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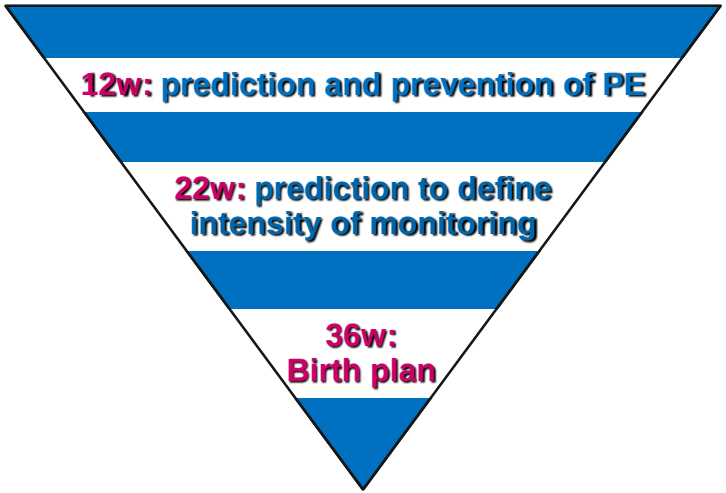
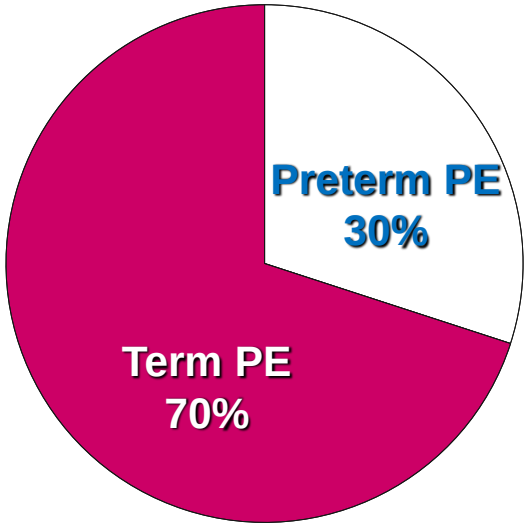
Prevention of late preeclampsia: The STATIN trial

Moritz Döbert



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:	**3.0%**
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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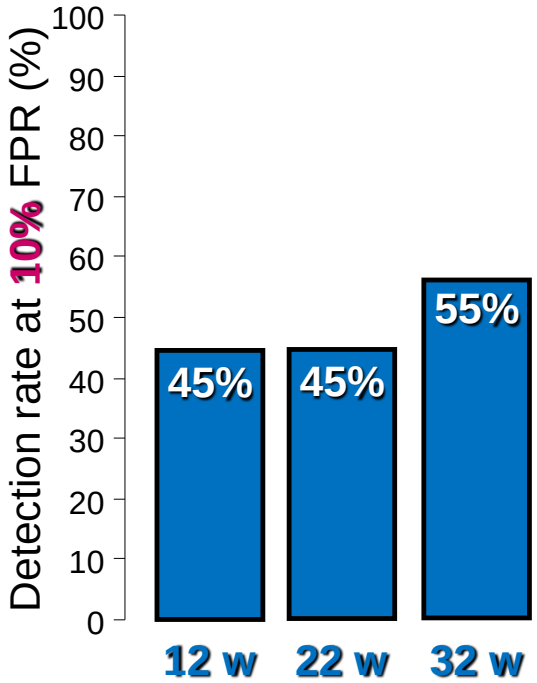
Prediction of PE at ≥37 w



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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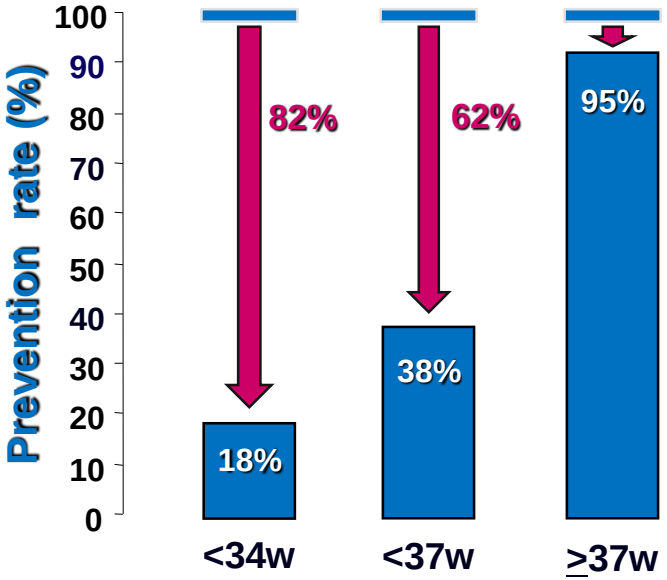
ASPRE project

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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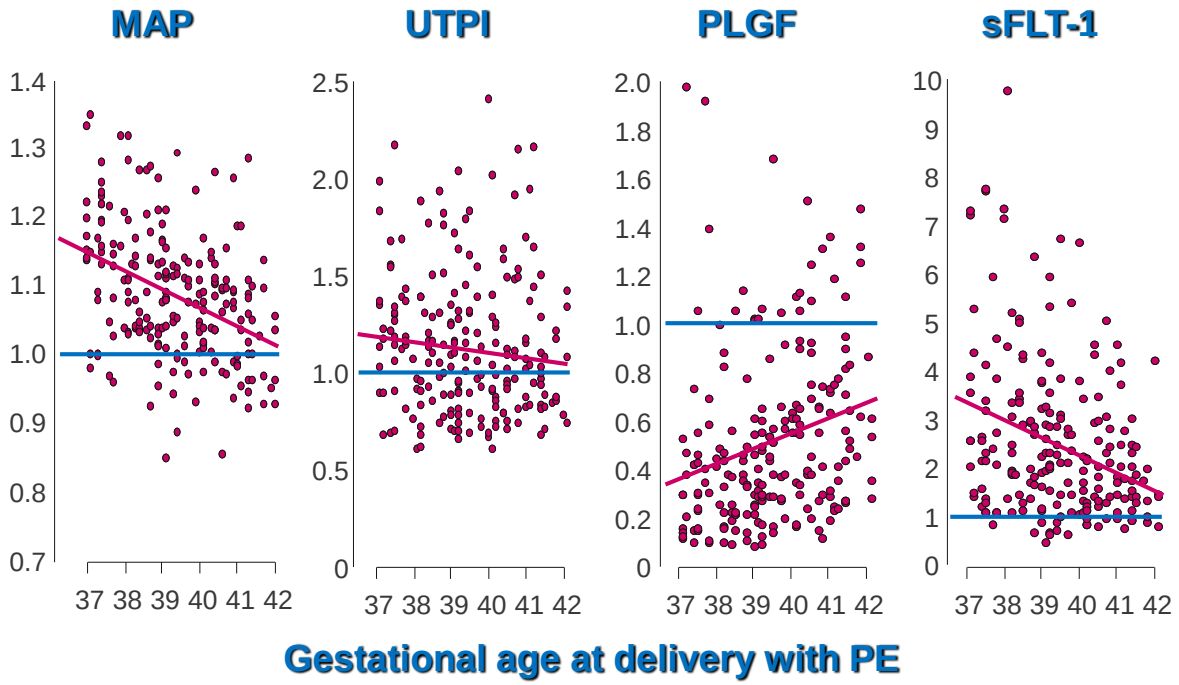
Prediction of PE at ≥37 w

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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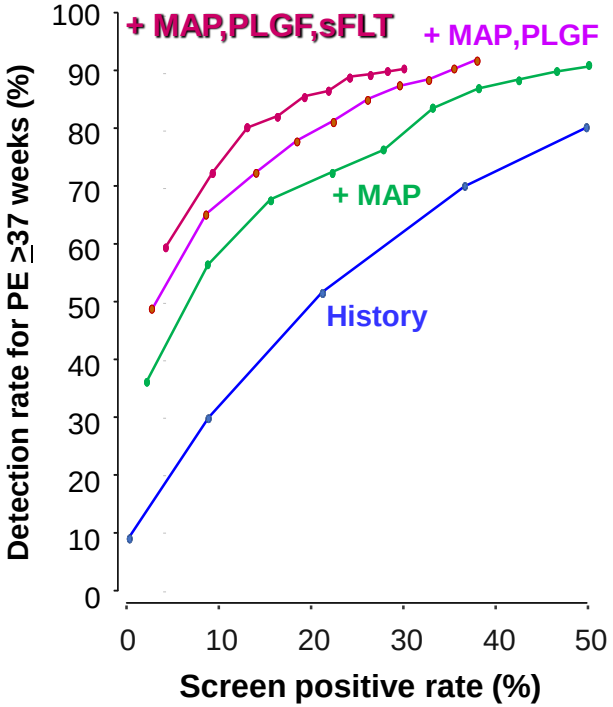
Prediction of PE at ≥37 w



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, UTPI	9.9%	65%
+ MAP, PLGF, sFLT, UTPI	**10.8%**	**73%**

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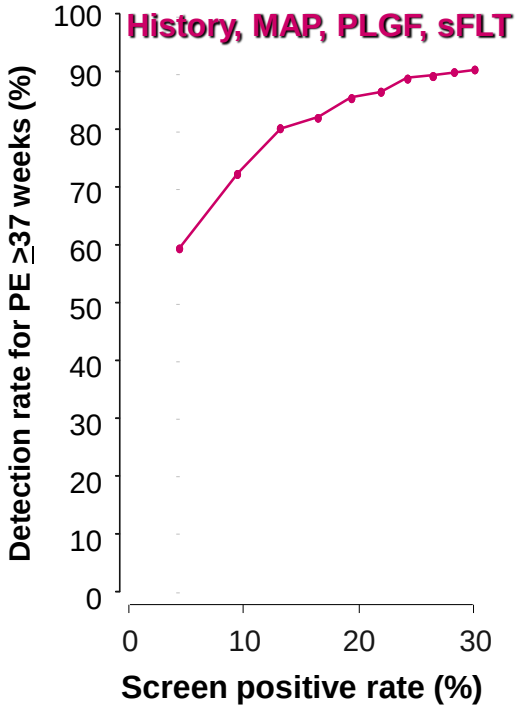
Prediction of PE at ≥37 w



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.

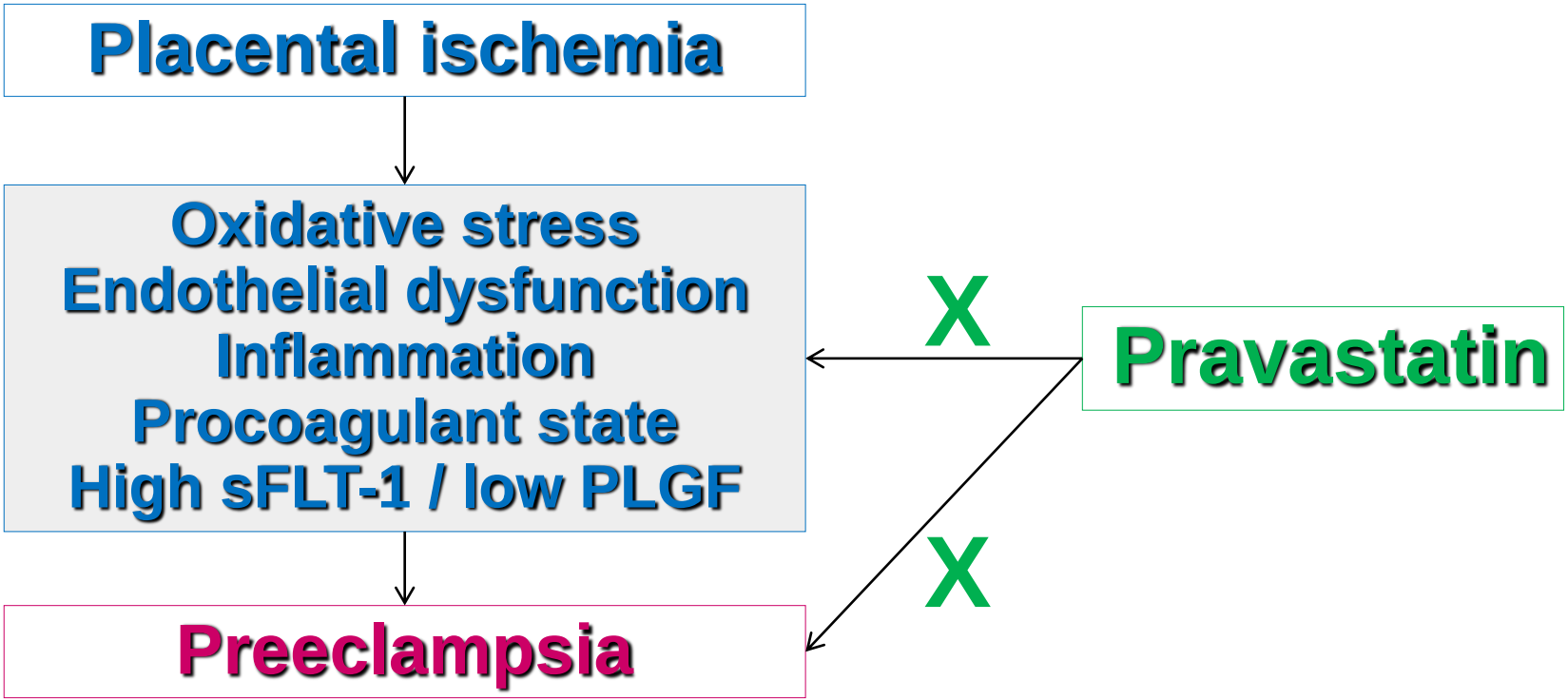
May be fine to induce >38w but not earlier

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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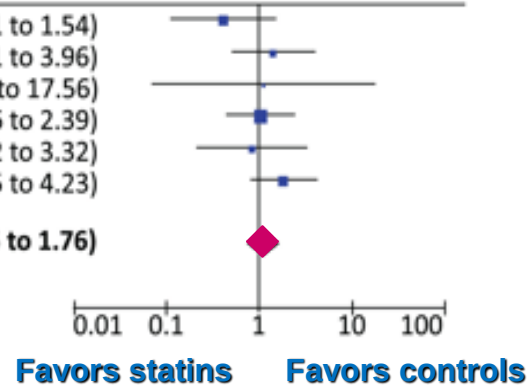
Safety of PRAVASTATIN in pregnancy

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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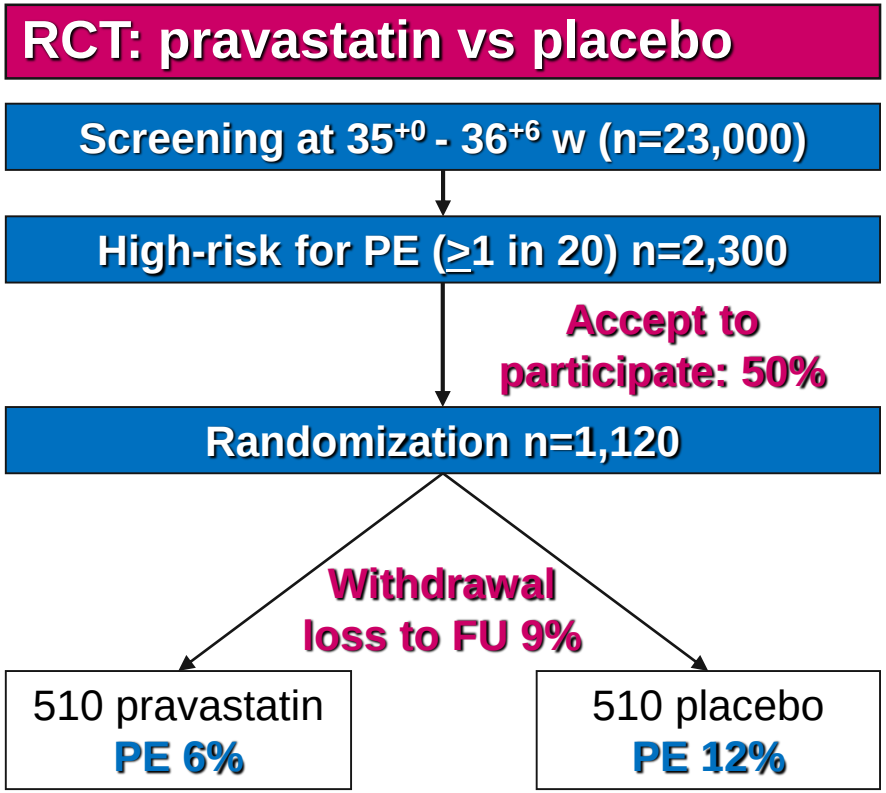
Prevention of PE at ≥37 w



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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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
Ospedale Maggiore Policlinico, Italy	Nicola Persico
Statistical analysis:	D Wright, A Wright
Companies:	Brahms-Kryptor 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.

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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