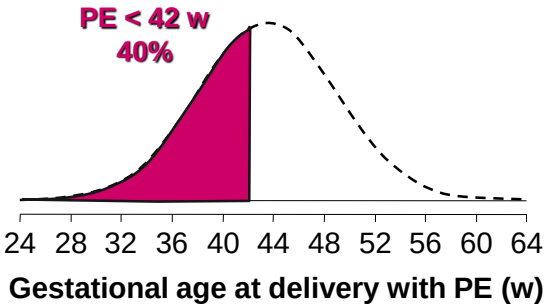
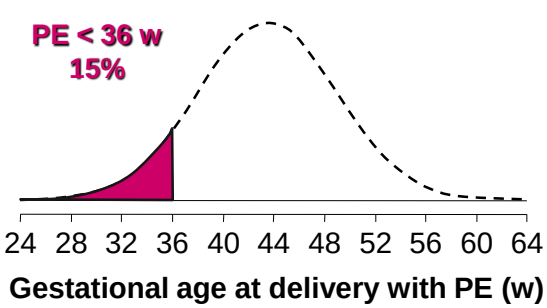
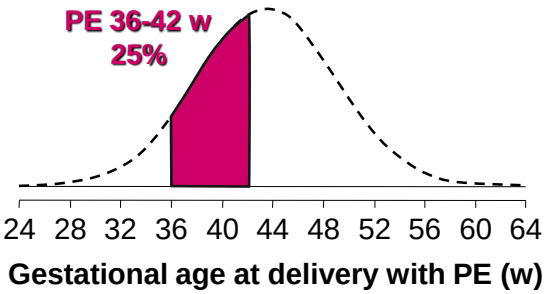
Competing risks approach







Gives personalized risk of PE at any desired gestation

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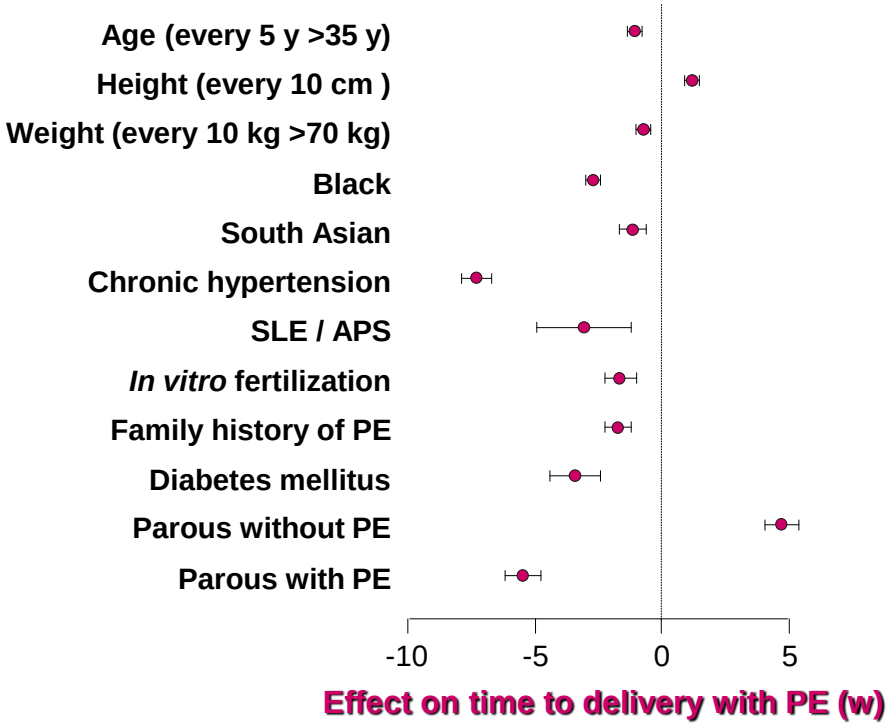
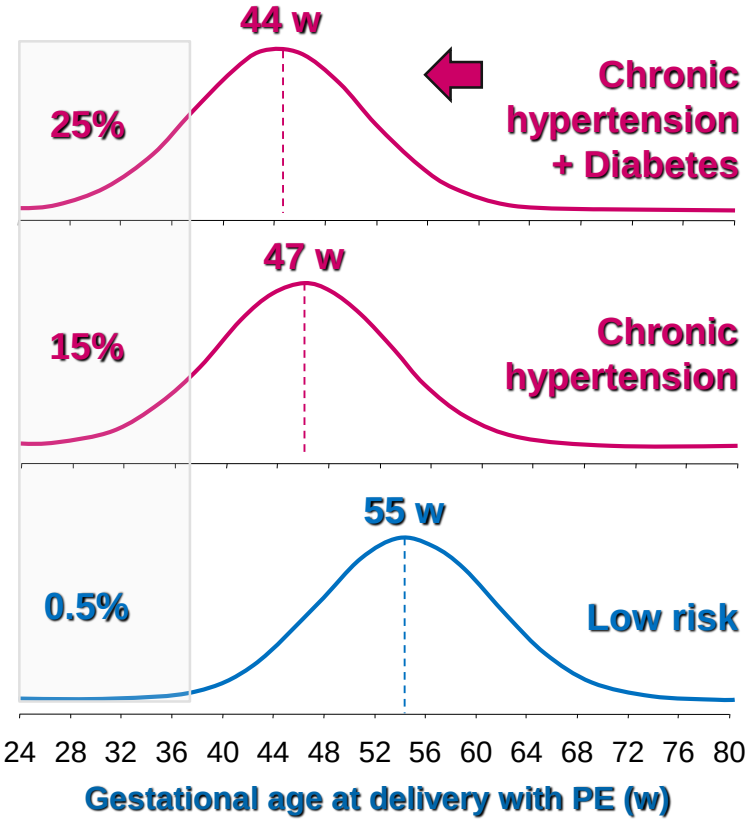
Competing risks approach

Effect of maternal factors





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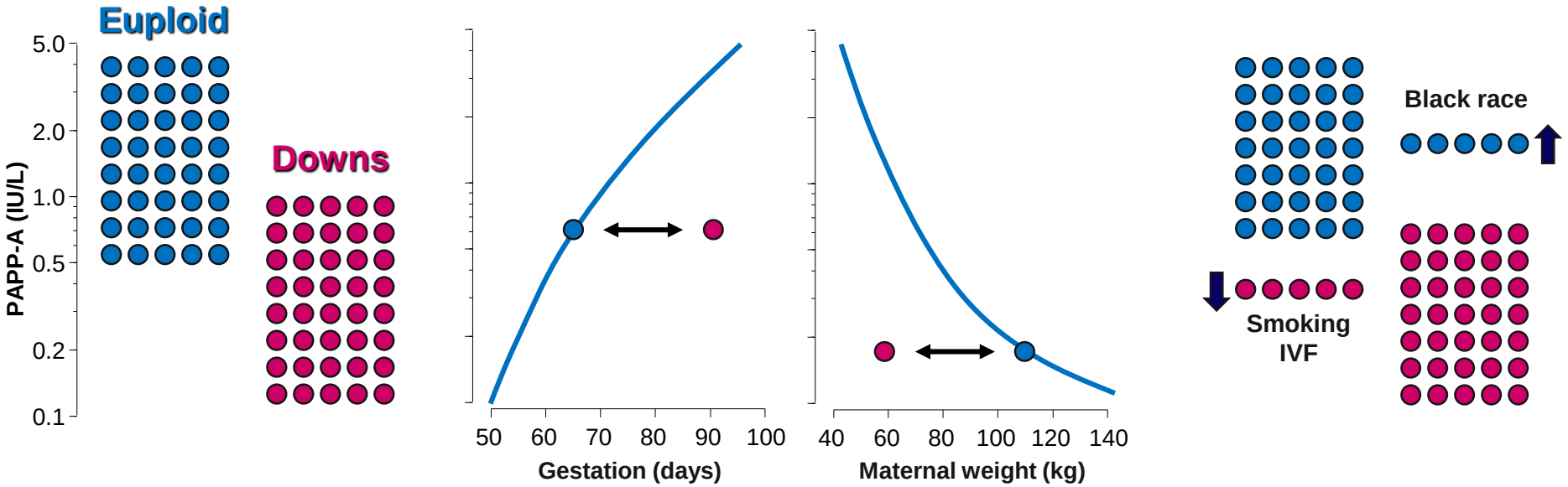
Competing risks approach

Effect of biomarkers and the concept of MoMs



Example of PAPP-A and trisomy 21

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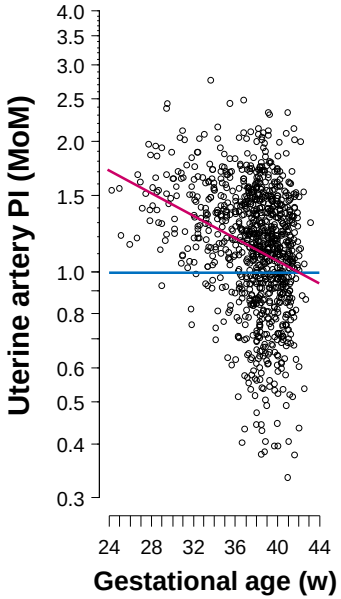
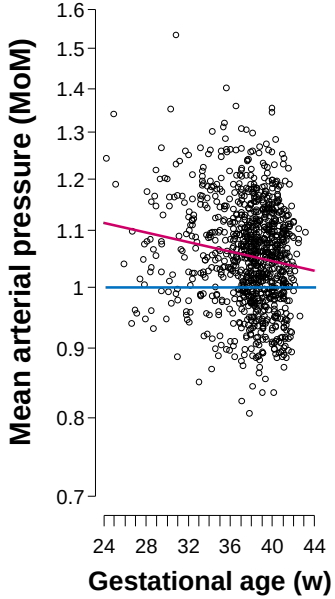
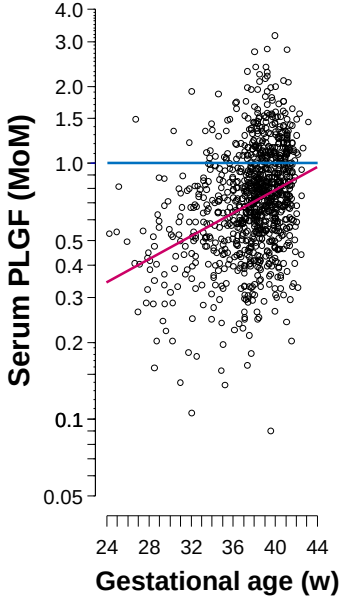
Competing risks approach







Effect of biomarkers according to severity of PE

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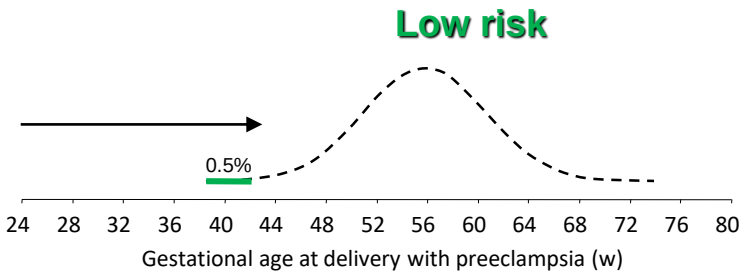
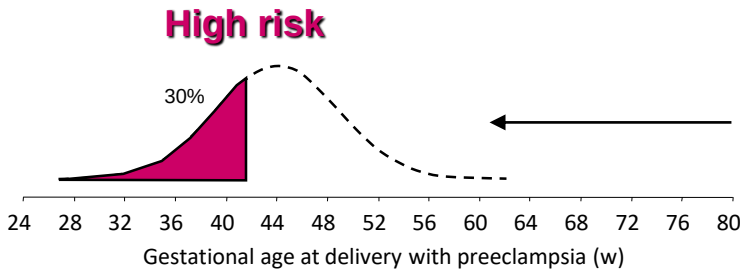
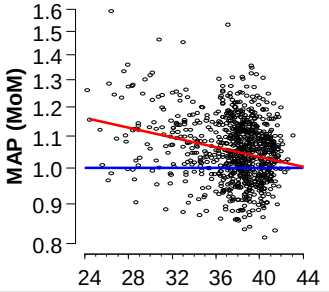
Competing risks approach





Determine *prior* risk from maternal factors

- Measure markers
- Express as MoMs
- Modify *prior* risk



Estimate posterior risk

- Gives personalized risk
- PE at any desired gestation
- Can be easily expanded to include additional biomarkers measured at any GA
- Takes into account the increasing effect of biomarkers with severity of PE

Prediction of preeclampsia:

- Objectives of screening at different gestations
  - 11-13 w aim to prevent by aspirin
  - 2nd or 3rd trimester aim to prevent harm

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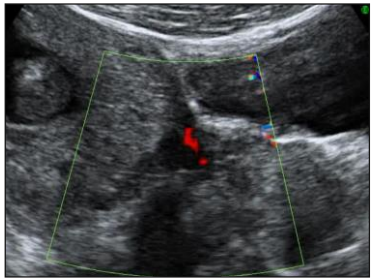
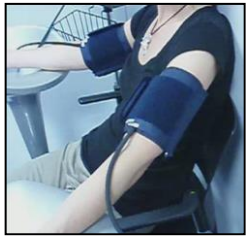
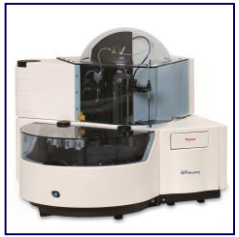
Prediction of PE at 11-13 w

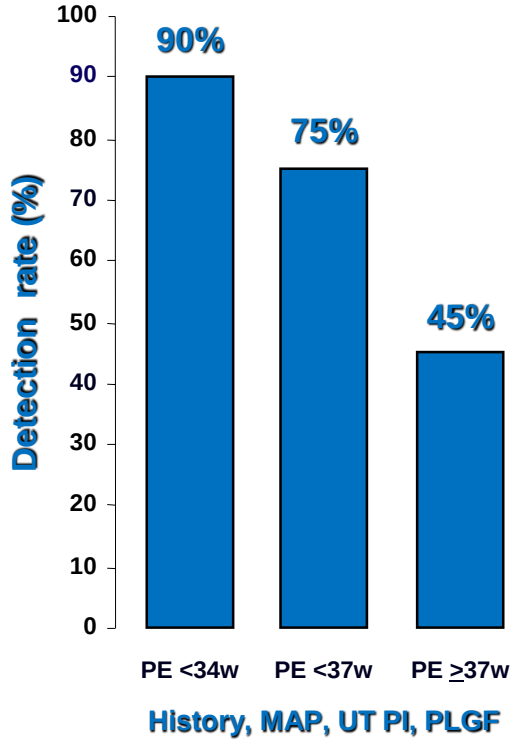
Maternal risk factors

- Age: every 10 years > 30 y
- Weight every 10 kg > 70 kg
- Black and South Asian race
- Previous preeclampsia
- Mother had preeclampsia
- Conception by IVF
- Chronic hypertension
- Diabetes mellitus
- Autoimmune: SLE, APS









- Campbell et al. **Doppler technique for assessing uteroplacental blood flow.** Lancet **1983**
- Kaminopetros et al. **Uterine artery Doppler** at 11-13 vs. 20-24 weeks. Fetal Diagn Ther **1991**
- Albaiges et al. **Uterine artery Doppler at 23 w:** adverse outcome. Obstet Gynecol **2000**
- Martin et al. **Uterine artery Doppler** at 11-13 weeks predicts PE. UOG **2001**
- Plasencia et al. **Uterine artery Doppler** at 11-13 weeks predicts PE. UOG **2007**
- Akolekar et al. **Placental growth factor** at 11-13 weeks predicts PE. UOG **2008**
- Poon et al. **Mean arterial pressure** at 11-13 weeks predics PE. Fetal Diagn Ther **2012**
- Akolekar et al. **Competing risks model** to predict PE. Fetal Diagn Ther **2013**
- O'Gorman et al. **Combined test** for early prediction of PE. Am J Obstet Gynecol **2016**

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funded by EU FP7 ASPRE project

Prevention of PE: aspirin

Screening at 11-13w
N = 26,941

↓

High-risk group agreeing to RCT

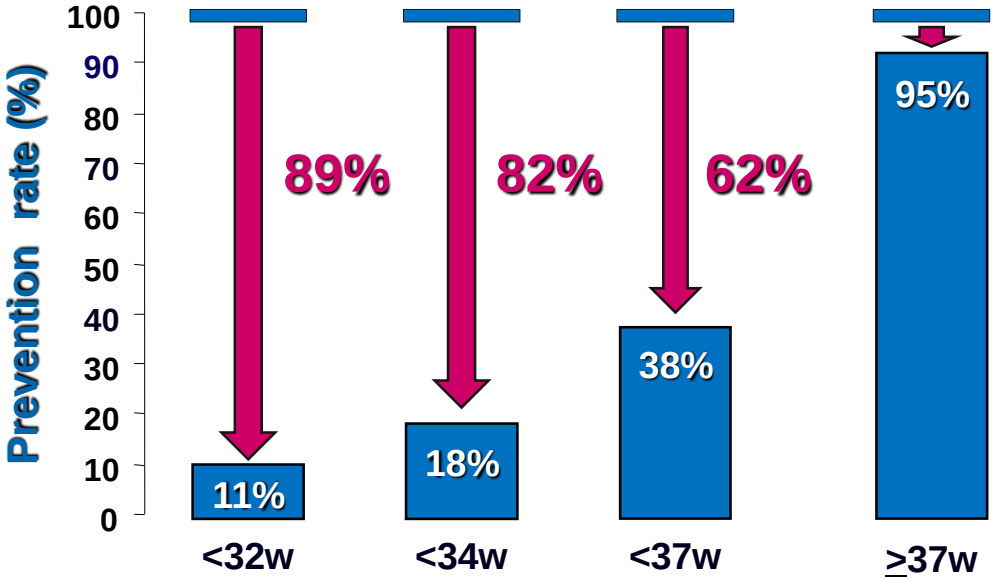
↙ ↘

Assigned to aspirin
N = 798

150 mg/day
12 to 36 w

Assigned to placebo
N = 822

Spain: Murcia, Granada, Tenerife
Belgium: Brussels
Greece: Athens
Italy: Milan
England: 6 NHS hospitals



The NEW ENGLAND JOURNAL of MEDICINE

Rolnik DL, Wright D, Poon L, *et al*. Aspirin versus placebo in pregnancies at high risk of preterm preeclampsia. N Engl J Med **2017**;377:613-22.

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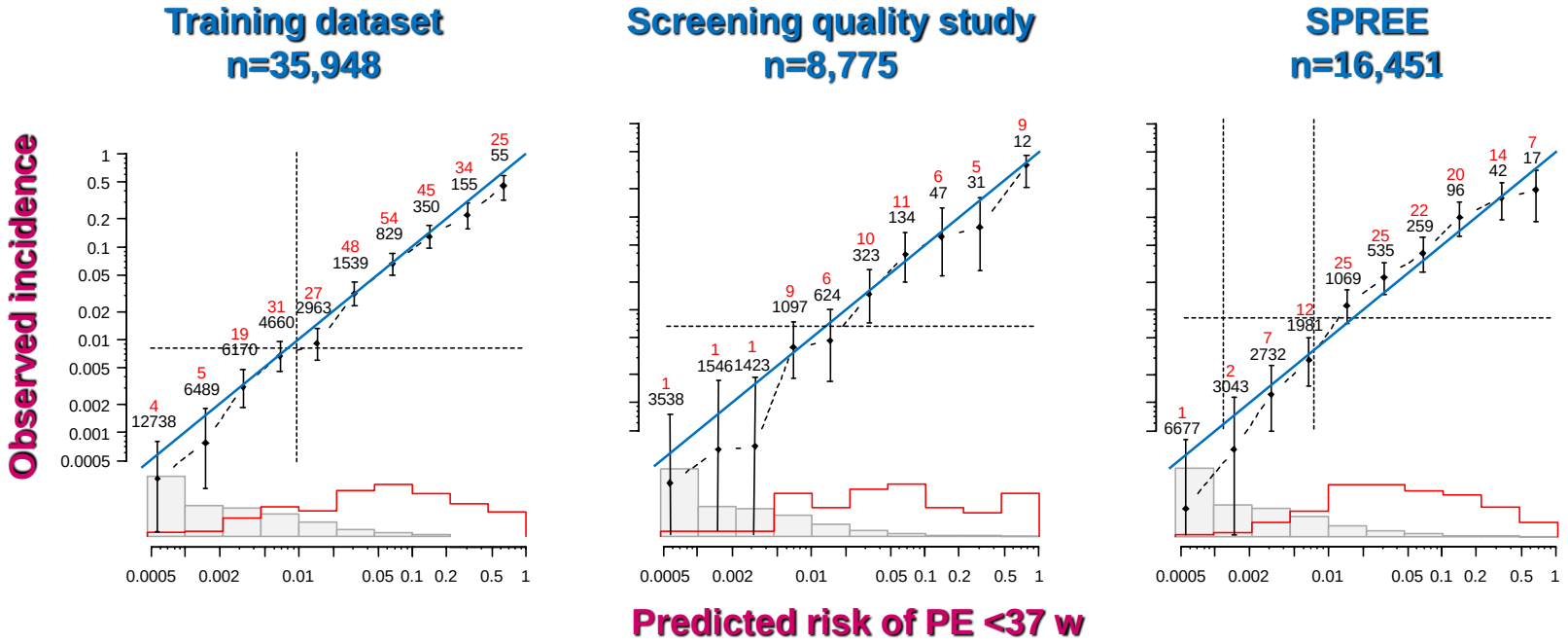
Calibration and validation



Wright D, Tan MY, O'Gorman N, Poon LC, Syngelaki A, Wright A, Nicolaides KH. Predictive performance of the competing risk model in screening for preeclampsia. Am J Obstet Gynecol 2018; pii: S0002-9378(18)32112-4.

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Additive value of biomarkers

Pregnancies: n = 61,174

Preeclampsia

- **Total: n = 1,770 (2.9%)**
- **<37 w: n = 493 (0.8%)**

DR for 10% SPR

Method of screening	<32 w	<37 w
Maternal factors	53%	45%
+ MAP	61%	51%
+ MAP, UtA-PI	83%	68%
+ MAP, PLGF	79%	66%
+ MAP, UtA-PI, PLGF	**90%**	**75%**

Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, Akolekar R, Konstantinidou L, Tsavdaridou M, Galeva S, Ajdacka U, Molina FS, Persico N, Jani JC, Plasencia W, Greco E, Papaioannou G, Wright A, Wright D, Nicolaides KH.Screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2018;52:186.

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Selection of risk cut-offs

Race	Risk cut-off	MAP, UTPI, PLGF	
		DR	SPR
White	100	70	11
	150	80	16
	200	84	20
Black	100	92	33
	150	95	43
	200	97	50

Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, Akolekar R, Konstantinidou L, Tsavdaridou M, Galeva S, Ajdacka U, Molina FS, Persico N, Jani JC, Plasencia W, Greco E, Papaioannou G, Wright A, Wright D, Nicolaides KH. Screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2018;52:186.

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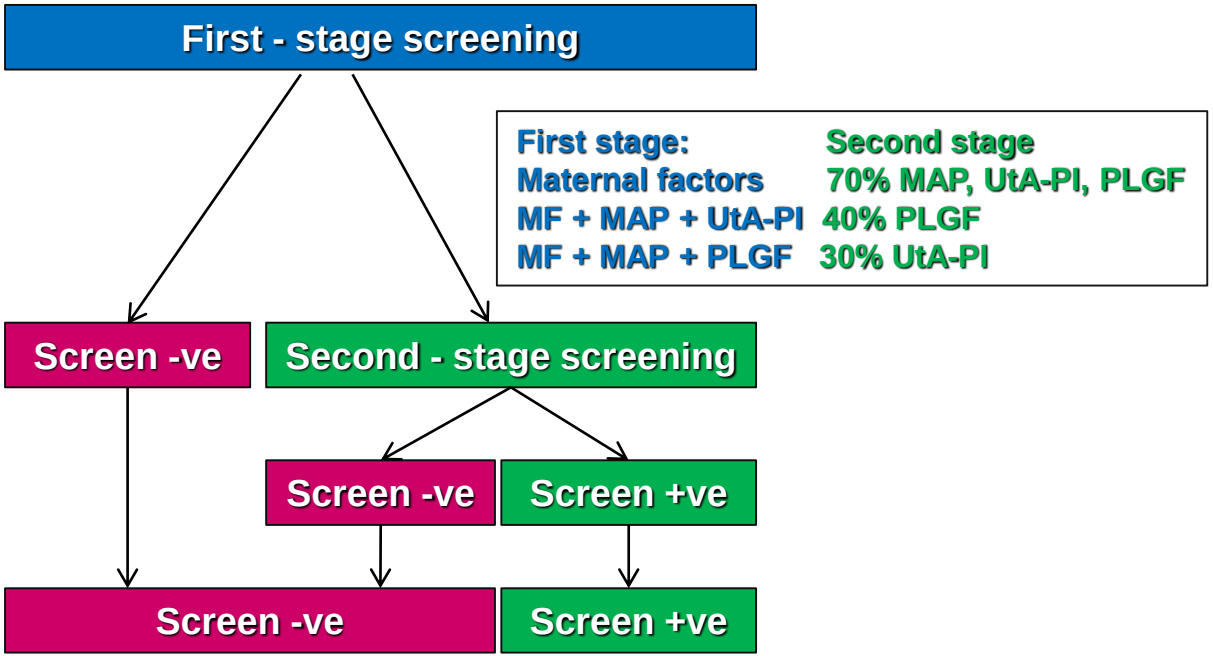
Two - stage screening

	DR for 10% SPR	
Screening everybody	<32 w	<37 w
Maternal factors + MAP, UTPI, PLGF	90%	75%



Wright A, Wright D, Syngelaki A, Georgantis A, Nicolaides KH. Two-stage screening for preterm preeclampsia at 11-13 weeks' gestation. Am J Obstet Gynecol 2018 Nov 7. pii: S0002-9378(18)30999-2.

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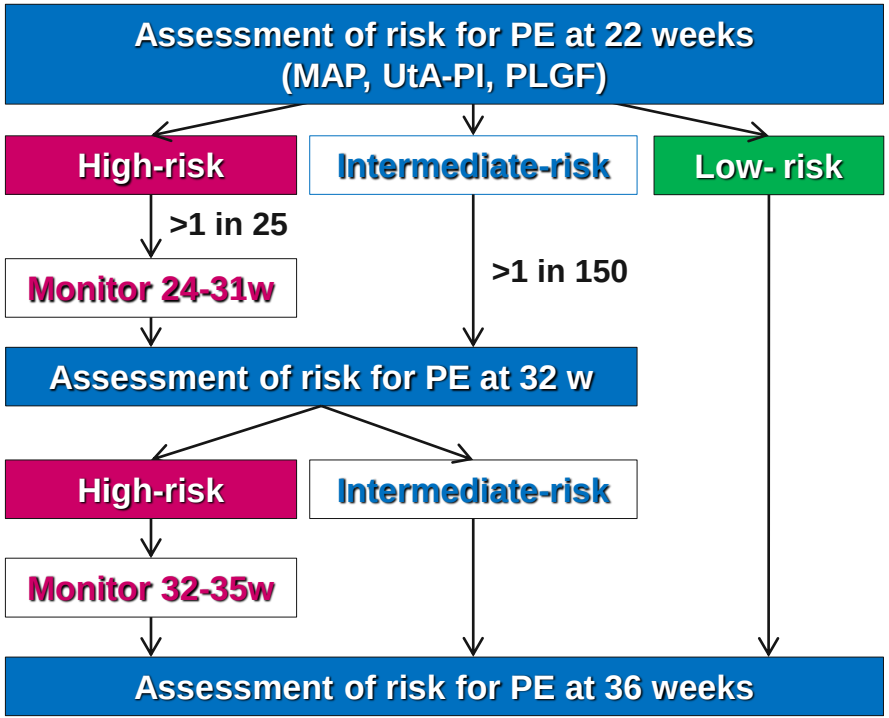
22w: Stratification of risk to define management



Combined screening at 22 w can individualize patient care and identifies:

- **A small group (1%) requiring monitoring at 24-32 w**
- **An intermediate group (10%) for reassessment at 32 w**
- **A large group (90%) at low-risk of developing PE <36 w**

Litwinska M, Syngelaki A, Wright A, Wright D, Nicolaides KH. Management of pregnancies after combined screening for PE at 19-24 weeks' gestation. Ultrasound Obstet Gynecol. 2018;52:365-372.

Prediction of preterm preeclampsia:

Clinical implementation

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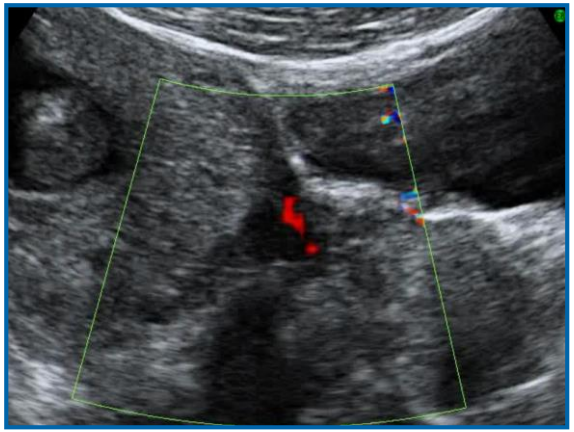
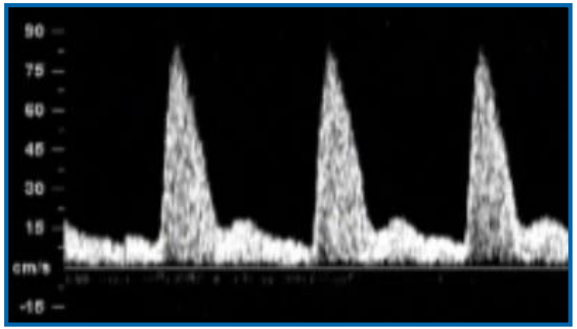
Uterine artery Doppler at 11-13 w





Transabdominal ultrasound

- **Identify uterine arteries:**
  - Sagittal section of the cervix
  - Color flow mapping
  - Move transducer from side to side
  - Arteries are at the level of the internal os
- **Sampling gate:** 2 mm to cover whole vessel
- **Angle of insonation:** less than 30º
- **Peak systolic velocity:** more than 60 cm/s
- **Mean PI:** average PI (left + right / 2) `

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Mean arterial pressure at 11-13 w

- **Device:** Automated (3BTO-A2, Microlife, Taipei, Taiwan), calibrated at regular intervals.
- **Method:** Women rested for 5 minutes, arms supported at the level of the heart.
- **Cuff size:** Small (<22 cm), medium (22-32 cm) or large (33-42 cm), depending on the mid-arm circumference.
- **Both arms:** Take average of two measurements in each arm.

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Prediction of preeclampsia

Maternal risk factors

- Age: every 10 years above 30 y
- Weight: every 10 kg above 70 kg

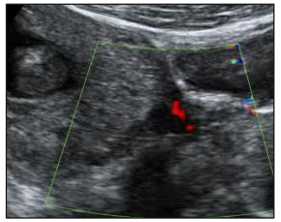
- Racial origin
  Afro-Caribbean
  South Asian

- Obstetric history
  First pregnancy
  Previous preeclampsia

- Family history of preeclampsia

- Conception by IVF

- Chronic hypertension
- Diabetes mellitus
- Autoimmune : SLE / APS



Collection of data
- Accurate recording of maternal factors
- Training & audit for MAP
- Training & audit for UtA-PI
- Use of validated reagents & audit for PLGF

Conversion of measurements to MoMs
- Use of appropriate factors
- Monitoring of distribution of values
- Adjustment of MoMing equations

Outcome measures
- Use of appropriate definition of PE
- Ensure that the diagnosis is correct
- Adjustment for use of aspirin

Performance of screening (DR and FPR)
- These depend on the *prior* risk
- The cut-off used for defining screen +ve

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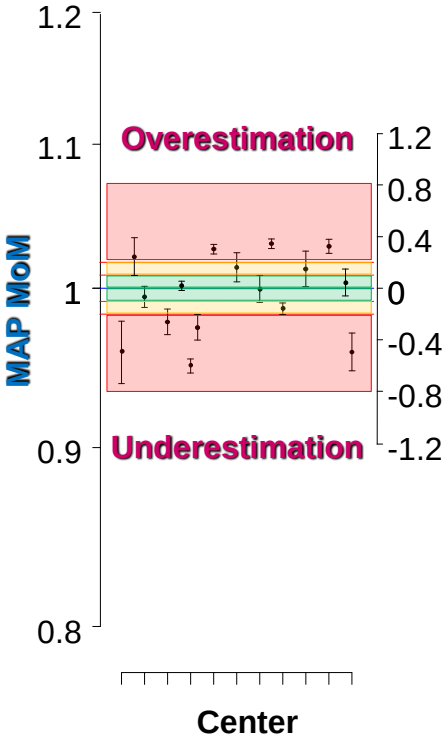
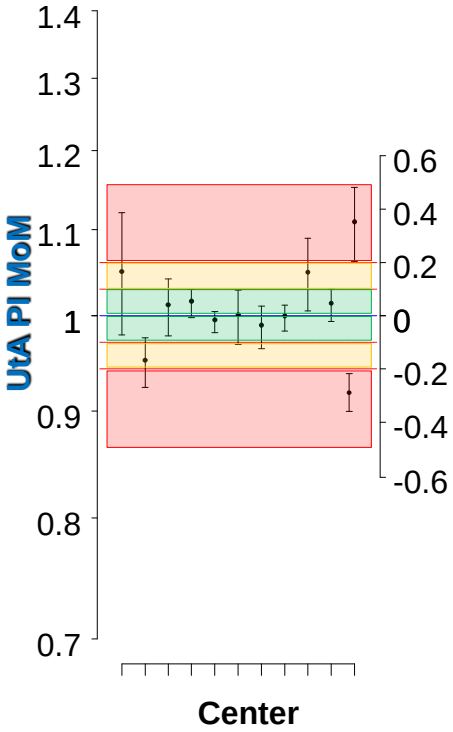
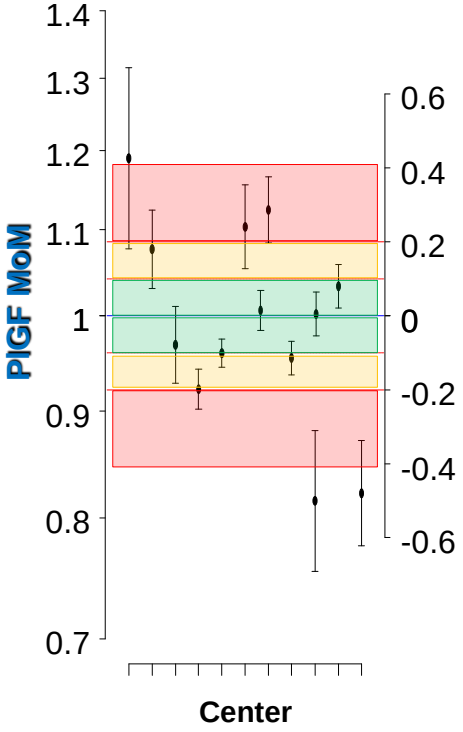
Collection of data

- Accurate recording of maternal factors
- Training & audit for MAP and UtA-PI
- Use of validated reagents & audit for PLGF







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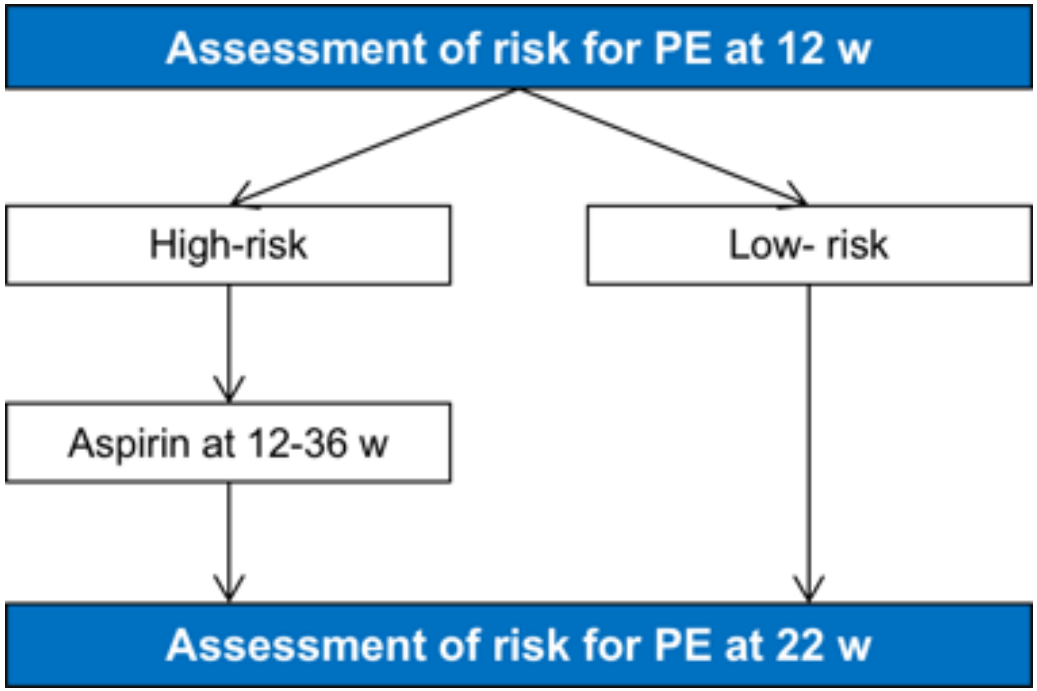
Risk stratification 12 weeks



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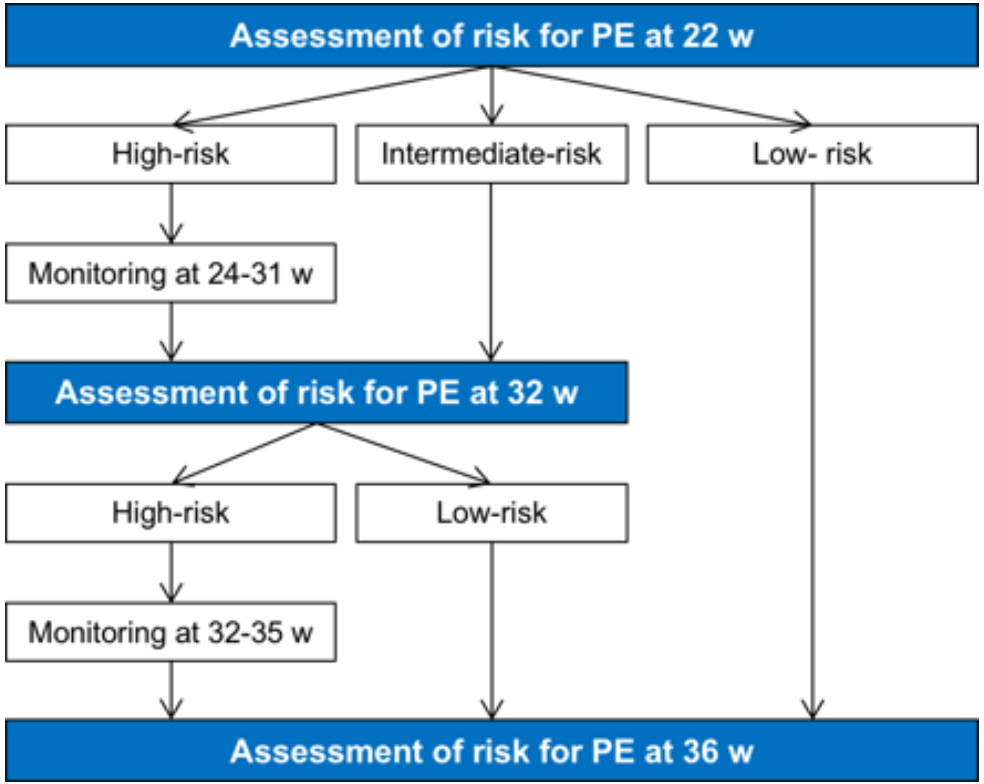
Risk stratification 22 weeks



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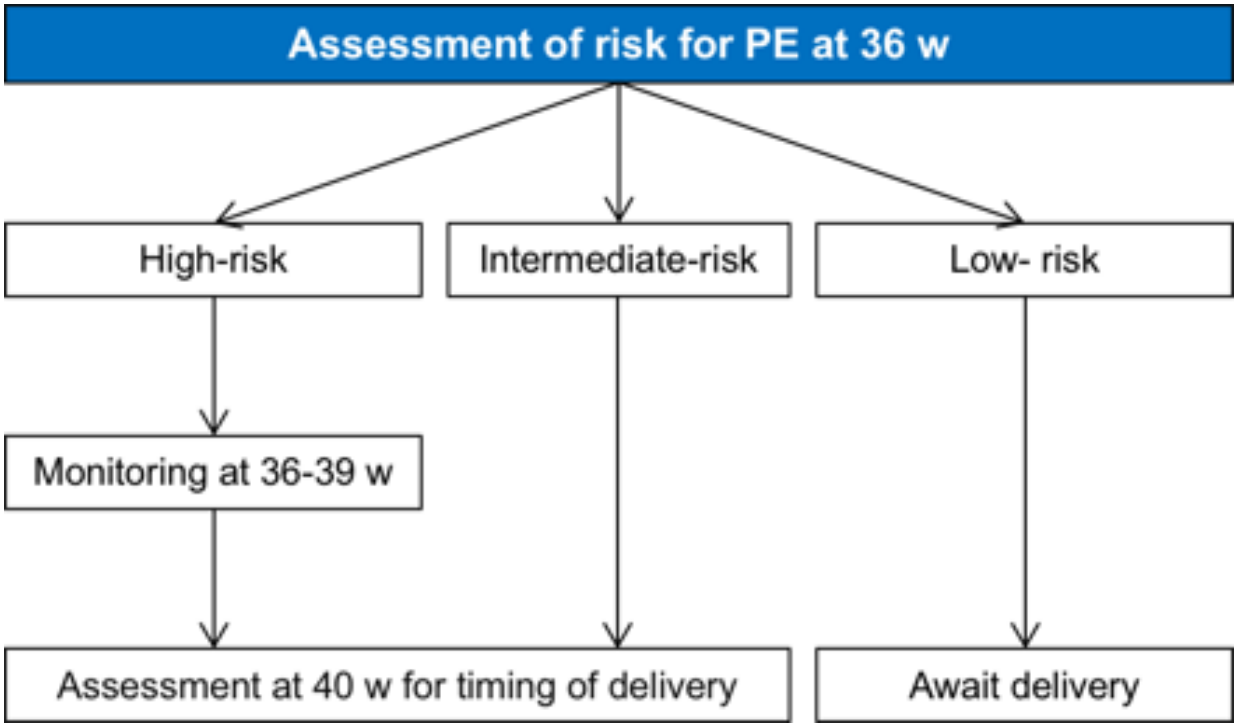
Risk stratification 36 weeks



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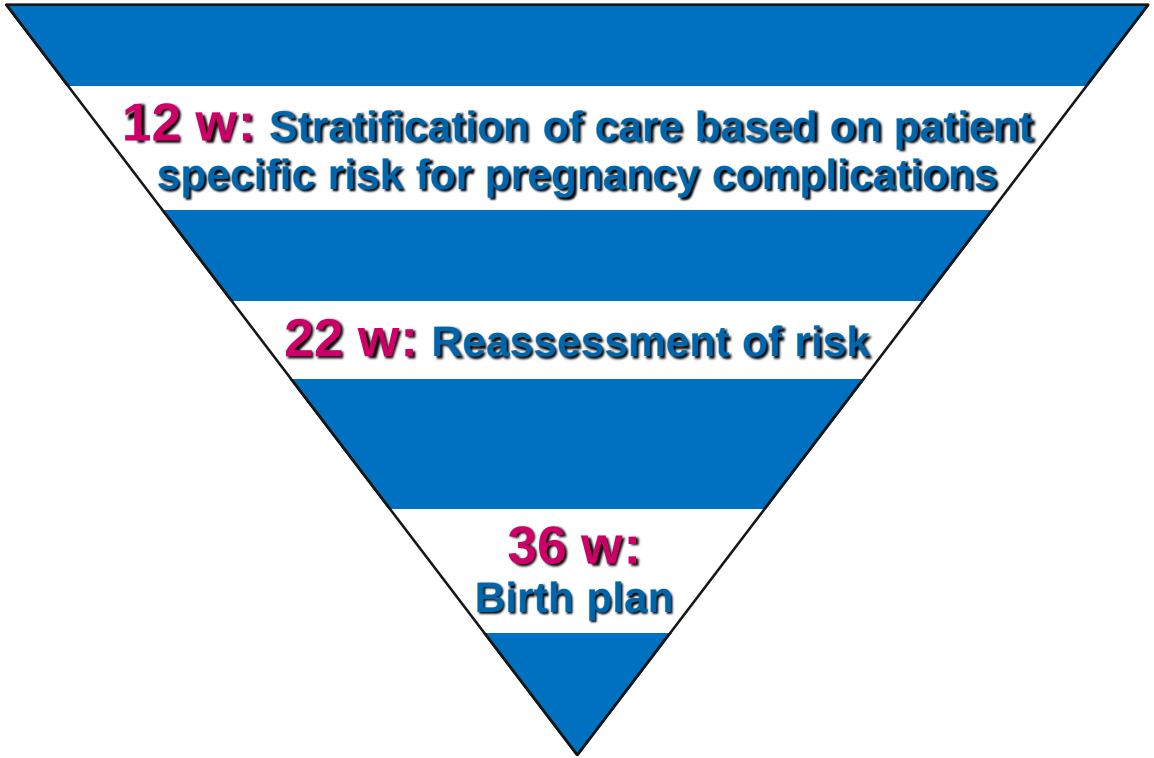
Inversion of pyramid of care



Prenatal care 2019

Thank you