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Preeclampsia screening: time for implementation

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Prediction of preeclampsia

NHS

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

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Prediction of preeclampsia

Determine *prior* risk:
- **Maternal characteristics**
- **Medical / obstetric history**

↓

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

↓

Estimate posterior risk

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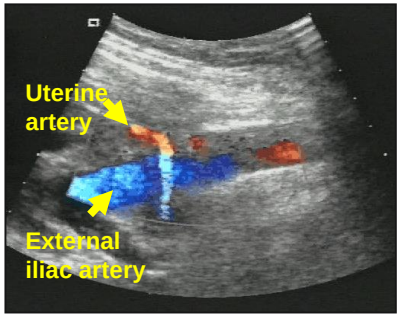
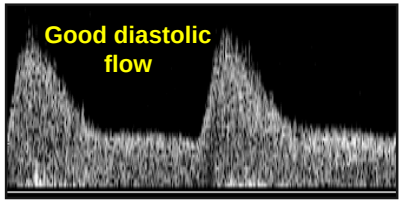
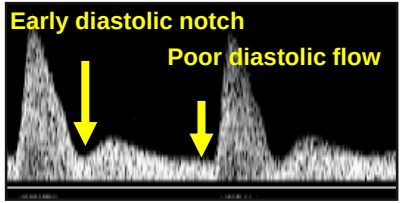
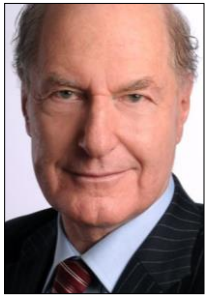
Uterine artery Doppler







Campbell S, Diaz-Recasens J, Griffin DR, Cohen-Overbeek TE, Pearce JM, Willson K, Teague MJ. New Doppler technique for assessing uteroplacental blood flow. Lancet **1983**; 1:675-7.



Soothill PW, Nicolaides K, Bilardo KM, Hackett GA, Campbell S. Uteroplacental blood velocity resistance index and umbilical venous pO2, pCO2, pH, lactate, and erythroblast count in **growth retarded fetuses**. Fetal Therapy **1986**; 1:176-9.

Lees C, Parra M, Missfelder-Lobos H, Morgans A, Fletcher O, Nicolaides KH. Individualized risk assessment for **adverse pregnancy outcome** by uterine artery Doppler at 23 weeks. Obstet Gynecol **2001**; 98:369-73

Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH. Prediction of **pre-eclampsia** by uterine artery Doppler imaging: relationship to gestational age at delivery and **small-for-gestational age**. Ultrasound Obstet Gynecol **2008**; 31:310-313.

Smith GC, Yu CK, Papageorghiou AT, Cacho AM, Nicolaides KH. Maternal uterine artery Doppler flow velocimetry and the risk of **stillbirth**. Obstet Gynecol **2007**; 109:144-151.

Poon LC, Volpe N, Muto B, Yu CK, Syngelaki A, Nicolaides KH. Second-trimester uterine artery Doppler in the prediction of **stillbirths**. Fetal Diagn Ther **2013**; 33:28-35.

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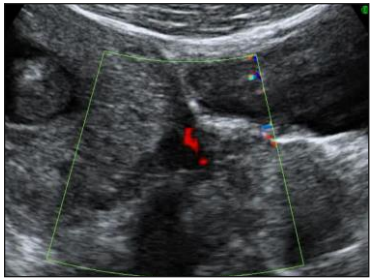
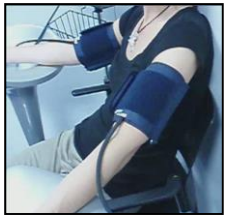
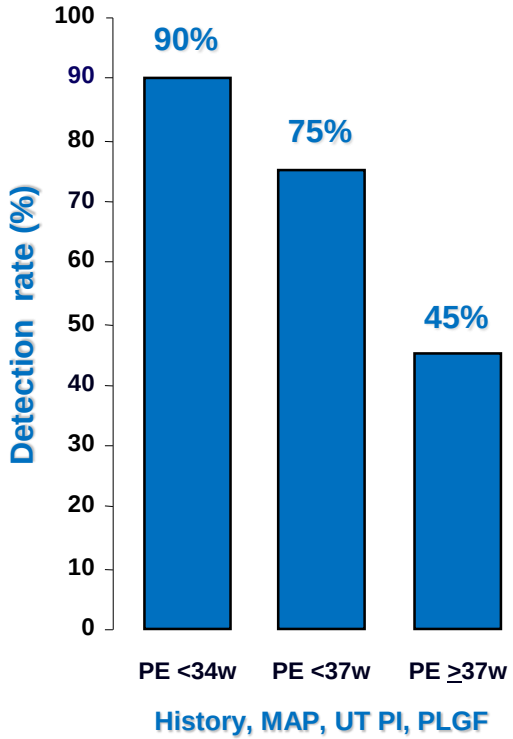
1991 - 2016 Prediction of PE at 11-13 w

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







- Kaminopetros et al. **Uterine artery Doppler** at 11-13 vs. 20-24 weeks. Fetal Diagn Ther **1991**
- 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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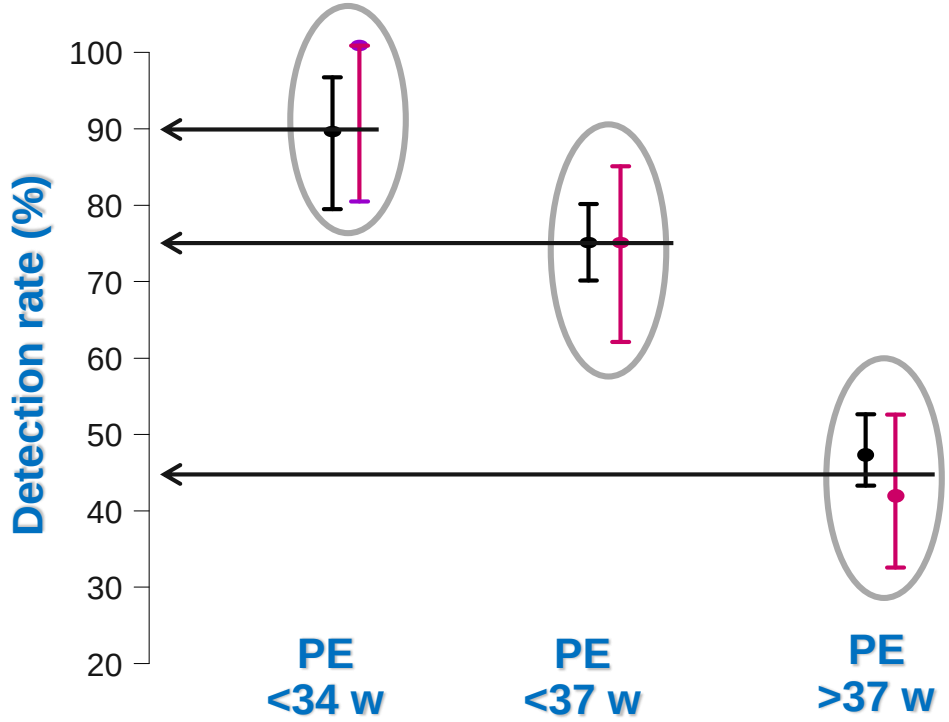
funded by EU FP7 ASPRE project

Validation of FMF algorithm

SPAIN:	**Murcia, Granada, Tenerife**
BELGIUM:	**Brussels**
ITALY:	**Milan**
GREECE:	**Athens**
ENGLAND:	**6 NHS hospitals**
Companies:	**PerkinElmer, Astraia, Viewpoint**



Screening n = 8,775; PE 239 (2.7%)

ULTRASOUND in Obstetrics & Gynecology

O'Gorman N, Wright D, Poon LC, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol **2017**; 49: 751–5.

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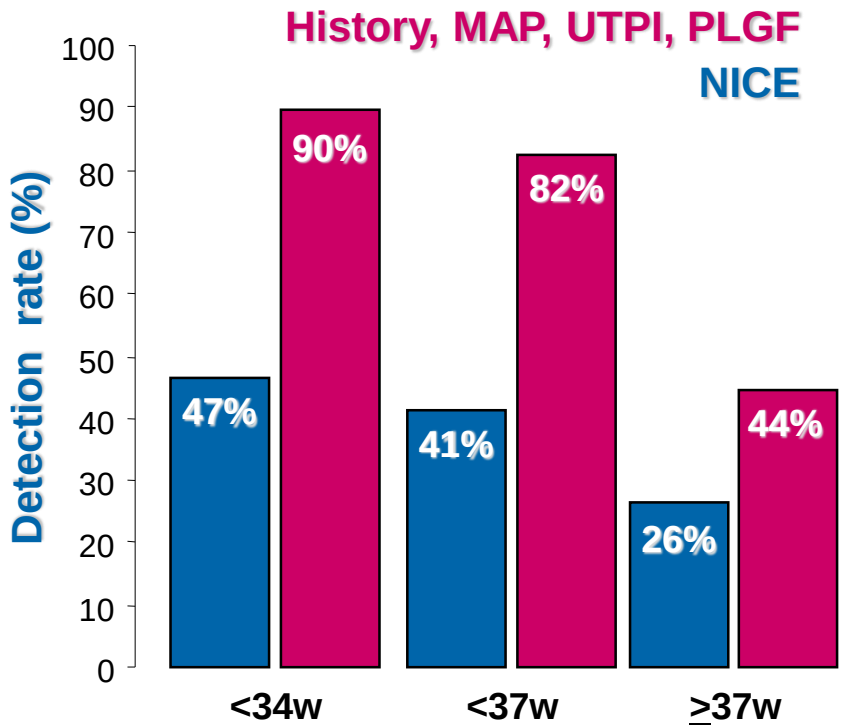
Validation of FMF algorithm

Screening for Preeclampsia

- 7 NHS hospitals in England
- Routine screening at 11-13 w
- Non-intervention study
- 16,747 singleton pregnancies
- Comparison of NICE vs. FMF
- Coordinated by UCL CCTU

National Institute For Health Research
Efficacy and Mechanism Evaluation Programme



ULTRASOUND in Obstetrics & Gynecology

Tan *et al*. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol **2018** doi: 10.1002/uog.19039.

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Prediction of PE at <37 w

Pregnancies: n = 61,174

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

Method of screening	DR %
History	45
+ MAP	51
+ MAP, PAPP-A	56
+ MAP, UTPI	68
+ MAP, UTPI, PAPP-A	68
+ MAP, PLGF	66
+ MAP, UTPI, PLGF	**75**
+ MAP, UTPI, PLGF, PAPP-A	75

ULTRASOUND in Obstetrics & Gynecology

Tan *et al*. Screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. **2018**

Prediction of preterm preeclampsia:

Selection of risk cut-off

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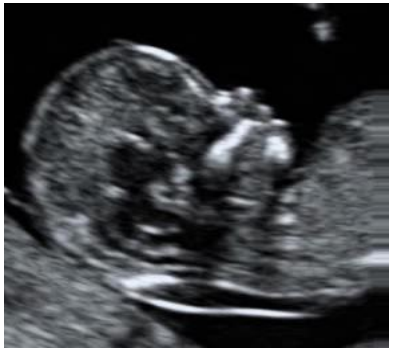
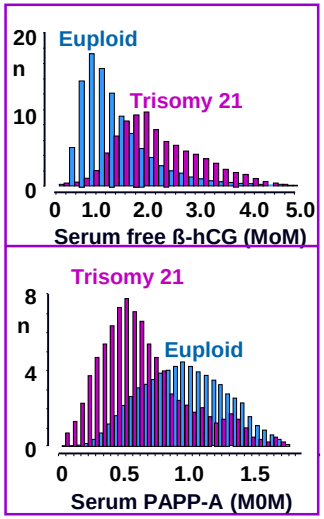
Lessons from screening for T21

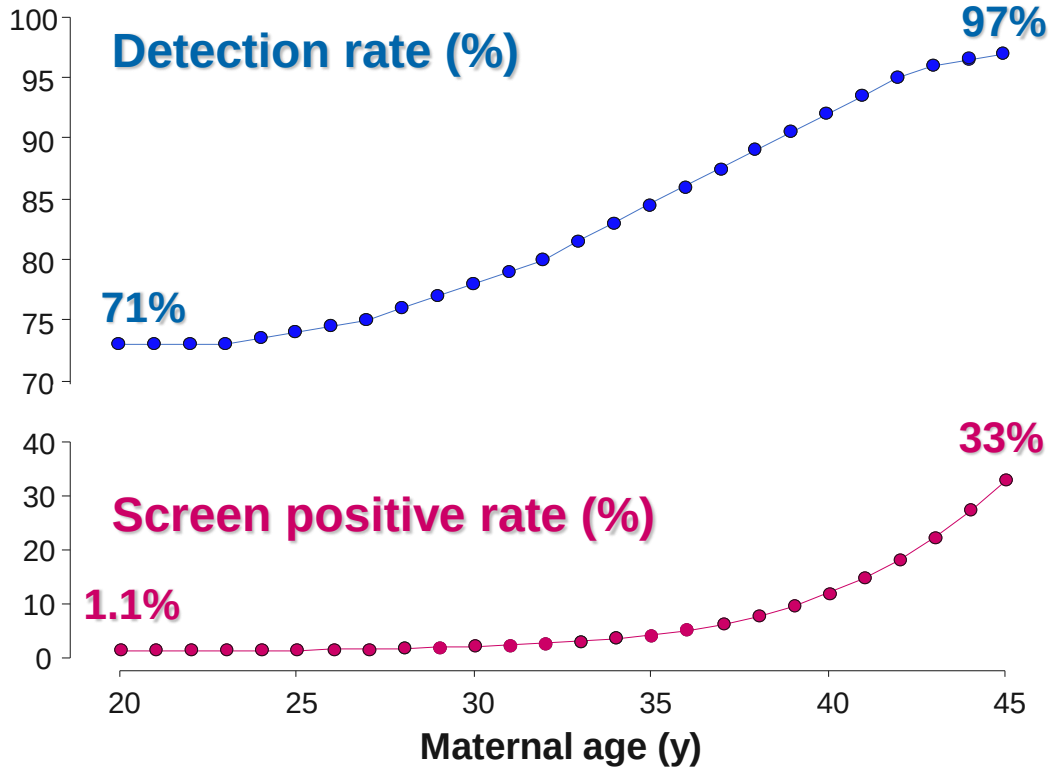


Detection rate 90%
for screen +ve rate 5%



NHS

At risk cut-off of 1 in 100
DR 86%, Screen +ve 2.7%



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Lessons from screening for T21

Screening by MAP, UTPI, PLGF

Risk Cut-off	White			Black		
	SPR	DR of PE <32 w	DR of PE <37 w	SPR	DR of PE <32 w	DR of PE <37 w
1 in 20	1.5	42	31	10.0	89	73
1 in 50	4.8	73	56	21.0	95	85
1 in 70	7.0	81	65	26.6	98	88
1 in 100	10.4	88	69	34.0	100	92
1 in 150	15.6	94	81	43.4	100	96
1 in 200	20.2	94	83	50.4	100	98

ULTRASOUND in Obstetrics & Gynecology

Tan *et al*. Screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. **2018**

Algorithm validation / adjustment in Spain

Spanish Multicenter Study: PREVAL

NHS
National Institute for Health and Clinical Excellence

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

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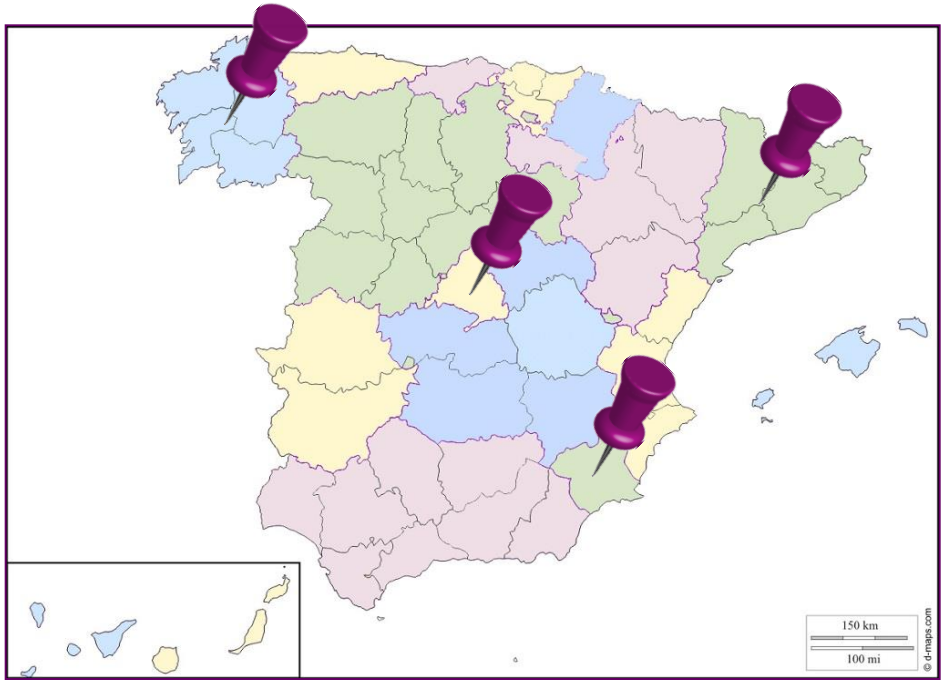
FETAL MEDICINE BARCELONA



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Hospital Universitario Fundación Alcorcón
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Arrixaca
Hospital Universitario "Virgen de la Arrixaca"

Hospital Universitario Quirón Madrid

Servizo Galego de Saúde
Complexo Hospitalario Universitario A Coruña
A Coruña

Vall d'Hebron
Hospital
Àrea Materno-infantil

GE Healthcare
ThermoFisher Scientific

8,000 patients

Prevention of preterm preeclampsia

Prevention of preeclampsia

Bed rest and dietary manipulations

The rate of PE is not reduced by:

- Bed rest or restriction of physical activity.
- Restriction of salt intake.
- Supplementation with magnesium, zinc, folate, vitamins C and E or fish oil.

The rate of PE is halved by:

- Dietary calcium (1.2 - 2.5 g/d) in women with low calcium intake (<600 mg/d).

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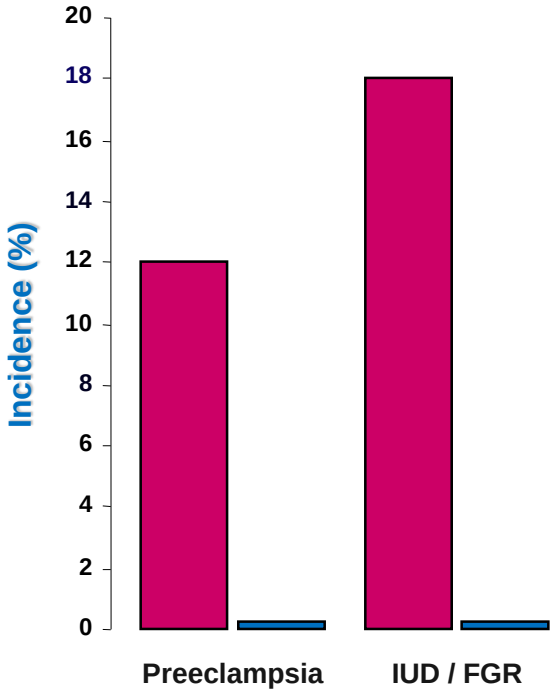
1985

Prevention of PE: aspirin

Prevention of pre-eclampsia by early antiplatelet therapy

Beaufils M, Uzan S, Donsimoni R, Colau JC, Lancet 1985

- RCT: 102 patients at high risk of PE and / or FGR
- **Aspirin 150 mg from 12 weeks (A)** vs **no treatment (B)**



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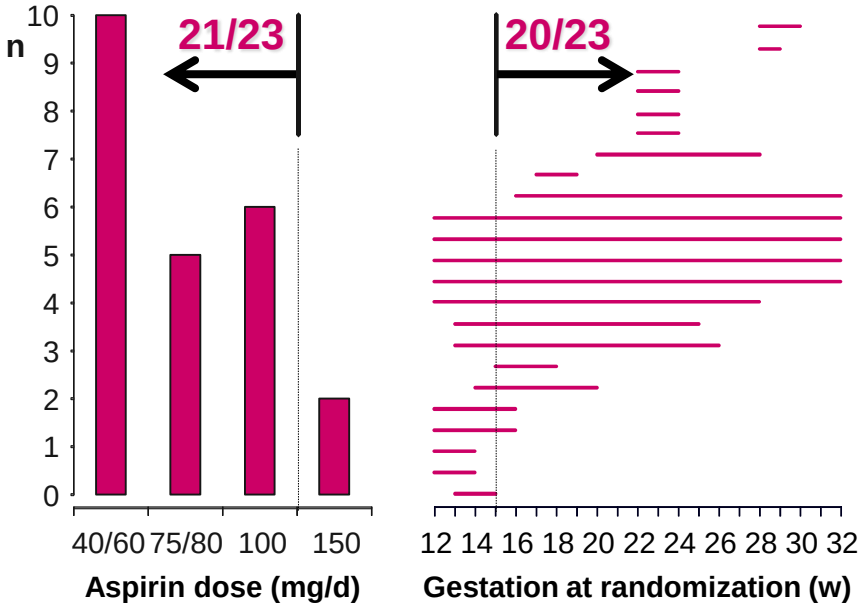
Prevention of PE: aspirin

Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data

Askie *et al*. Lancet 2007; 369: 1791

- Meta-analysis of individual patient data from **32,217 women in 31 RCTs (aspirin 23)**

- RR for PE: **0.90** (95% CI 0.84-0.97)
- RR for birth <34 w: **0.90** (95% CI 0.83-0.98)



14 different definitions of PE

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SEVENTH FRAMEWORK PROGRAMME

Prevention of PE: aspirin

Virgen de la Arrixaca, Murcia, Spain
San Cecilio Hospital, Granada, Spain
Hospiten Sur, Tenerife, Spain

Chu Brugmann Brussels, Belgium
Attikon University Hospital, Greece
Ospedale Maggiore Policlinico, Italy

King's College Hospital, UK
Medway Maritime Hospital, UK
Lewisham University Hospital, UK
North Middlesex Hospital, UK
Southend University Hospital, UK
Homerton University Hospital, UK

Statistical analysis: D Wright, A Wright

Companies: Perkin Elmer, Astraia, Viewpoint

DOSE: 150 mg / day

Aspirin resistance: 30% at 81mg and 5% at 160 mg

Caron et al: J Obstet Gynaecol Can 2009;31:1022-7

START: 12 weeks

FINISH: 36 weeks

Avoid potential neonatal hemorrhage

TIME: Bed time

RCT aspirin 100 mg vs placebo

morning, afternoon, night

Aspirin at night: lower PE, FGR, PTB or IUD

Ayala DE, Ucieda R, Hermida RC: Chronobiol Int 2013; 30:260-279

OUTCOME: Preterm PE

STUDY POPULATION:

High-risk group defined by FMF algorithm

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Prevention of preterm-PE

11-13w risk assessment

10%

Screen +ve (risk 1:100)

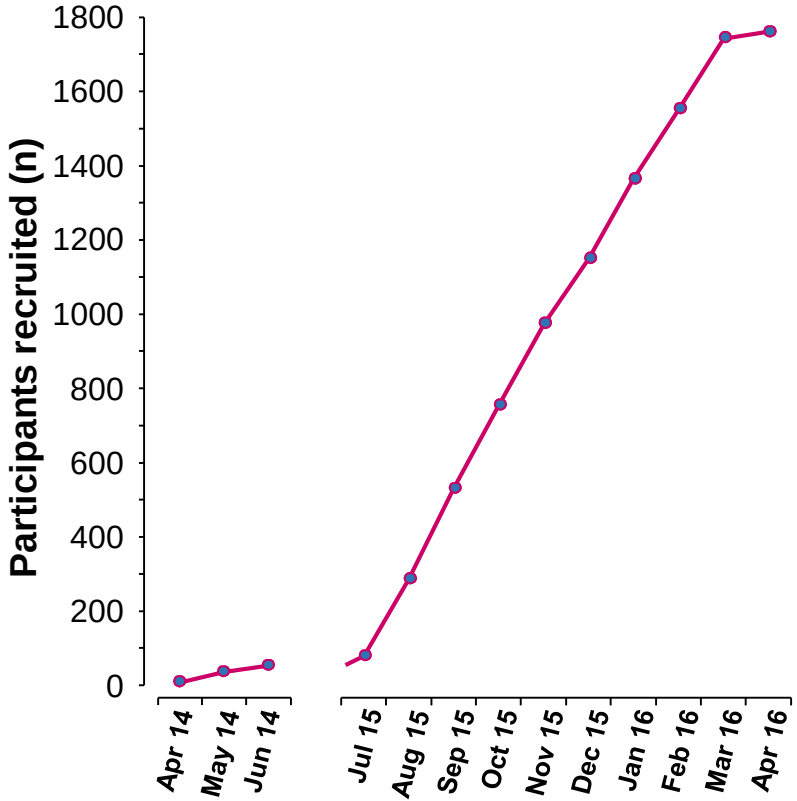
60%

Agree to participate

Placebo

Aspirin 150 mg

1,600 needed to prove significant difference with 90% power



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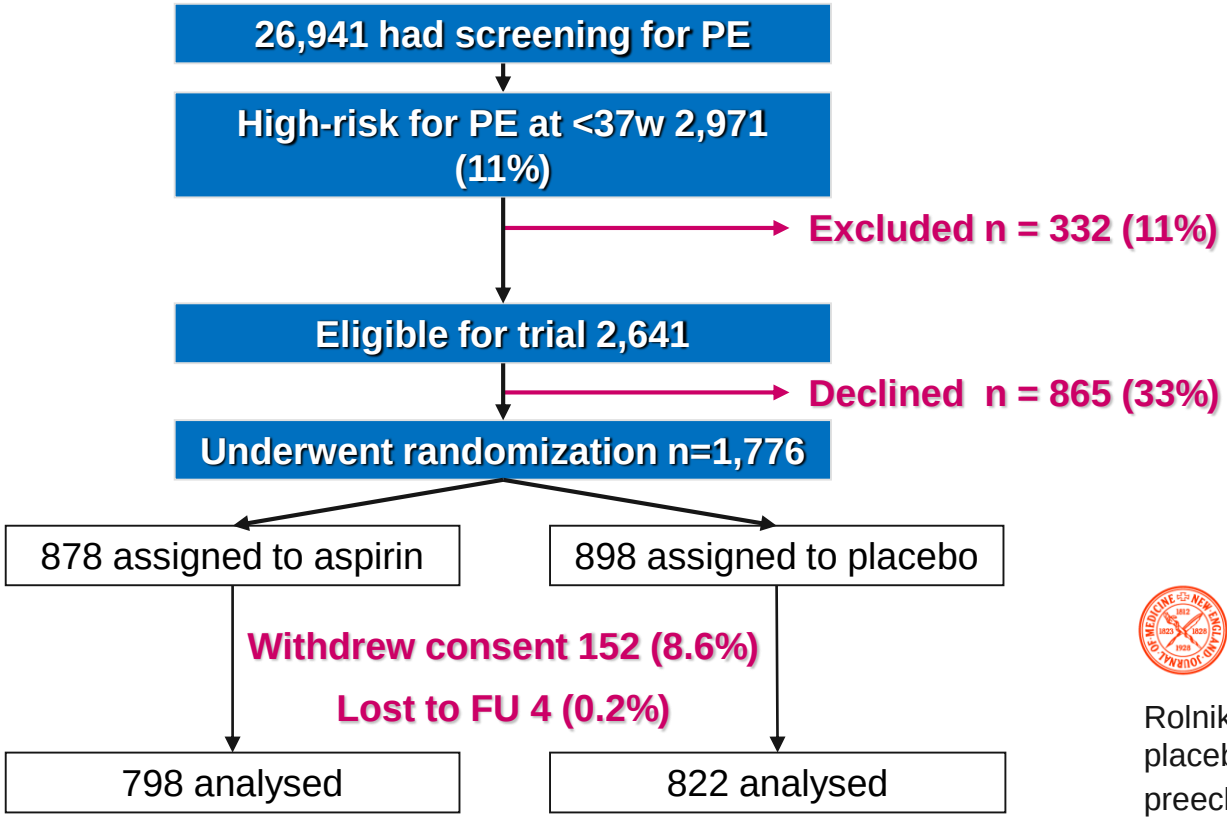
Prevention of preterm-PE



253	Receiving aspirin
47	Hypersensitivity to aspirin
17	Peptic ulcer, bleeding disorders
10	Participation in another drug trial
2	Miscarriage before randomization
3	Termination before randomization

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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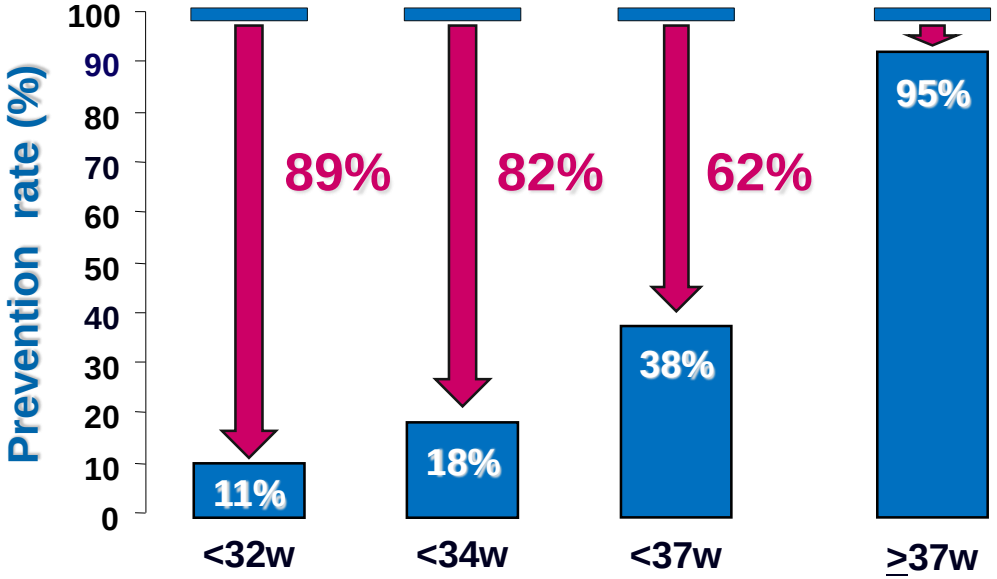
Prevention of preeclampsia



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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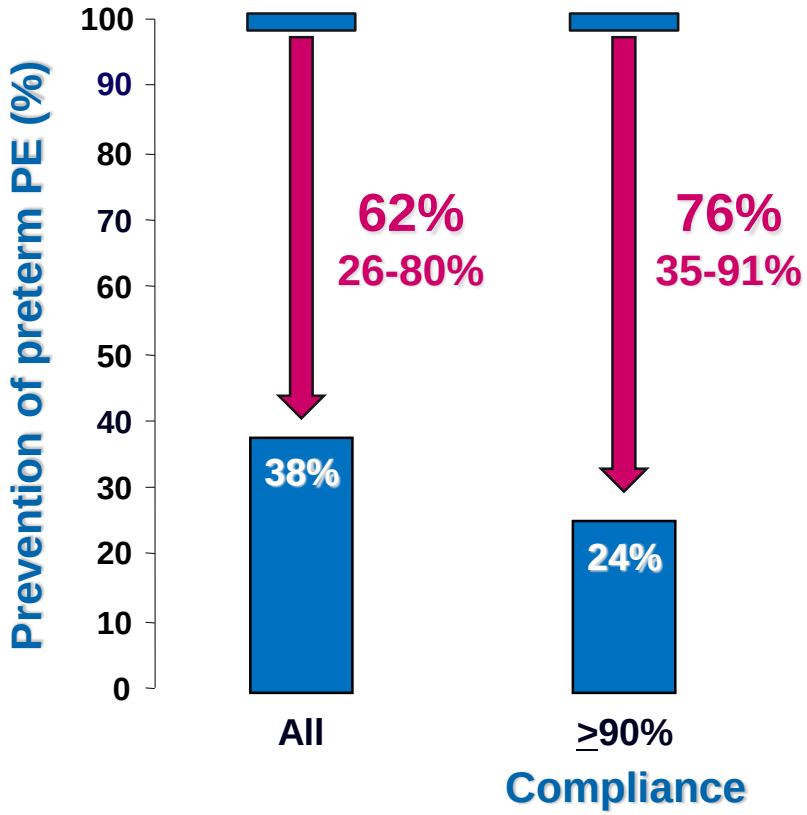
ASPRE project

Effect of compliance



AJOG American Journal of Obstetrics & Gynecology

Wright D *et al*. ASPRE trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. Am J Obstet Gynecol **2017**; 17: 31097.

Compliance:
86% of women took ≥80% of tablets
71% of women took ≥90% of tablets

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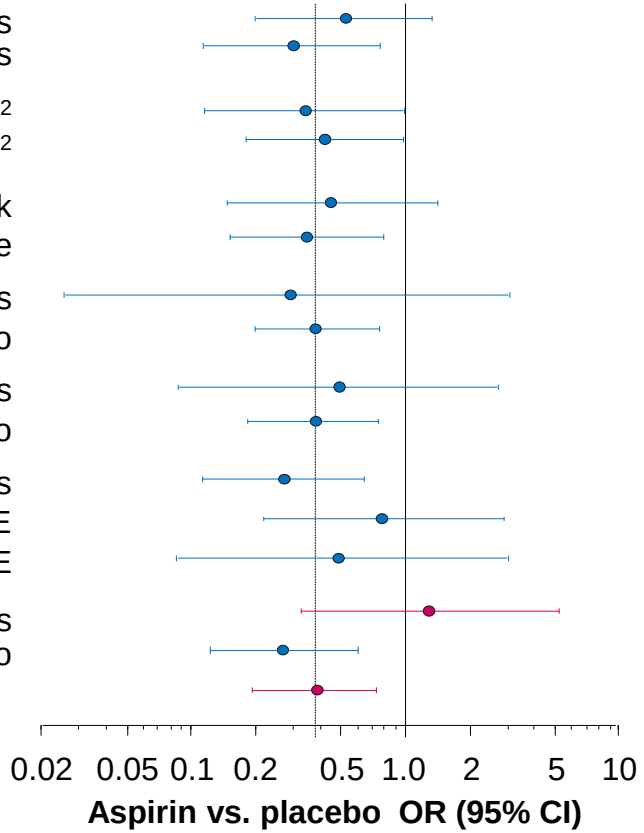
ASPRE project

Effect of maternal factors



* 5 / 49 vs. 5 / 61

AJOG American Journal of Obstetrics & Gynecology

Poon *et al*. ASPRE trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. Am J Obstet Gynecol **2017**; 217: 585.e1-585.e5.

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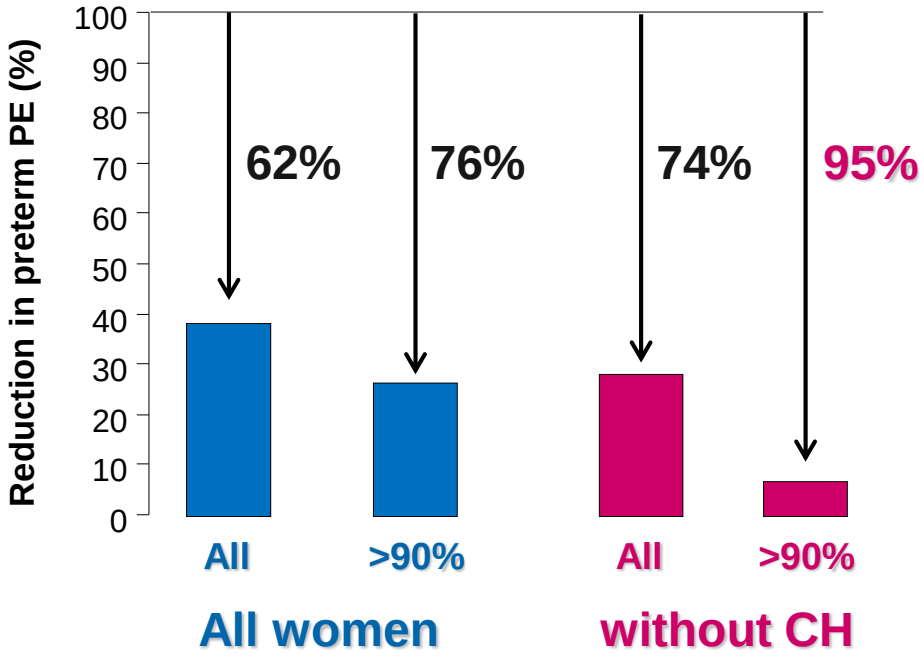
Effect of maternal factors and compliance



AJOG American Journal of Obstetrics & Gynecology

Poon *et al*. ASPRE trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. Am J Obstet Gynecol **2017**; 217: 585.e1-585.e5.

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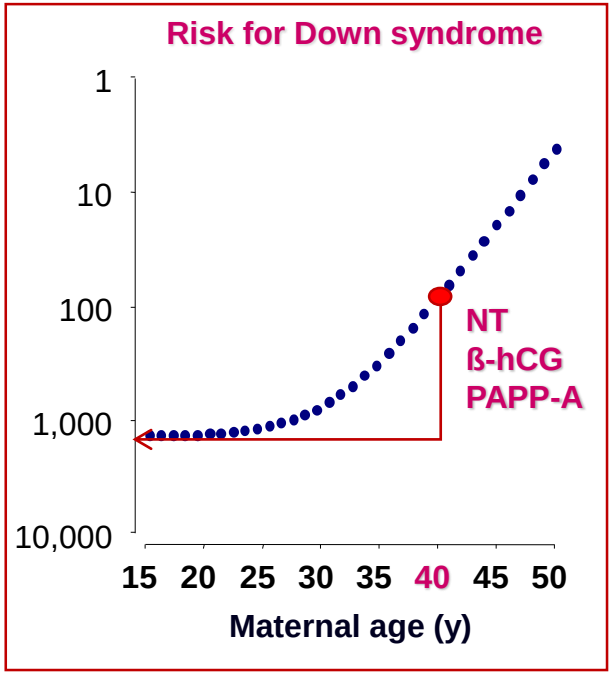
ASPRE project

NICE +ve but FMF -ve

	High risk factors	Moderate-risk factors
NICE +ve / FMF +ve	8.7 (6.9-10.9)	4.9 (3.5-6.8)
NICE +ve / FMF -ve	**0.65** (0.2-1.7)	**0.42** (0.2-0.9)
RR (95% CI)	0.08 (0.03-0.2)	0.09 (0.04-0.2)

34,573 singleton pregnancies at 11-13 w: preterm-PE 239 (0.7%)



ULTRASOUND in Obstetrics & Gynecology

Poon *et al*. ASPRE trial: incidence of preterm preeclampsia in patients fulfilling ACOG and NICE criteria according to risk by the FMF algorithm. Ultrasound Obstet Gynecol **2018**; 1002/uog.19019.

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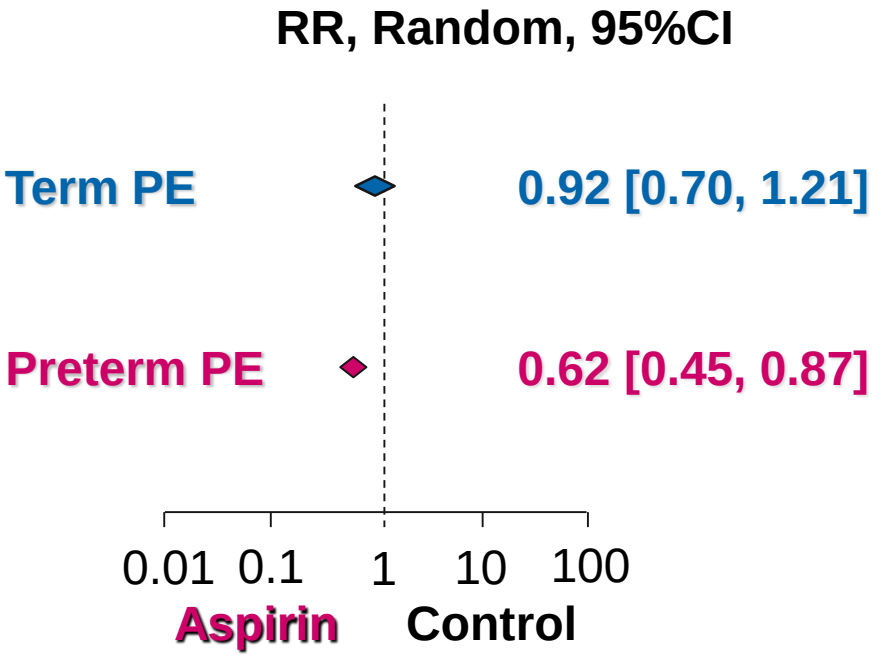
Prevention of preeclampsia



AJOG American Journal of Obstetrics & Gynecology

Roberge S, Bujold E, Nicolaides K. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol **2017**;pii: S0002-9378(17)32326-8.

Meta-analysis 16 trials: 18,907 participants

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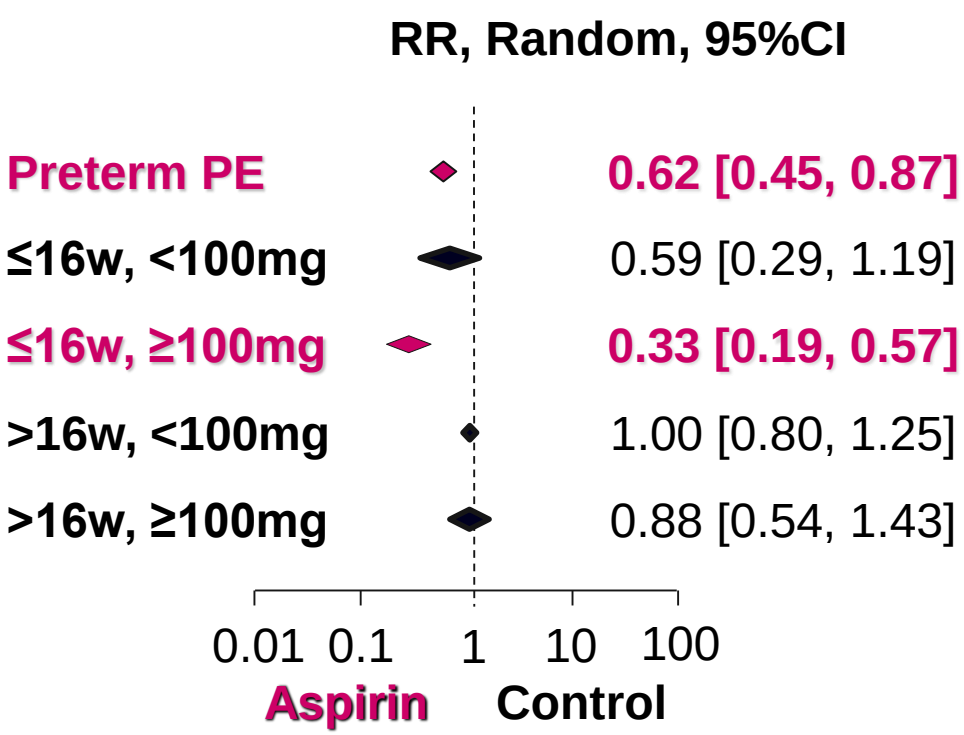
Prevention of preterm-PE



AJOG American Journal of Obstetrics & Gynecology

Roberge S, Bujold E, Nicolaides K. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol **2017**;pii: S0002-9378(17)32326-8.

Meta-analysis 16 trials: 18,907 participants

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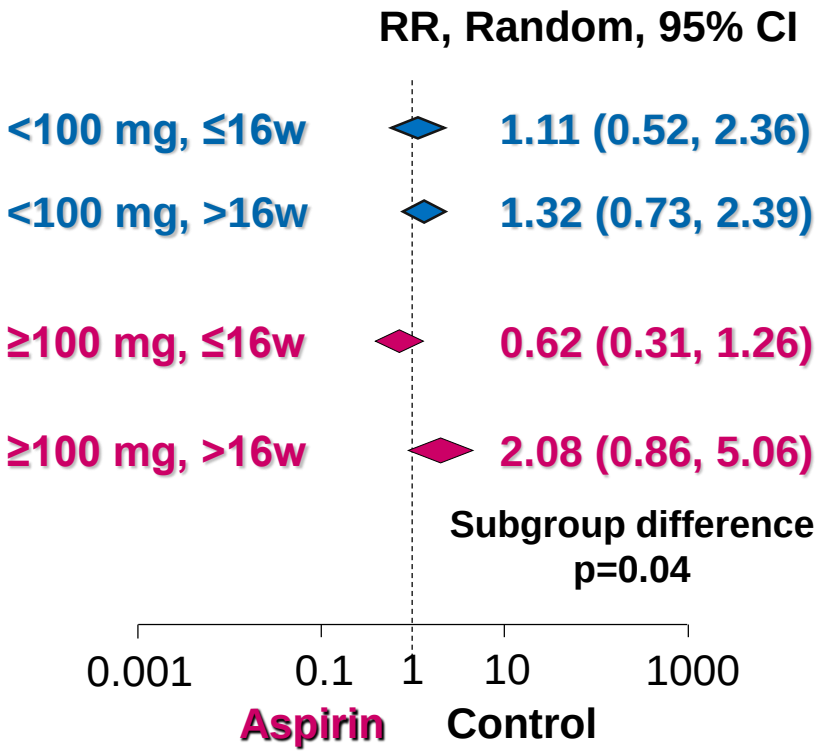
Aspirin and placental abruption



AJOG American Journal of Obstetrics & Gynecology

Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. Am J Obstet Gynecol **2018**; pii: S0002-9378(17)32812-0

Meta-analysis 20 trials: 12,585 participants

First trimester prediction and prevention of preterm-PE

Cost effectiveness

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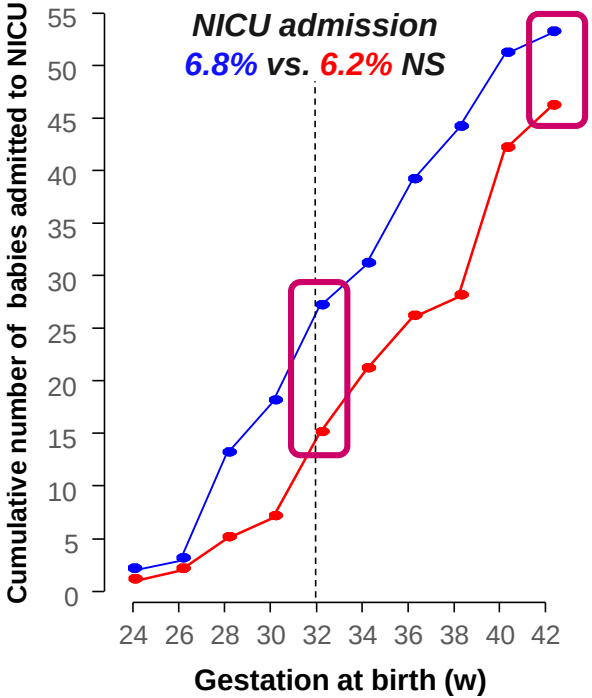
funded by EU FP7 ASPRE project

Admission to NICU



AJOG American Journal of Obstetrics & Gynecology

Wright *et al*. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol **2018**, doi: 10.1016/j.ajog.2018.02.014.

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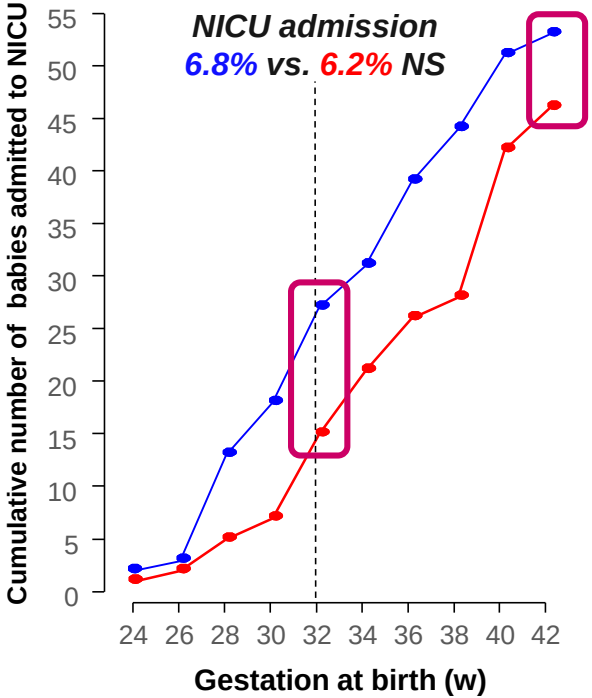
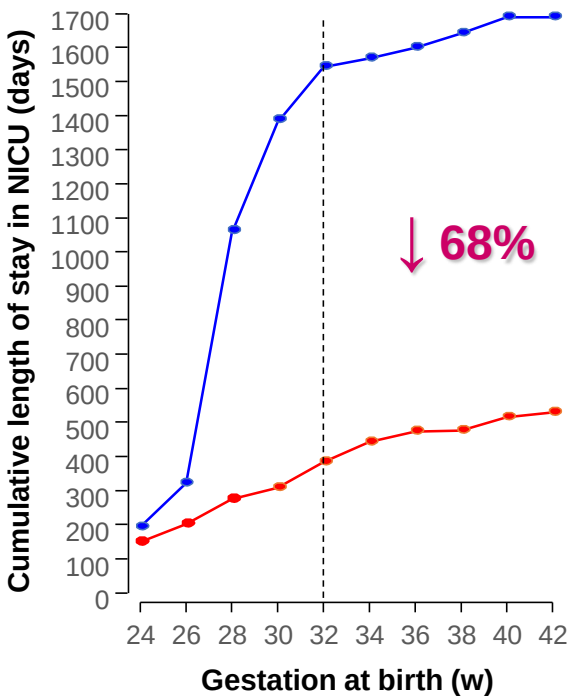
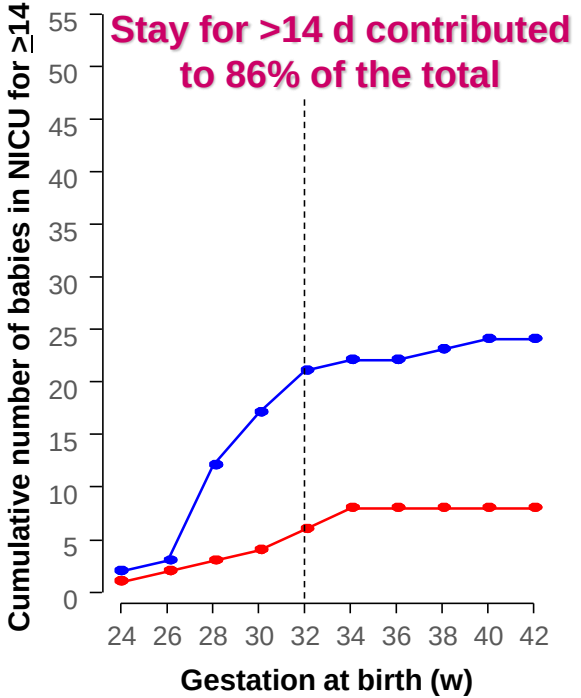
ASPRE project

Admission to NICU







Babies born at <32 weeks' gestation contributed to 83% of total length of stay in NICU

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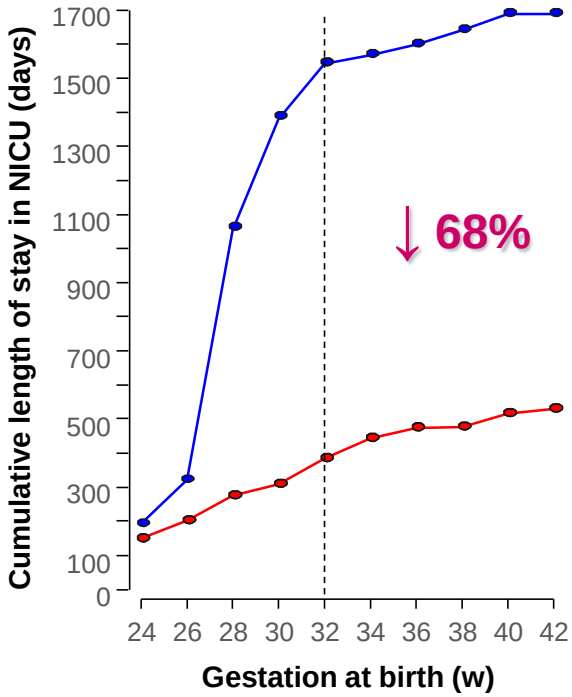
Admission to NICU



10,000 pregnancies

1,000 Screen +ve
Rx aspirin

Aspirin ↓ length of stay by 1.4 d per baby

1.4 x 1,000 = 1,400 d
1400 x $2,000 = $2.8 m

$2,800,000 / 10,000
Cost per screen $280

What is the cost?

History, MAP: part of routine care

UTPI: extra 2 min on 11-13 w scan

PLGF: marginal

AJOG American Journal of Obstetrics & Gynecology

Wright *et al*. ASPRE trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol **2018** doi: 10.1016/j.ajog.2018.02.014.

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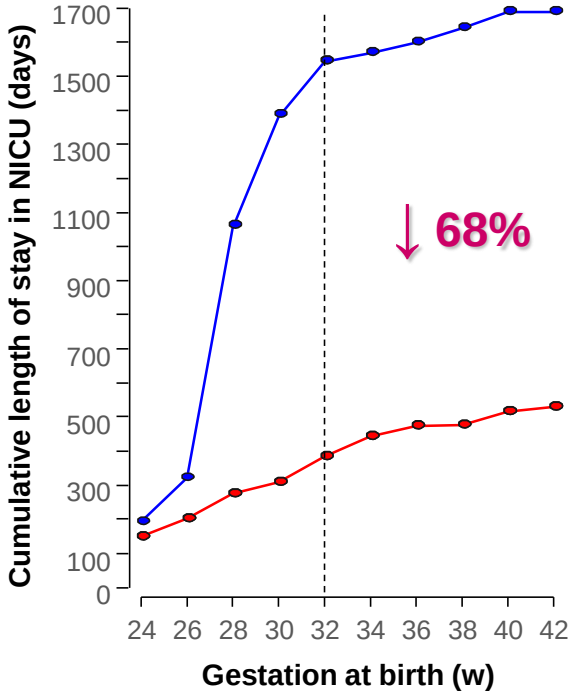
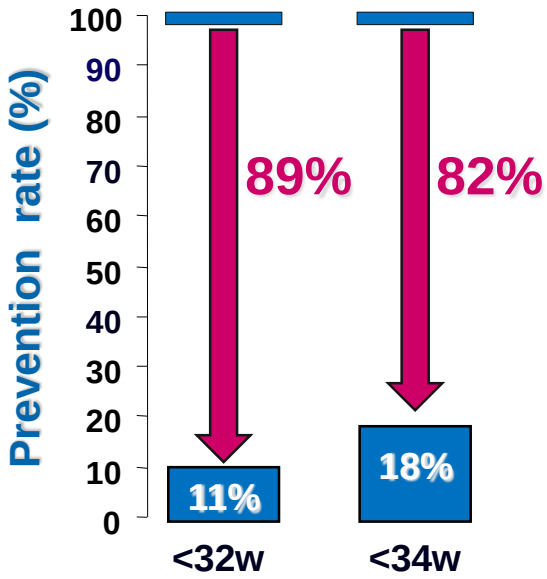
ASPRE project

Admission to NICU





Rolnik et al. N Engl J Med 2017;377:613

At 2 y: death or disabilities

22-31 w: 19% 32-34 w: 2%

5,567 live births at 22-34 w France 2011

Pierrat et al. BMJ 2017;358:j2338

Birth	Death <5 y	Cerebral palsy	Impaired work capacity
23-27w	80%	9.1%	10.6%
28-30w	40%	6.0%	8.2%
31-33w	11%	1.9%	4.2%
34-36w	2.3%	0.3%	2.4%
≥37w	0.6%	0.1%	1.7%

867,692 live births Norway 1967-1983

Moster et al. NEJM 2008;359:262

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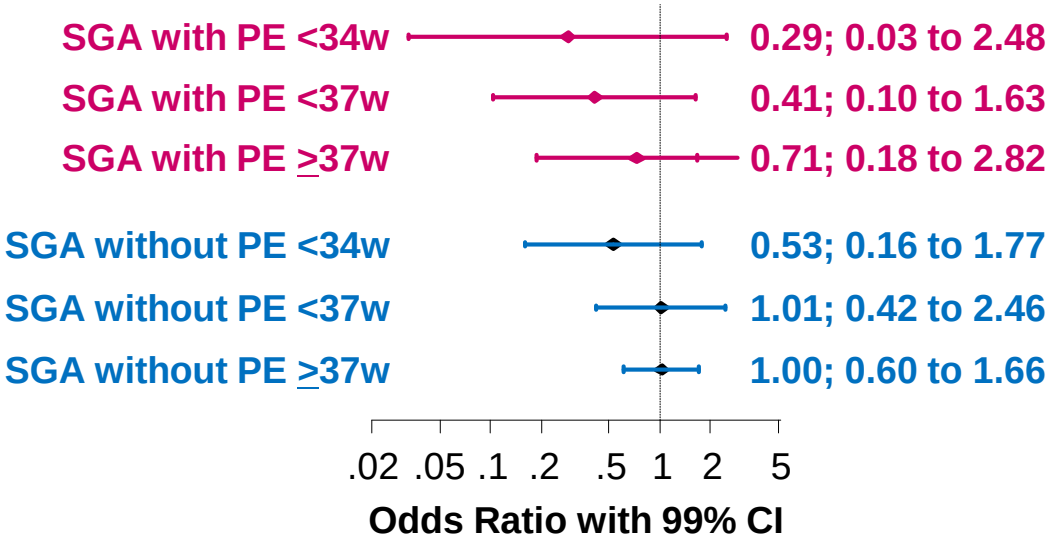
funded by EU FP7 ASPRE project

Prevention of SGA



SGA <32 w	RR (95% CI)
<10th centile	0.268 (0.113 to 0.636)
<5th centile	0.280 (0.117 to 0.668)
<3rd centile	0.294 (0.122 to 0.703)

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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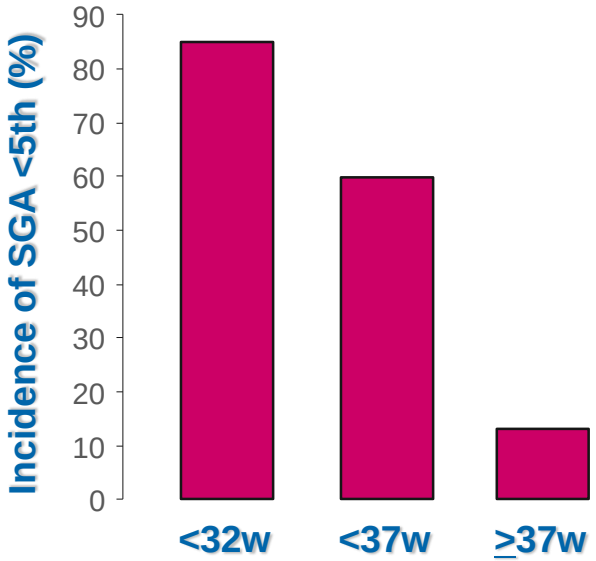
Prevention of SGA

Proportion of SGA in PE



SGA neonates <5th centile born at <32 w:
- **40% are from pregnancies with PE**
- **60% have risk for PE of >1 in 100**
- **72% (33-88%) reduction in risk by aspirin**

First trimester screening for PE and use of aspirin in the high-risk group could reduce the incidence of early-SGA by about 40%.

ULTRASOUND in Obstetrics & Gynecology

Tan *et al*. Prediction and prevention of small for gestational age neonates: evidence from SPREE and ASPRE. Ultrasound Obstet Gynecol **2018**. doi: 10.1002/uog.19077.

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Prevention of preterm-PE: aspirin

Aspirin >100 mg onset at <16 w:

- Reduction in PE <32 w	90%
- Reduction in PE <34 w	80%
- Reduction in PE <37 w	65%
- Reduction in abruption	30%*
- Reduction in SGA <32 w	40%
- Reduction in LOS in NICU	65%

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Screening for PE in the 2nd and 3rd trimesters

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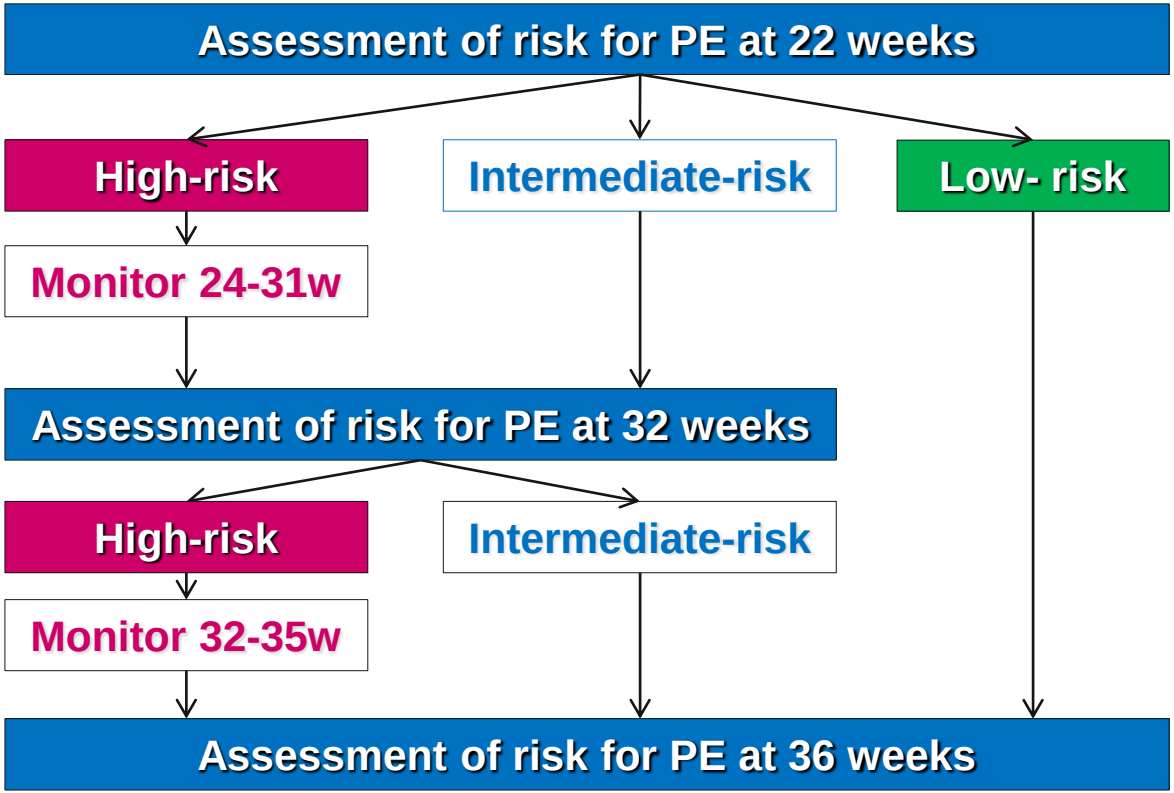
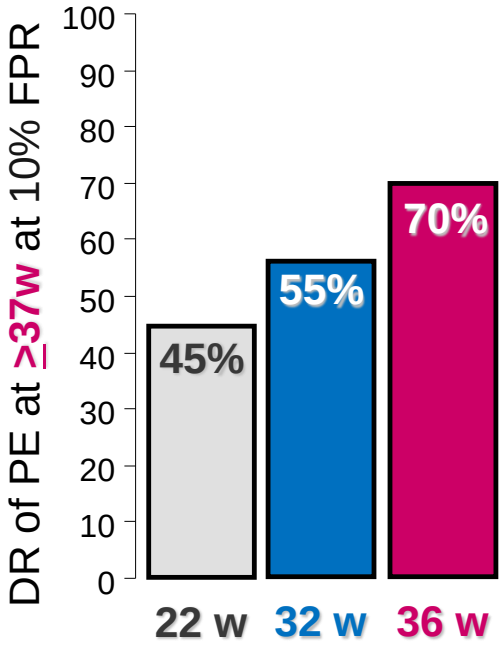
Combined screening for PE at 22 weeks

Objective: define pregnancy management





Gallo et al. AmJOG 2016;214:619
Tsiakkas et al. AmJOG 2016;215:87
Panaitescu et al. UOG 2018; in press

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Screening for PE at 22 w

- Select cut-off for PE <32 w
  to include 95% of cases of PE <32 w

- Select cut-off for PE <36 w
  to include 90% of cases of PE at 32-36 w

High-risk group: Very small

High / intermediate risk group: Small

Low-risk group: Very big
- Contains very few cases of PE <37w

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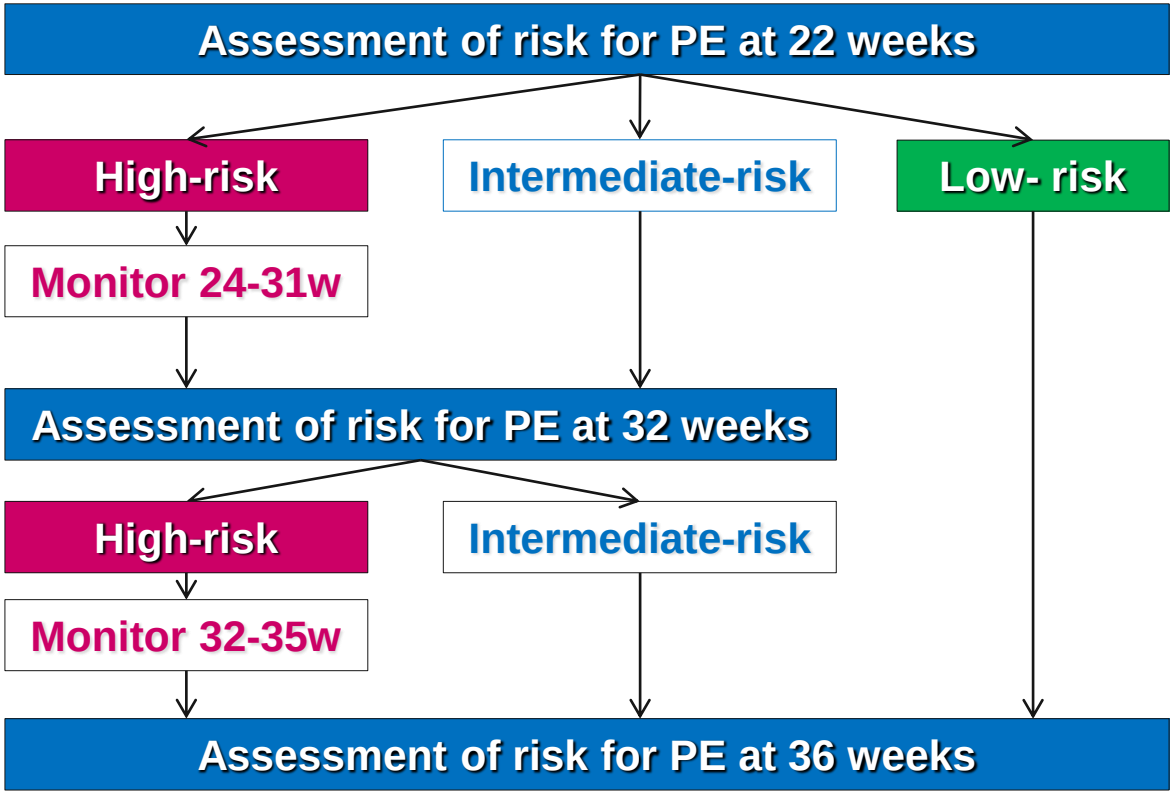
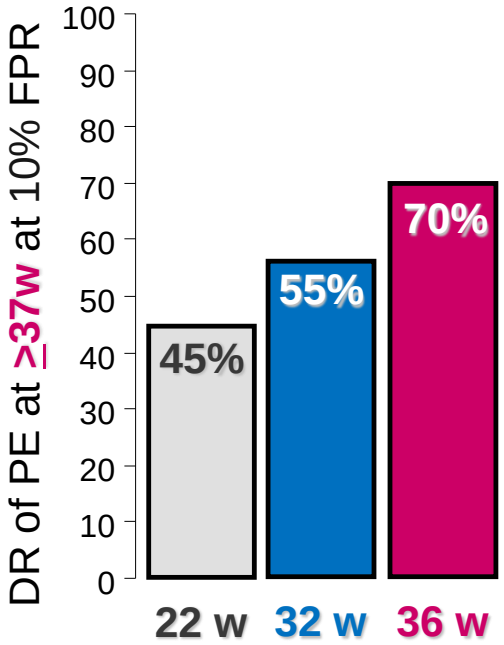
Combined screening for PE at 22 weeks

Objective: define pregnancy management





Gallo et al. AmJOG 2016;214:619
Tsiakkas et al. AmJOG 2016;215:87
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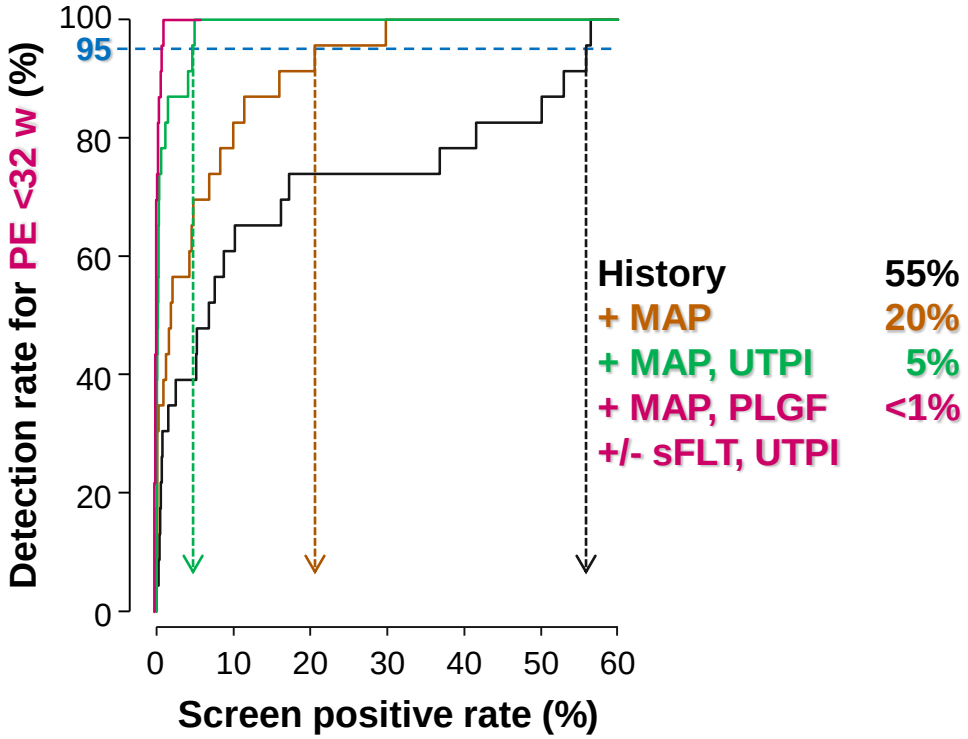
Combined screening at 22 w
Prediction of PE at <32 w



Risk cut-off 1 in 25
Screen positive rate <1%

Method of screening	DR
History	9%
+ MAP	35%
+ MAP, UTPI	78%
+ MAP, PLGF	91%
+ MAP, UTPI, PLGF	100%
+ MAP, UTPI, PLGF, sFLT	100%

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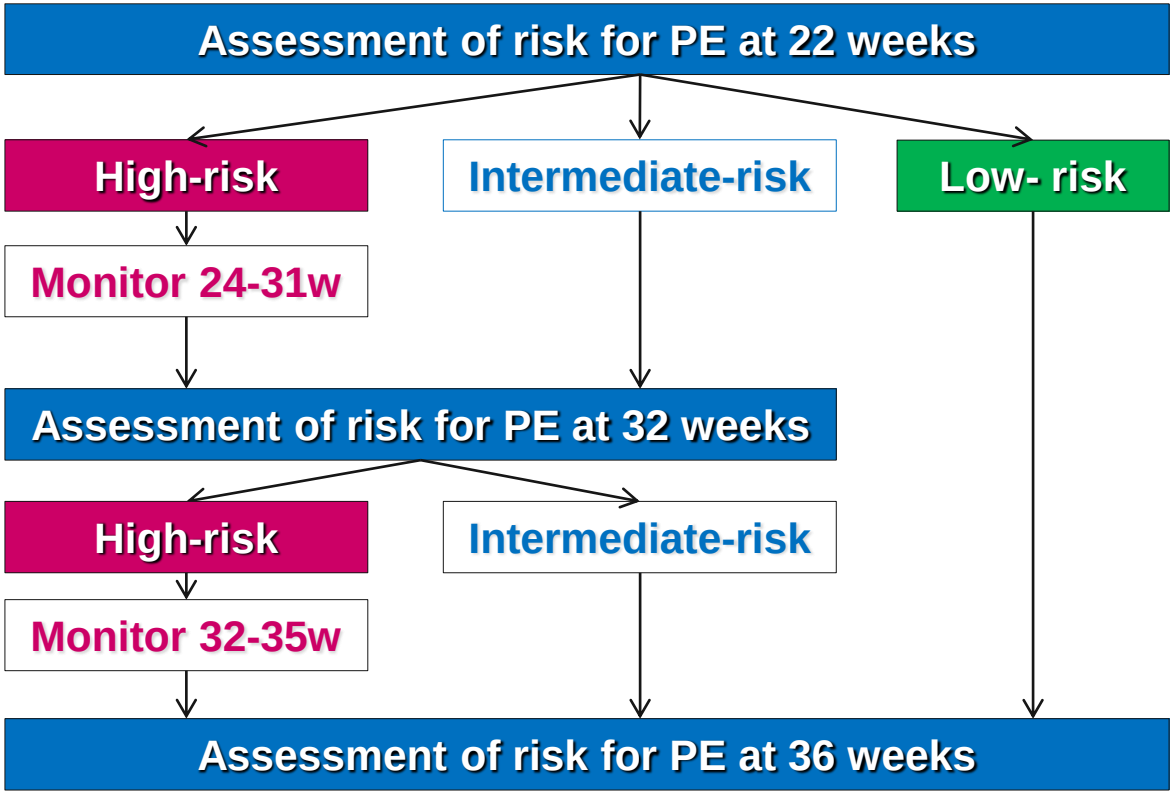
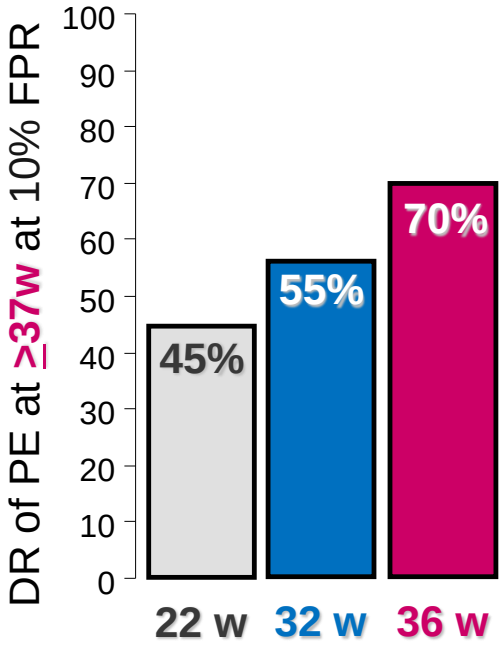
Combined screening for PE at 22 weeks

Objective: define pregnancy management





Gallo et al. AmJOG 2016;214:619
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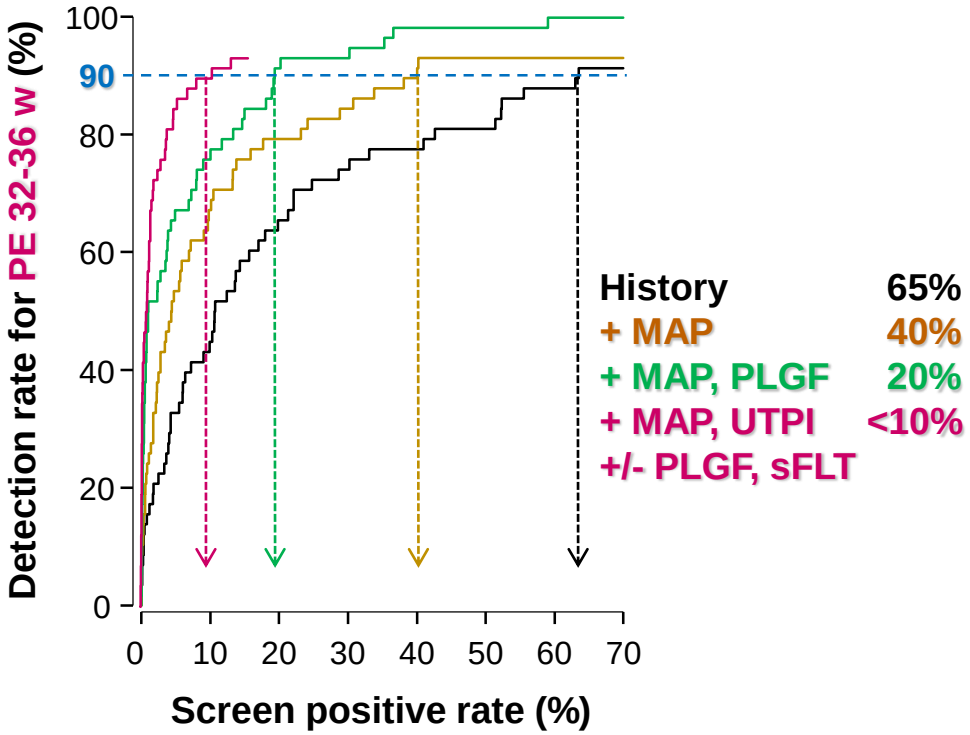
Combined screening at 22 w
Prediction of PE at 32-36 w



Risk cut-off 1 in 150
*Screen positive rate 10%

Method of screening	DR
History	62%
+ MAP	79%
+ MAP, PLGF (sFLT) *	78%
+ MAP, UTPI *	90%
+ MAP, UTPI, PLGF *	91%
+ MAP, UTPI, PLGF, sFLT *	90%

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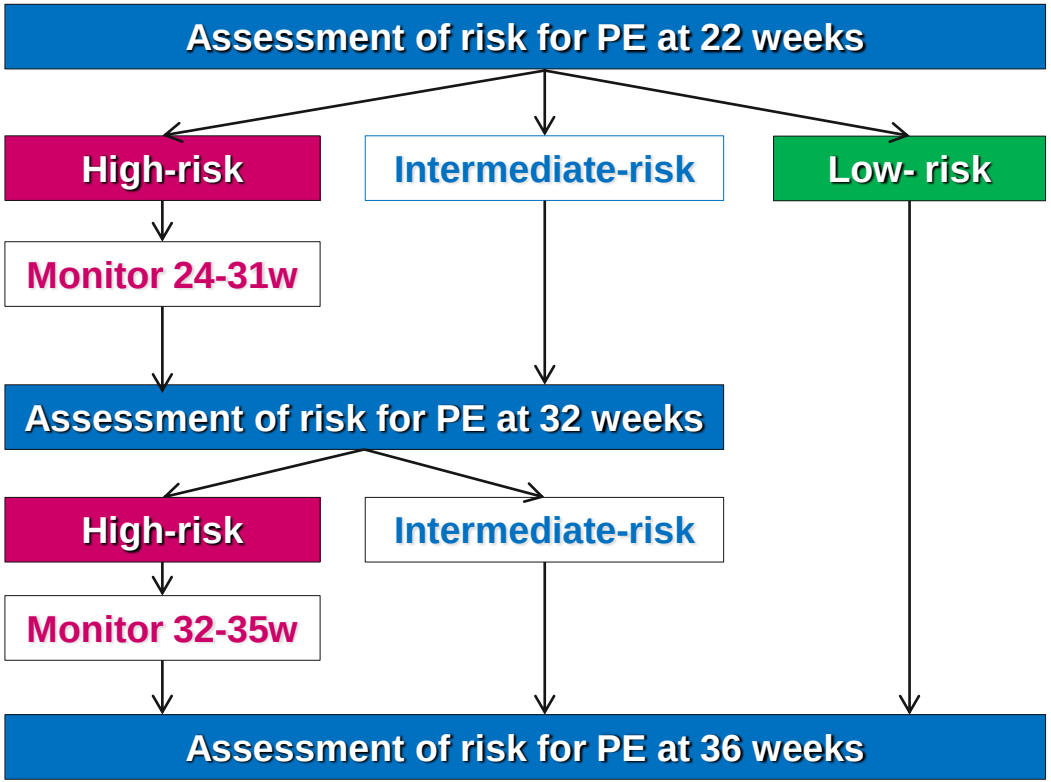
Combined screening for PE at 22 w



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**

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Preeclampsia screening: time for implementation

11 – 13 weeks → We are ready

- Reduction on maternal and fetal morbi-mortality
- Reduction in costs

20 – 22 weeks → More evidence is coming

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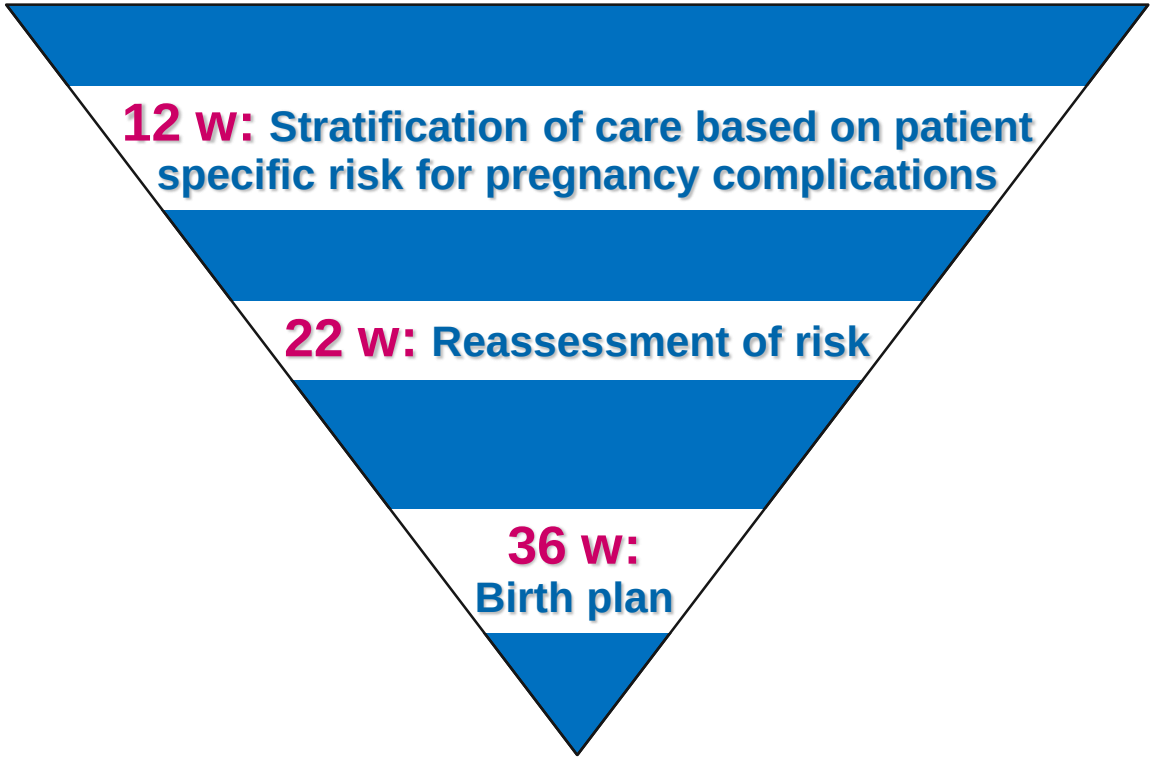
Inversion of pyramid of care



Prenatal care 2018

Thank you

The Fetal Medicine Foundation

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