Pravastatin for recurrent miscarriage and implantation failure

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Pravastatin for recurrent miscarriage and implantation failure

- Purpose: to investigate whether pravastatin is effective in treating resistant cases of recurrent miscarriage and implantation failure.

Can we use statins in pregnancy

- Originally based on the argument of limited benefit when used short term in pregnancy.
- *Concerns regarding fetal cholesterol during development.*
- Category (X) no reevaluated for newer generation statins.

FDA Reg 1980
Diaz-Zagoya et al. Life Sci 1999
Edison et al. Am J Med Genet 2004
Kazmin et al. J Obstet Gynaecol Can 2007
Taguchi et al. Reprod Toxicol 2008

Pravastatin animal studies

- Non teratogenic
  - Rats1000mg/kg/day-120k human exposure
  - Rabbits 50mg/kg/day-10k human exposure

  - No effect on placental weight ,pup birth weight, and pup adult weight.

Diaz- Zagoya et al, Life Sci 1999
Brent (personal communication) BMS 1999
Kumasawa et al. PNAS 2011

Pravastatin: pregnancy experience

- No increased rate of :
  - congenital anomalies
  - IUGR
  - Spontaneous abortion
  - IUFD

- 2^{nd}-3^{rd} trimester
  - No effect of fetal growth

Bateman et al. BMJ 2015

Edison et al. Am J Med Genet2004

Taguchi et al. Reprod Toxicol 2008

Ofon et al. Br J Clin Pharm 2007

Winterfeld et al. Br J Obstet Gynecol 2013

Kumasawa K et al. PNAS 2011

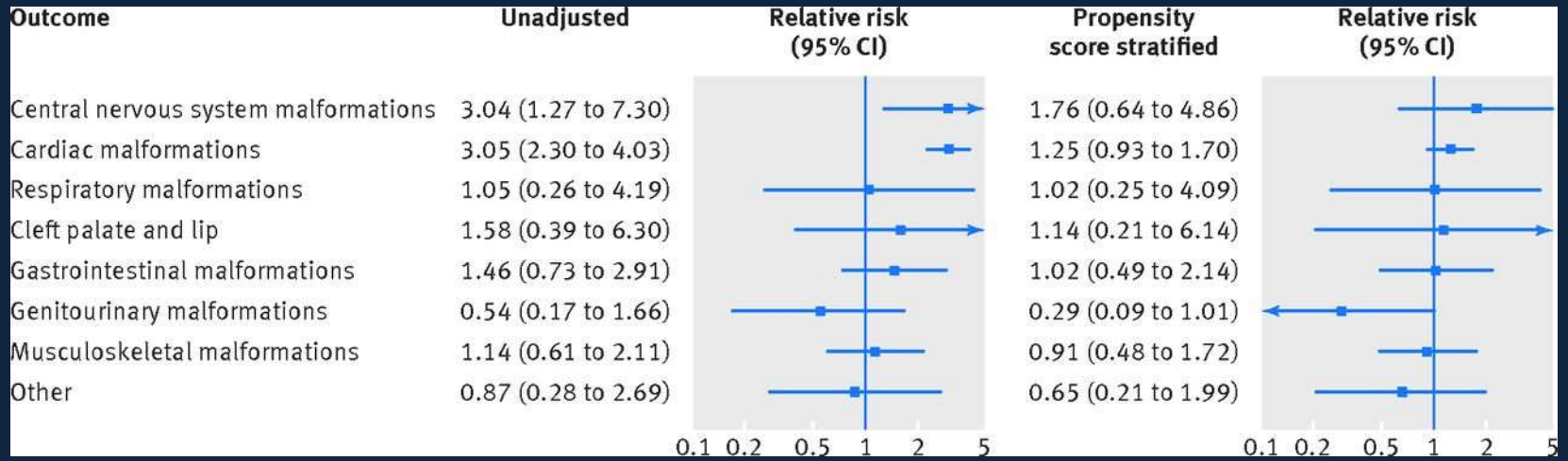
Armental & Brent, personal communication

Pravastatin: pregnancy experience Bateman et al. BMJ 2015

- Cohort study (n=1,152, pravastatin, n=75)
- Statin exposure during first trimester vs. propensity score matched control group.
- Congenital malformations with statin exposure similar to controls (6,3% vs. 3.6% OR 1.04 (0.85-1.37).

Pravastatin: pregnancy experience
Bateman et al. BMJ 2015

- **None of the organ specific malformations were significantly associated with statin use, though confidence intervals were wide.** There were no cases of limb reduction anomalies or holoprosencephaly in the infants of women who used statins in the first trimester; malformations previously hypothesized to be associated with exposure to statins.



Effects of Pravastatin on Human Placenta, Endothelium, and Women With Severe preeclampsia. Brownfoot et al. Hypertension 2015

- Preeclampsia (PE) is a major pregnancy complication where excess placental release of soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin causes maternal endothelial and multisystem organ injury. Placental growth factor (PLGF) decreases.

- Scope: whether pravastatin reduced sFlt-1 and soluble endoglin secretion and decreased endothelial dysfunction in primary human tissues.

- Pravastatin reduced sFlt-1 secretion from primary endothelial cells, purified cytotrophoblast cells, and placental explants obtained from women with preterm PE.

Effects of Pravastatin on Human Placenta, Endothelium, and Women With Severe preeclampsia. Brownfoot et al. Hypertension 2015

- It increased soluble endoglin secretion from endothelial cells but did not change secretion from placental explants.

- Pravastatin also reduced markers of endothelial dysfunction, including vascular cell adhesion molecule-1 expression and leukocyte adhesion on endothelial cells and increased endothelial cell migration and invasion.

- 4 women with preterm PE (<30 W) were treated with daily pravastatin. Pravastatin stabilized BP, proteinuria, and serum uric acid levels. In these women, serum sFlt-1 levels decreased.

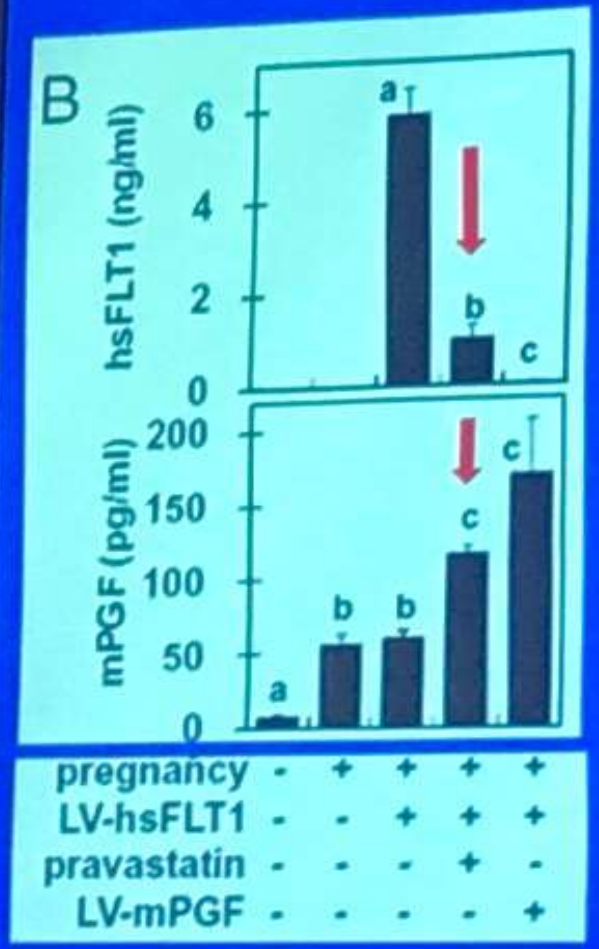
Placental transfer of pravastatin
Nanovskaya et al. Am J Obstet Gynecol 2014

- Pravastatin crosses the human placenta in both the Maternal to fetal (18%), and fetal to Maternal directions (13%).

- The transfer of pravastatin in both directions suggest that intrauterine feral exposure to the drug is possible and that the main route for drug elimination from the fetus is its transfer back to the maternal circulation.

Statins for preeclampsia prevention

Pravastatin in Animal Models of Preeclampsia

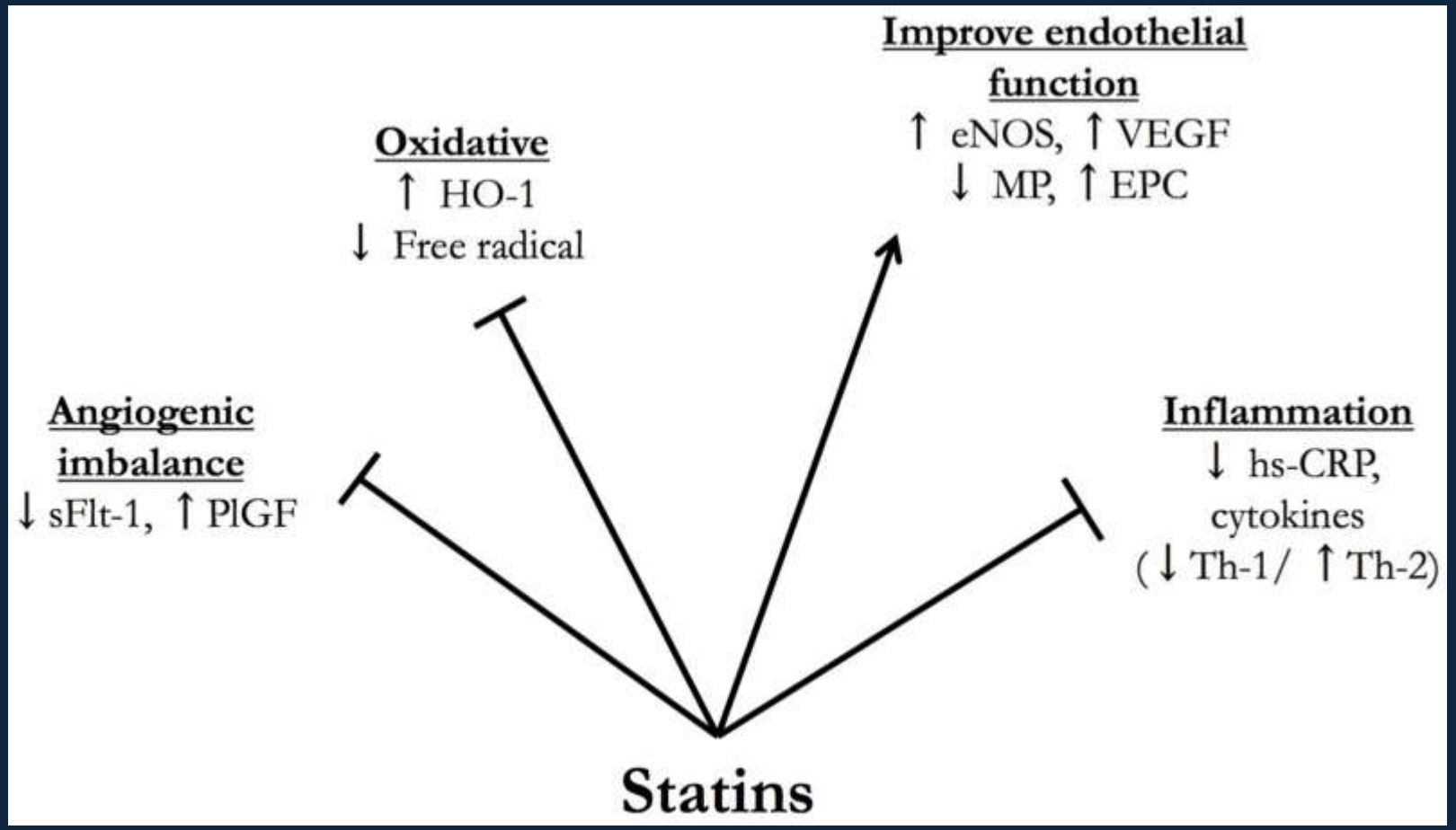


- ↓ sFlt-1 & ↑ PlGF
- ↓ BP
- ↑ eNOS
- Improves vascular reactivity
- ↓ Proteinuria
- ↓ Oxidative stress
- Restores fetal growth

- No ↑ pup resorption
- No pup deformation

Kumasawa et al. PNAS 2010
Costantine et al., Obs Gyn 2010
Ahmed et al., PLoS ONE 2010
Singh et al, HTN 2011
Fox et al., AJOG 2011
Bauer et al, HTN 2013

Biological plausibility and pleiotropic actions of statin when used to treat/prevent preeclampsia. Expert Opin investig Drugs 2017 Costantine et al.



(HO-1: heme oxygenase-1; sFlt-1: soluble fms-like tyrosine kinase 1 ; PlGF: placental growth factor; eNOS: endothelial nitric oxide synthase; MP: microparticles, EPC: endothelial progenitor cells.

Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia (PE) in high-risk pregnant women: a pilot randomized controlled trial. Costantine MM at al., NICHD AJOG 2016.

- OBJECTIVE: To evaluate the utility of pravastatin in preventing PE and (after consultation with the FDA) to determine pravastatin safety and pharmacokinetic parameters when used in women at high risk of PE.

- A pilot, multicenter, double-blind, placebo-controlled, randomized trial of women with singleton pregnancies at high risk for PE. Women between 12 and 16(6/7) weeks were assigned to daily pravastatin 10 mg or placebo orally until delivery. Primary outcomes were maternal-fetal safety and pharmacokinetic parameters of pravastatin during pregnancy.

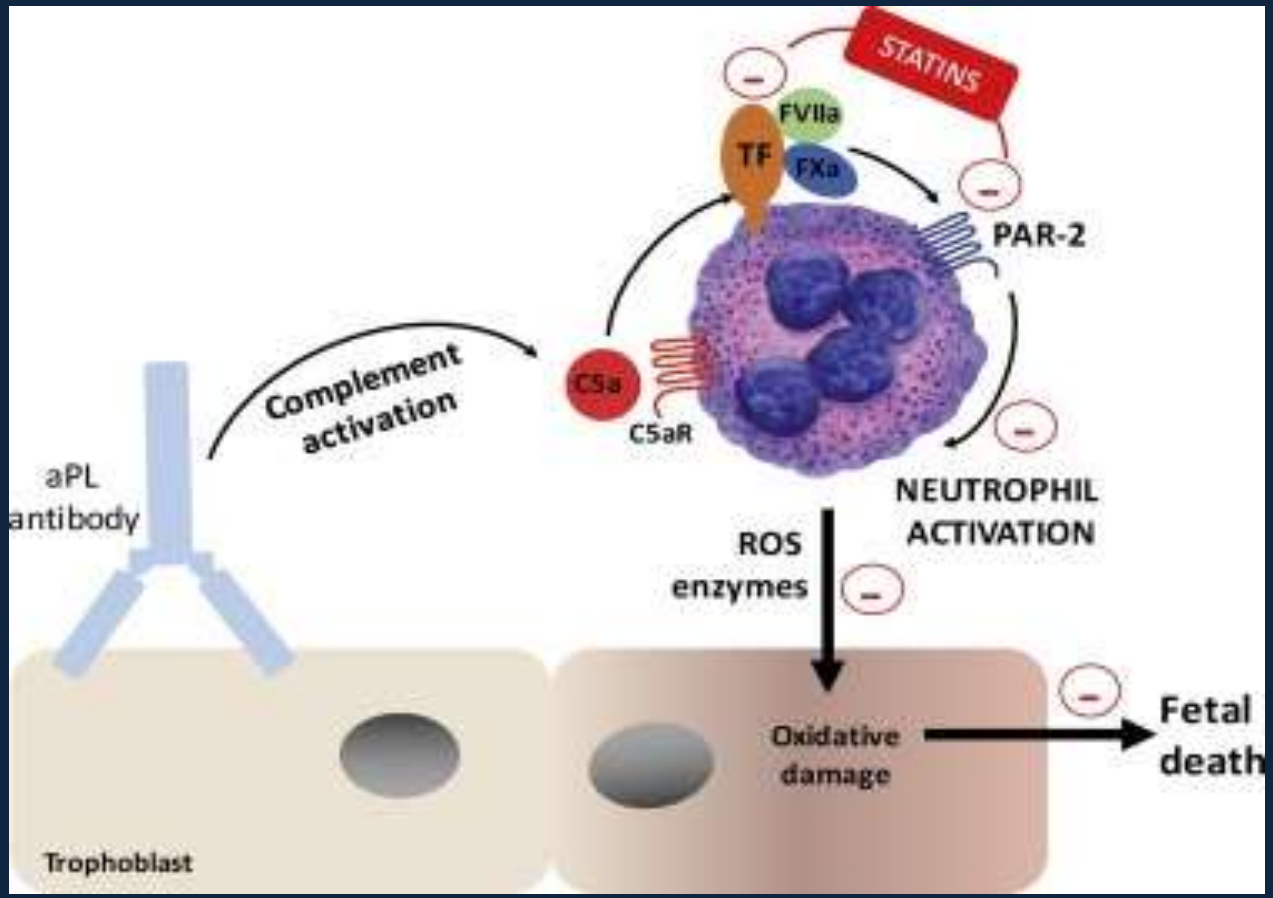
Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Costantine MM at al., NICHD AJOG 2016.

- RESULTS: 10 women assigned to pravastatin and 10 to placebo. There were no differences between the 2 groups in rates of drug side effects, congenital anomalies, or other adverse or serious adverse events. There was no maternal, fetal, or neonatal death. 4 subjects in the placebo group developed PE compared with none in the pravastatin group. Infant birth weight were not different between the groups.

- CONCLUSION: This study provides preliminary safety and pharmacokinetic data regarding the use of pravastatin for preventing PE in high-risk women. No identifiable safety risks were associated with pravastatin use in this cohort.

Statins for APS prevention

- Pravastatin, downregulates tissue factor (TF) and protease activated receptor 2 (PAR-2) expression in neutrophils, prevent neutrophil activation, trophoblast injury and fetal death (Redecha et al., 2008). By downregulating TF and PAR-2, statins target the proinflammatory phenotype of neutrophils in mouse model of **obstetric APS** (OAPS-mice) leading to normal pregnancies.



Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. Lefkou E, et al. J Clin Invest. 2016.

- The study included 21 pregnant women with APS who developed PE and/or IUGR although treated with LDA+LMWH.

- A control group of 10 patients received only LDA+LMWH. Eleven patients received pravastatin (20 mg/d) in addition to LDA+LMWH at the onset of PE and/or IUGR.

- In the control group, all deliveries occurred preterm and only 6 of 11 neonates survived. Of the 6 surviving neonates, 3 showed abnormal development. Patients who received both pravastatin and LDA+LMWH exhibited increased placental blood flow and improvements in PE features.

Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. Lefkou E, et al. J Clin Invest. 2016

- Those who received pravastatin had improved BP and delivered at a later gestational age (36 weeks vs. 26.5 weeks), and had infants with higher birth weight at delivery (2,390 grams, vs. 900 grams).

- Pravastatin use was also associated with improved neonatal outcomes, as survival rate was 100% in the pravastatin cohort compared with 45% in the control cohort.

- The rates of admission to the neonatal intensive care unit and later neurodevelopmental delays were reduced in the pravastatin cohort.

Pravastatin and recurrent miscarriage

- Material and methods:

- 35 women with ≥ 3 recurrent first trimester miscarriage between 6 and 13 weeks (group A):

  - 10 women had had 6 miscarriages
  - 9 women had had 5 miscarriages
  - 11 women had had 4 miscarriages
  - 5 women had had 3 miscarriages

Pravastatin and recurrent miscarriage

- All 35 in group A had workup for recurrent miscarriage:

- Uterine cavity on hysteroscopy.

- Inherited and acquired thrombophilias: protein S,
- protein C, antithrombin III, factor V Leiden, prothrombin mutation, lupus anticoagulant, anti cardiolipin IgG , Beta2 glycoprotein, homocystein, factor VIII.

- Auto antibodies (thyroglobulin, thyroid peroxidase, anti smooth muscle, anti mitochondrial).

- Karyotype of the couple.

Pravastatin and recurrent miscarriage

- 30 women with failure ≥ 3 of embryo transfer in IVF, with good quality embryos, and no pregnancy (group B).

- 12 had had 5 implantation failure
- 11 had had 4 implantation failure
- 5 had had 3 implantation failure
- 2 had had 7 implantation failure

Pravastatin and recurrent miscarriage

- All the 30 women in group B had workup:

  - Uterine cavity on hysteroscopy.
  - Inherited and acquired thrombophilias.
  - Auto antibodies.

Pravastatin and recurrent miscarriage

- Women in group A, had had at least 1 pregnancy in which they were treated with low molecular weight heparin (Enoxaparin) but had again miscarriage.

- In the following pregnancy, they were treated with 10 mg pravastatin from positive pregnancy test until week 13 or miscarriage.

- Women in group B, were treated with pravastatin 10 mg from day of ET until week 5 if pregnant, or until menstruation.

Pravastatin and recurrent miscarriage

- Results:
- In group A all women had normal uterine cavity on hysteroscopy.
- 8/35 (23%) had inherited or acquired thrombophilia.
- 2/35 (5.7%) had thyroid peroxidase antibodies.

Pravastatin and recurrent miscarriage

- Results:
- In group B all women had normal uterine cavity on hysteroscopy.
- 5/30 (16.6%) had inherited or acquired thrombophilia.
- 1/30 (3.3%) had thyroid peroxidase antibodies.

Pravastatin and recurrent miscarriage

- Results:

- The mean age of women in group A was 33±7 years, and of women in group B, 35±8 years.

- In group A, 27/35 (77.1%) resulted in delivery of healthy newborn. Two of the 27 delivered preterm at 32 and 34 weeks. 8 had miscarriage between 6-12 weeks.

- In group A, the mean gestational week at delivery was 37± 3.1, and the mean birth weight 2920 ±430 grams.

Pravastatin and recurrent miscarriage

- Results:

- In group B, 19/30 (63%), delivered at term and 1 delivered at 31 weeks, health newborns (66%), another 2 (6.7%) had miscarriage, and 9 did not get pregnant.

- In group B, the mean gestational week at delivery was 39 ± 4.2 and the mean birth weight 3020 ±340 grams.

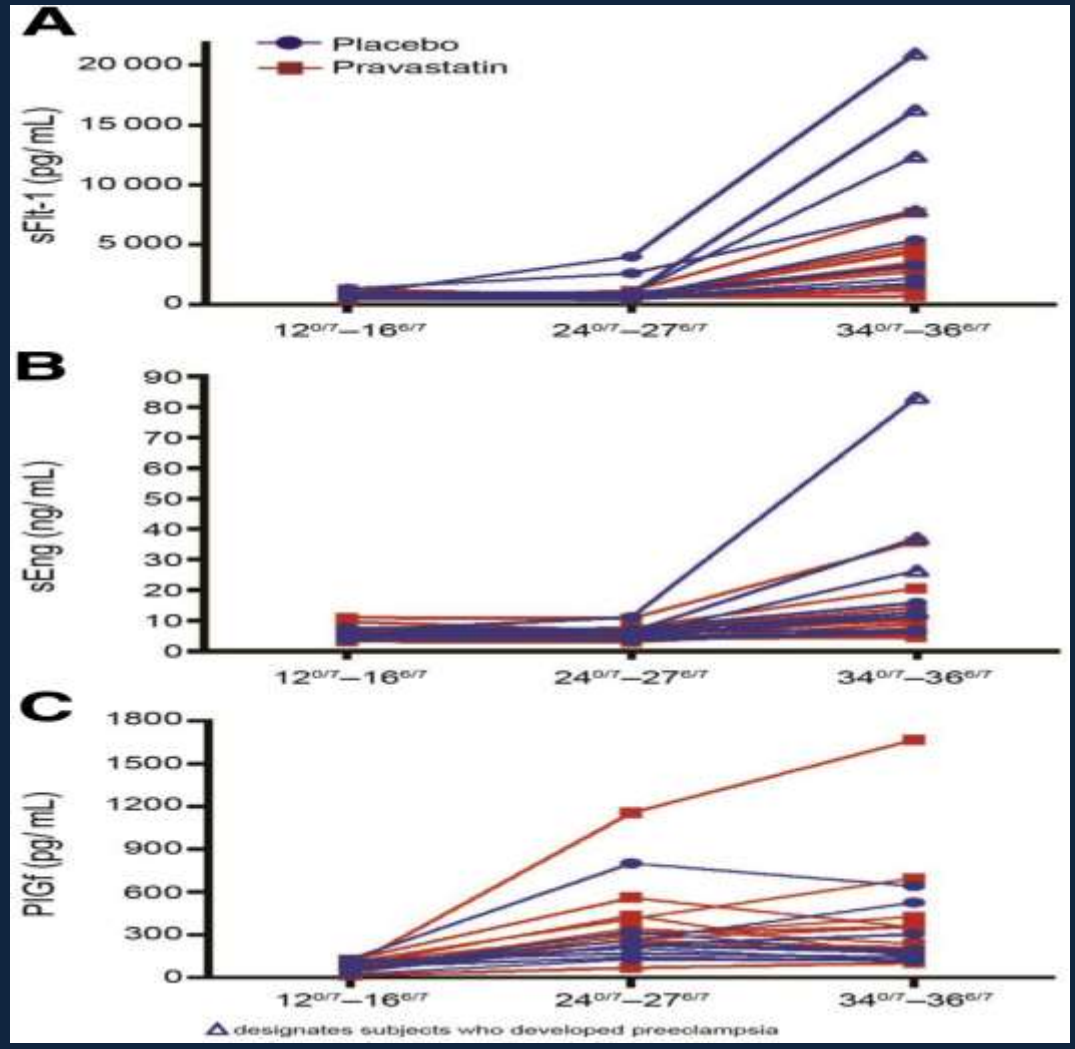
Summary Pravastatin

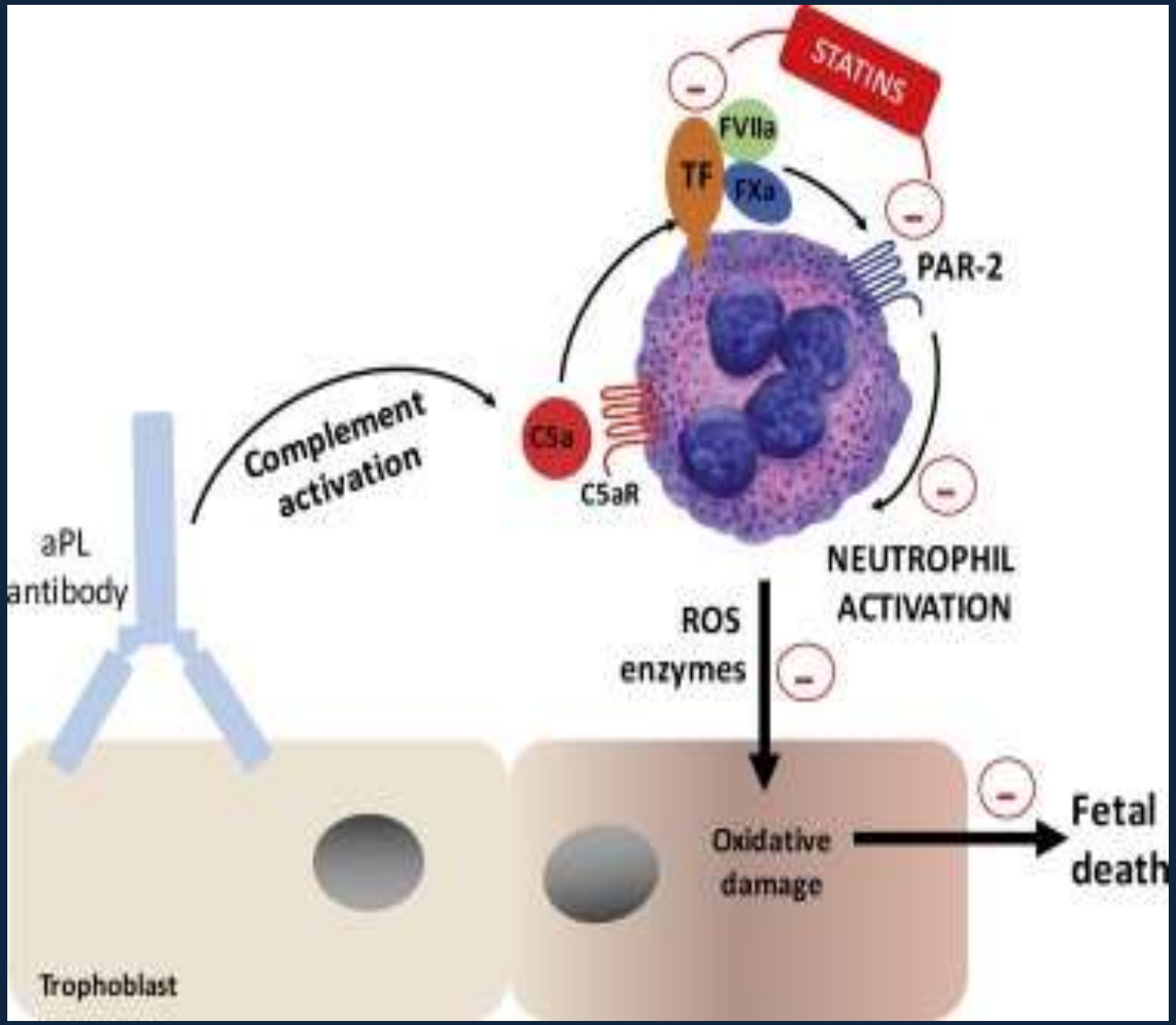
- Pravastatin may be a promising therapy in cases of recurrent miscarriage and recurrent implantation failure.

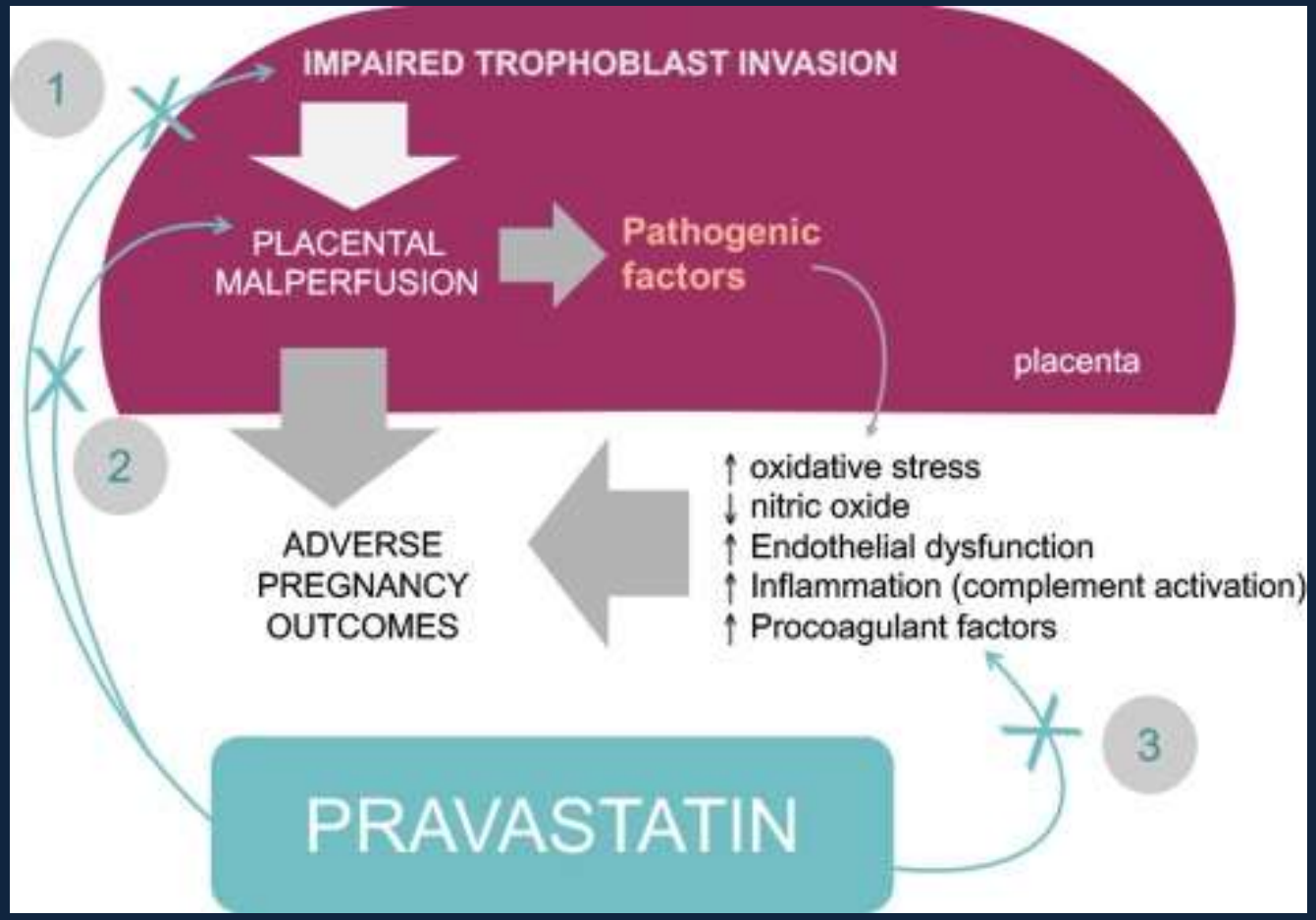
- Large prospective studies are necessary to determine the role of pravastatin in recurrent miscarriage implantation failure and placental mediated complications.

Thank you

Longitudinal plots of serum concentrations of sFlt-1 (**panel A**), sEng (**panel B**), and PlGF (**panel C**) within individual subjects who received pravastatin (*red*) or placebo (*blue*) according to the gestational age at time of collection: 12 to 16 weeks (baseline and before treatment), 24 to 27, and 34 to 36 weeks. Δ designates the subjects who developed preeclampsia. (Am J Obstet Gynecol 2016)




STATINS
FVIIa
TF
FXa
PAR-2
Complement activation
C5a
C5aR
aPL antibody
NEUTROPHIL ACTIVATION
ROS enzymes
Oxidative damage
Fetal death
Trophoblast


1
IMPAIRED TROPHOBLAST INVASION
PLACENTAL MALPERFUSION
Pathogenic factors
placenta
2
ADVERSE PREGNANCY OUTCOMES
↑ oxidative stress
↓ nitric oxide
↑ Endothelial dysfunction
↑ Inflammation (complement activation)
↑ Procoagulant factors
3
PRAVASTATIN