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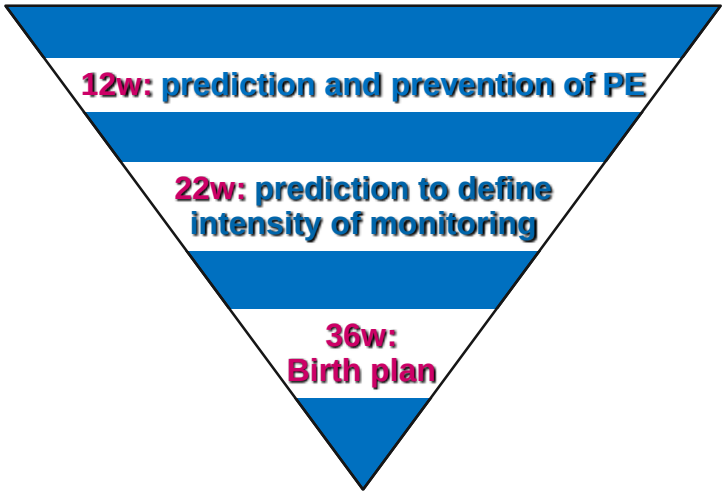
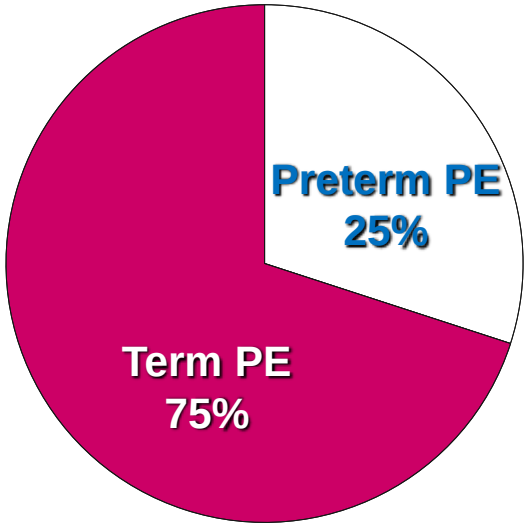
# Prevention of late preeclampsia: The STATIN trial

Anca Panaitescu



# Late preeclampsia is important

# Preeclampsia at ≥37 w




**50% of all maternal deaths in association with PE**

SPREE study n = 16,452 births >20 w
Preeclampsia n = 473 (2.9%)

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# Early vs. late Preeclampsia

**670,120 singleton births**
**Washington State 2000 – 2008**

| | |
|---|---|
| **Preeclampsia:** | **3%** |
| **Early <34 w:** | **0.3%** |
| **Late ≥34 w:** | **2.7%** |

| | Early PE (2,374) | Late PE (17,890) | No PE (649,856) |
|---|---|---|---|
| **Maternal death** / 100,000 births | 42.1 n=1 | 11.2 n=2 | 4.2 n=29 |
| **Severe morbidity** / 100 births | 12.2 n=289 | 5.5 n=985 | 3.0 n=19,262 |

Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol 2014;124:771-81.

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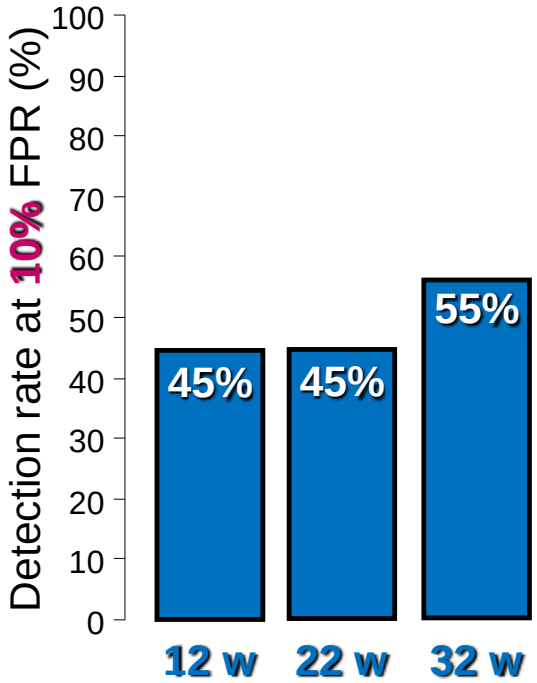
# Prediction of PE at ≥37 w




**Prediction of PE at ≥37 w by the combined test at 12, 22, 32 w is poor**

O'Gorman et al. AmJOG 2016;214:103; Gallo et al. AmJOG 2016;214:619; Tsiakkas et al. AmJOG 2016;215:87

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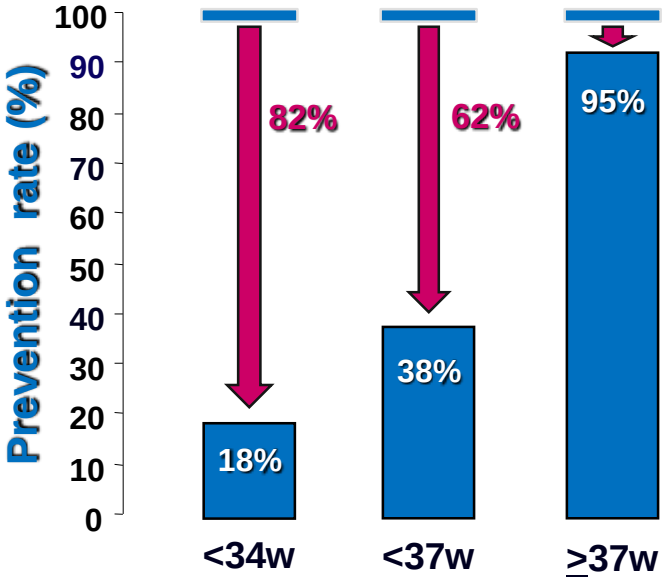
ASPRE project

# Prevention of PE at ≥37 w




**Prevention of PE at ≥37 w by Aspirin from 12 w is poor**

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.

# Screening for late preeclampsia

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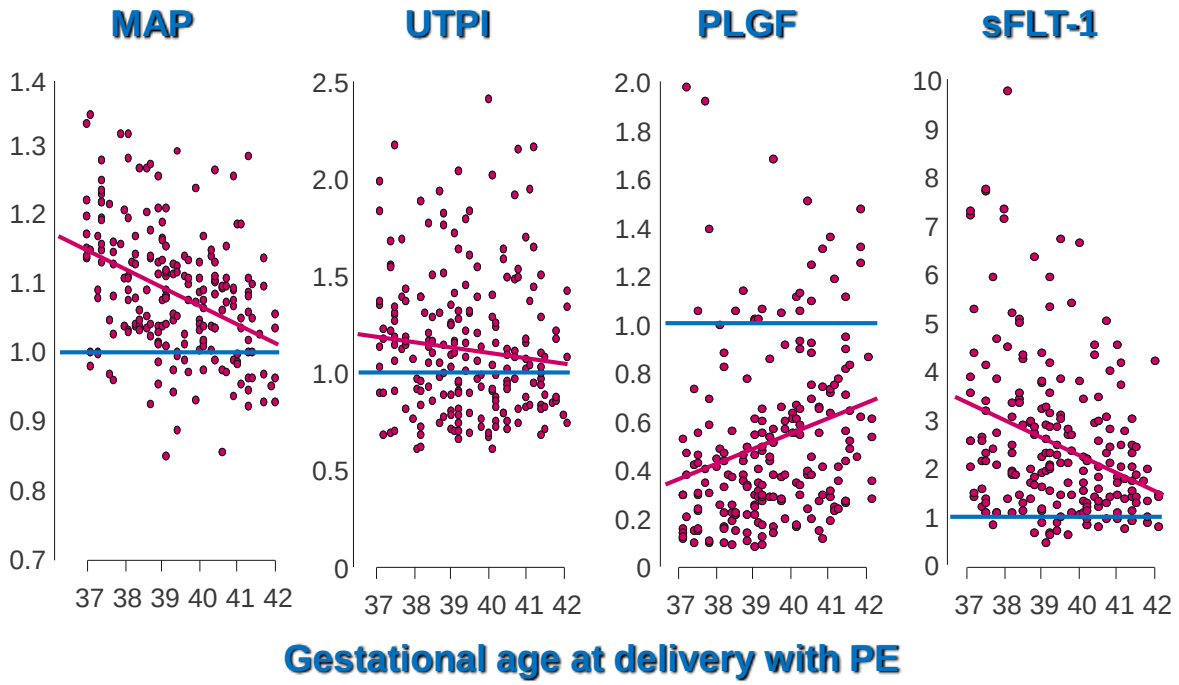
# Prediction of PE at ≥37 w

## Methods:

- 11,438 singleton pregnancies
- Preeclampsia n = 216 (1.9%)
- **Screening at $35^{+0}$ – $36^{+6}$ w**
- Maternal factors and history
- Uterine artery PI
- Mean arterial pressure
- Serum PLGF and sFLT-1 (Roche or Kryptor)

- FMF algorithm to calculate risk for **PE at ≥37 w**



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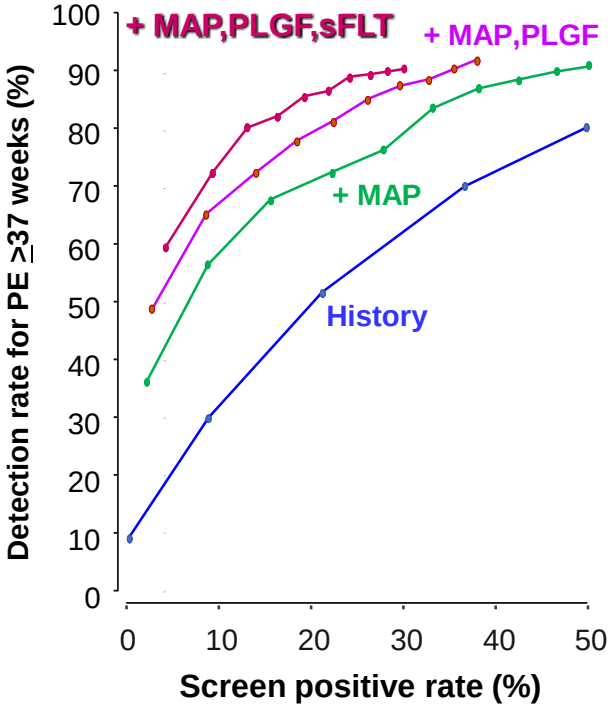
# Prediction of PE at ≥37 w




| Method of screening | Risk cut-off 1 in 20 | |
|---|---|---|
| | SPR | DR |
| History | 10.4% | 30% |
| + MAP | 10.3% | 57% |
| + MAP, UTPI | 9.7% | 54% |
| + MAP, PLGF | 10.1% | 66% |
| + MAP, PLGF, sFLT | **10.8%** | **73%** |

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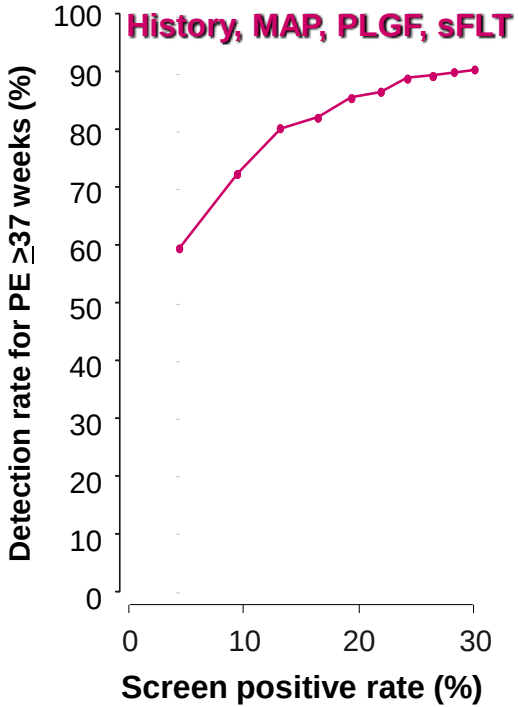
# Prediction of PE at ≥37 w




| Screening by history, MAP, PLGF and sFLT-1 | | |
|---|---|---|
| **Risk cut-off** | **DR** | **SPR** |
| 1 in 10 | 63% | 6% |
| **1 in 20** | **73%** | **11%** |
| 1 in 30 | 81% | 14% |
| 1 in 40 | 85% | 18% |
| 1 in 50 | 87% | 20% |
| 1 in 60 | 89% | 23% |
| 1 in 90 | 91% | 30% |

# Prevention of late preeclampsia

# Prevention of PE at ≥37 w

- **Early delivery**

**Screening by history, MAP, PLGF, sFLT-1**

- 11,438 singleton pregnancies
- Preeclampsia n = 216 (1.9%)

| | |
|---|---|
| Screen +ve 11%: | 1,258 |
| Detection rate 70%: | 151 |
| Risk of PE in screen +ve: | 12% |

**Induce labor at 37 w in 8 to prevent 1 PE**

# Pregnancy hypertension: Delivery vs. expectant monitoring

## HYPITAT - I : 39 (38 - 40) w

| | |
|---|---|
| **Improved maternal outcome:** | **RR 0.7, 95% CI 0.6-0.9** |
| No adverse neonatal outcome: | RR 0·8, 95% CI 0.5-1.3 |

Koopmans *et al*. Lancet 2009;374:979.

## HYPITAT - II : 36 (35 – 37) w

| | |
|---|---|
| No improved maternal outcome: | RR 0·4, 95% CI 0·1-1·1 |
| **Respiratory distress syndrome:** | **RR 3·3, 95% CI 1·4-8·2** |

Broekhuijsen *et al*. Lancet 2015;385:2492.

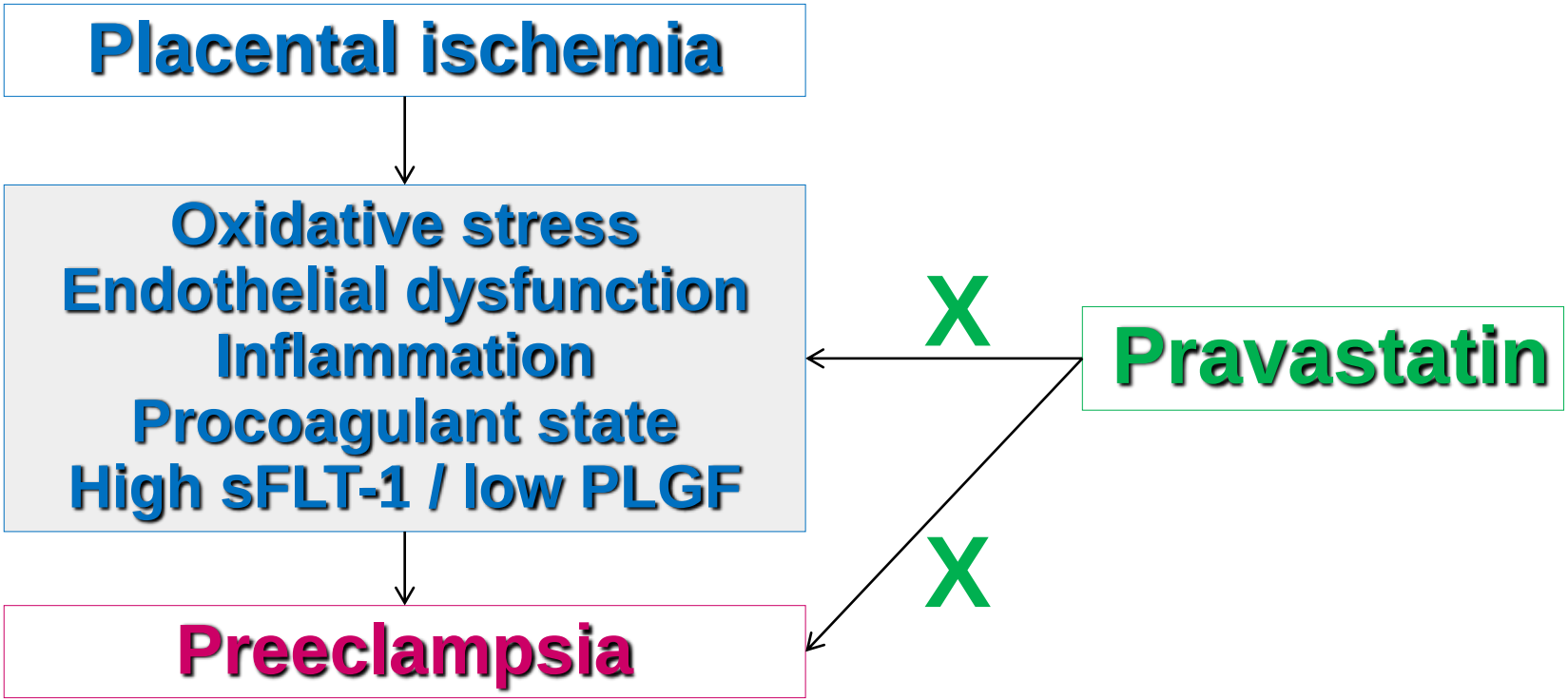
**May be fine to induce >38w but not earlier**

# Prevention of PE at ≥37 w
# Pharmacologic intervention

## Statins:

- Used for prevention of cardiovascular disease
- Reduce cholesterol synthesis in the liver
- Have ‘pleiotropic’ effects
  - Improve endothelial function
  - Decrease oxidative stress & inflammation
  - Inhibit thrombogenic response

# Prevention of PE at ≥37 w



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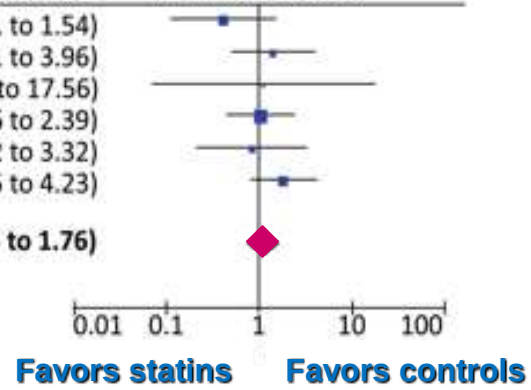
# Safety of PRAVASTATIN in pregnancy

| Study or subgroup | Experimental Events | Experimental Total | Control subjects Events | Control subjects Total | Weight | Risk ratio M–H fixed, 95% CI |
|---|---|---|---|---|---|---|
| Ofori et al 2007[23] | 3 | 69 | 7 | 67 | 19.4% | 0.42 (0.11 to 1.54) |
| Paulus et al 2008[27] | 4 | 63 | 26 | 584 | 13.8% | 1.43 (0.51 to 3.96) |
| Taguchi et al 2008[24] | 1 | 46 | 1 | 52 | 2.6% | 1.13 (0.07 to 17.56) |
| McGrogan et al 2009[25] | 6 | 192 | 58 | 1943 | 28.5% | 1.05 (0.46 to 2.39) |
| Colvin et al 2010[26] | 2 | 51 | 3968 | 86 339 | 12.8% | 0.85 (0.22 to 3.32) |
| Winterfeld et al 2013[28] | 15 | 197 | 9 | 224 | 23.0% | 1.90 (0.85 to 4.23) |
| **Total (95% CI)** | | **618** | | **89 209** | **100.0%** | **1.15 (0.75 to 1.76)** |
| Total events | 31 | | 4069 | | | |

Heterogeneity: $\tau^2 = 4.20$; $df = 5$ ($P = 0.52$); $I^2 = 0\%$

Test for overall effect: $z = 0.64$ ($P = 0.52$)




Zarek J, Koren G. The fetal safety of statins: a systematic review and metaanalysis. J Obstet Gynecol Can 2015; 36: 506 - 509.

**Risk of fetal defects in pregnancies exposed to statins - similar to general population**

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# Safety of PRAVASTATIN in pregnancy

## Pravastatin

- Hydrophilic molecule – limited capacity to cross the placenta
- Statin of choice for treatment of hypercholesterolemia in pregnancy
- Statin of choice for treatment of hyperlipidemia in neonates and children
- **STATIN trial** – only used after 35 weeks and maximum 6 weeks

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# Studies on PRAVASTATIN in pregnancy

## Antiphospholipid syndrome with PE and/or FGR during treatment with aspirin & heparin

- 10 Rx aspirin & low dose heparin
- 11 Rx aspirin & low dose heparin plus pravastatin (20 mg/d)


Lefkou E, Mamopoulos A, Dagklis T, Vosnakis C, Rousso D, Girardi G. Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. J Clin Invest 2016;126:2933

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# Studies on PRAVASTATIN in pregnancy

## RCTs using pravastatin for prevention of PE in pregnancy

**Constantine, 2016:** 20 women at high-risk for PE
- Pravastatin (10 mg/d) vs. placebo, 16-20 w to term
- Preeclampsia: 4/10 in placebo group vs. 0/10 in pravastatin group
- Cord blood: normal cholesterol, no detectable pravastatin

**STAMP trial:** 62 women with PE < 32 w
- Pravastatin (40 mg/d) vs. placebo
- No improvement in maternal blood sFLT-1 or pregnancy prolongation
- Cord blood: normal cholesterol

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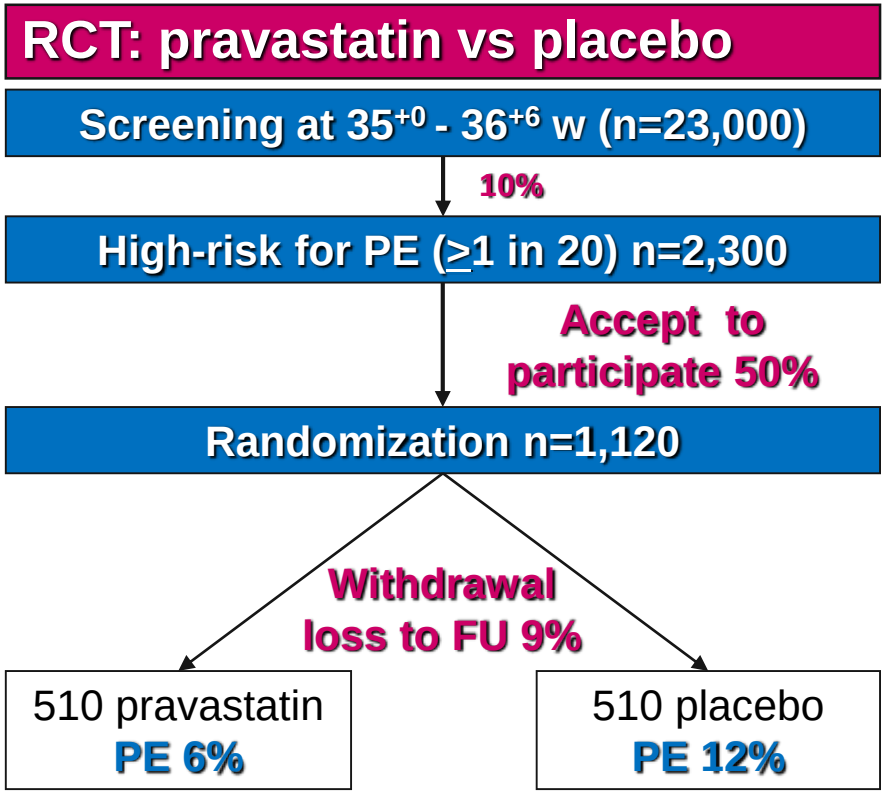
# Prevention of PE at ≥37 w




**Primary outcome**

- Incidence of preeclampsia

**Secondary outcomes**

- Incidence of gestational hypertension
- BW < 3rd, 5th & 10th percentile
- Stillbirth or neonatal death
- Placental abruption
- Rate of neonatal morbidity
- SFLT-1 and PLGF values at 1 and 3 w
- Pravastatin safety during pregnancy

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# Prevention of PE at ≥37 w

## RCT: pravastatin vs placebo

Screening at $35^{+0}$ - $36^{+6}$ w (n= 12,499 / 23,000)

12% (10%)

High-risk for PE (≥1 in 20) (n= 1,541 / 2,300)

Not eligible 11% (0%)

High-risk & eligible (n= 1,372 / 2,300)

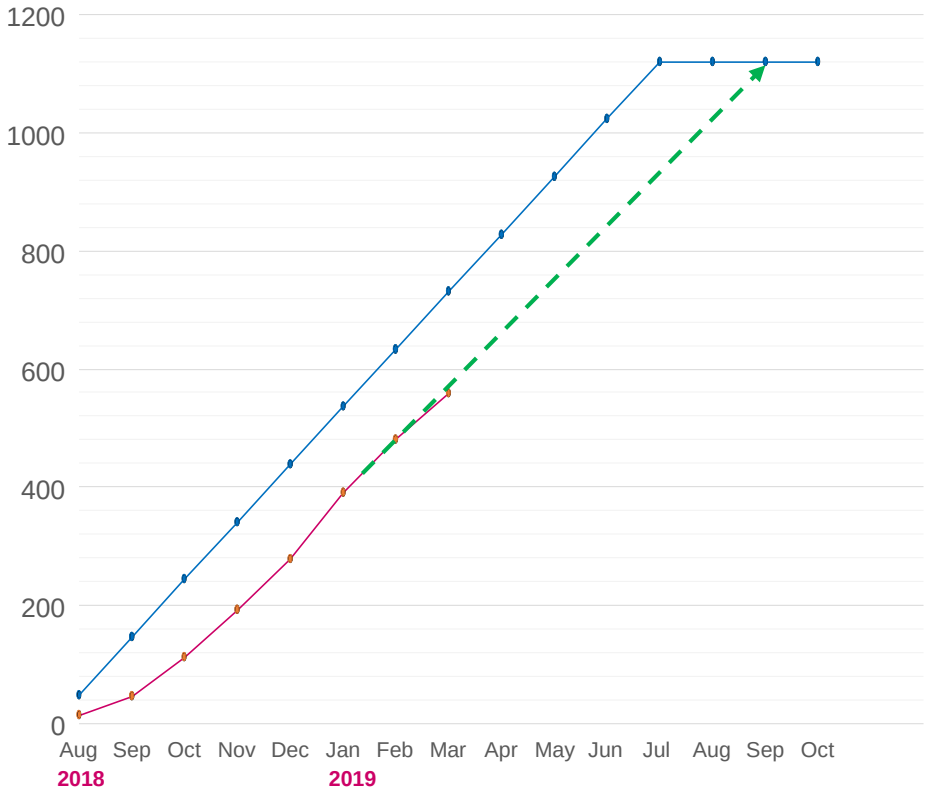
Accept to participate 39% (50%)

Randomization n= 536 / 1,120

Withdrawal loss to FU 2% (9%)

?(510) pravastatin
PE ? (6%)

?(510) placebo
PE ? (12%)



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| | |
|---|---|
| King's College Hospital | Kypros Nicolaides |
| Medway Maritime Hospital | Ranjit Akolekar |
| Royal London Hospital | Elena Greco |
| North Middlesex Hospital | Deepa Jenga |
| Southend University Hospital | Mandeep Singh |
| Homerton University Hospital | Simona Cicero |
| Virgen de la Arrixaca, Murcia, Spain | Katy DePaco |
| La Paz, Madrid, Spain | Jose Barta |
| Torejon, Madrid, Spain | Mar Gil |
| Chu Brugmann Brussels, Belgium | Jaques Jani |
| Spitalul Filantropia, Bucharest, Romania | Anca Panaitescu |
| Statistical analysis: | D Wright, A Wright |
| Companies: | Brahms-Kryptor<br>Astraia, Viewpoint |

*Thank you*

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# Eligibility criteria for *STATIN*

## Inclusion criteria

- Singleton pregnancy
- Live fetus at 35-36 weeks' gestation
- Risk from combined screening >1 in 20
- Written informed consent

## Exclusion criteria

**Screening:** Age <18 years; multiple pregnancy; unconscious or very ill; serious mental illness; learning difficulties; does not understand local language

**Randomized trial:**

- Major fetal abnormality;
- Women with established PE;
- Statin use within 28 days prior to randomization;
- Women with contraindications for statin therapy:
- Hypersensitivity to pravastatin or any component of the product.

# Eligibility criteria for *STATIN*

## Exclusion criteria (continued)

- Lactose intolerance
- Current or previous cancer
- Previous solid organ transplant
- Active liver disease (acute hepatitis, chronic active hepatitis) in the past 6 months
- Chronic renal disease / insufficiency (serum creatinine >1.5 mg/dL)
- History of myopathy or rhabdomyolysis;
- ALT and/or AST levels ≥ 2 x the upper limit of normal
- Creatine kinase levels ≥ 5 x the upper limit of normal
- Concurrent and chronic (>6 months) use of medications with potential drug interactions with statins, such as immunosuppressive drugs, fibrates, gemfibrozil, niacin, protease inhibitors, efavirenz (non-nucleoside reverse transcriptase inhibitor), erythromycin, clarithromycin, itraconazole, cholestyramine, digoxin, rifampicin
- Participating in another intervention study that influences the outcomes of this study

**Data collection**

- Patient demographics
- Routine third trimester screening (growth and fetal wellbeing)
- Height & weight
- Maternal & family history
- Measurement of MAP
- Measurement of SFLT-1 & PLGF

**Risk assessment for term-PE**

**Randomisation:** $35^{+0}$-$37^{+3}$

**Informed consent**

Drug history

Randomisation (online)

Test drug dispensing