

WHAT'S NEW IN PREECLAMPSIA

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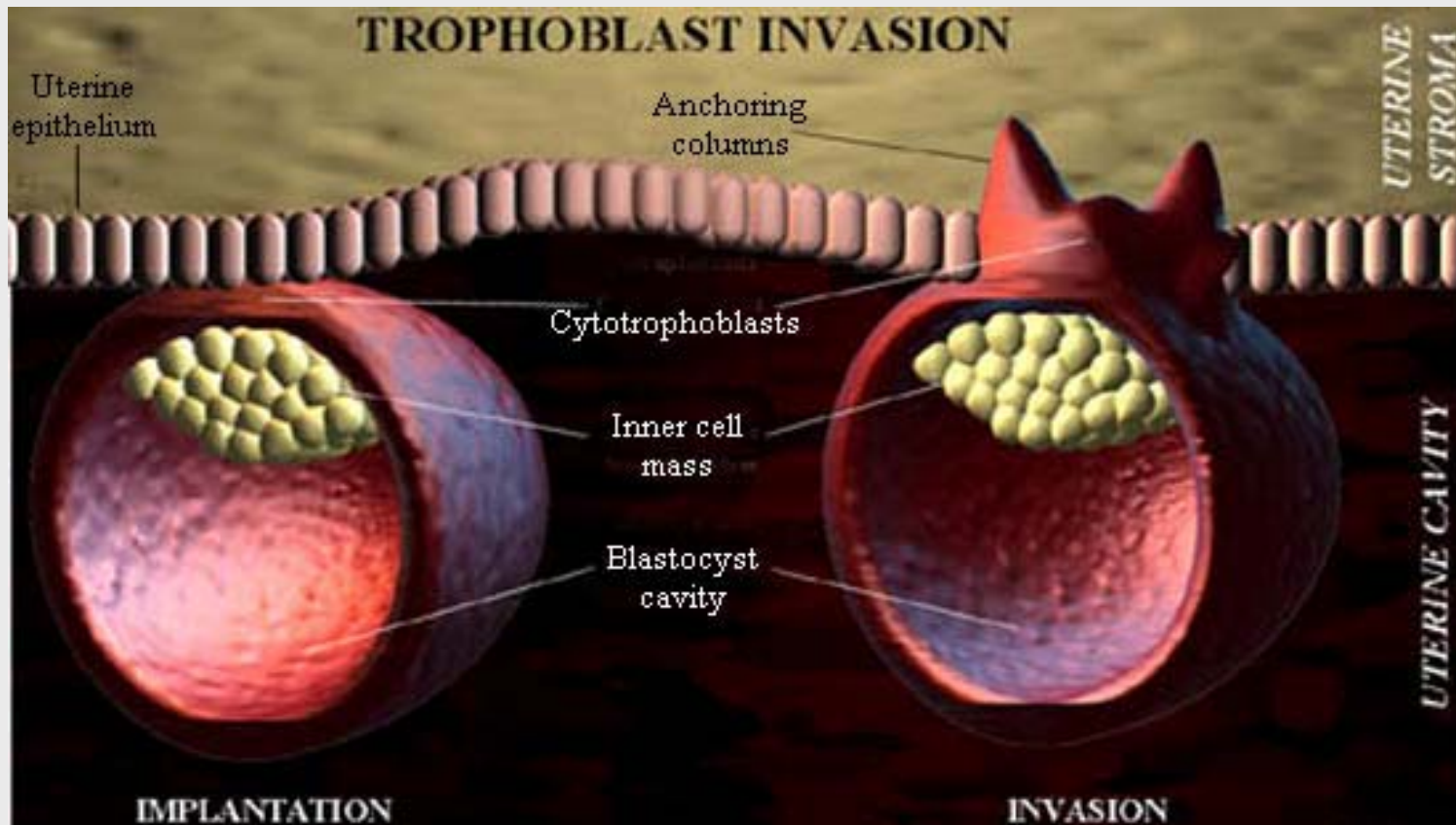
NASOM-GEMOQ 2012

OBJECTIVES

- **Pathological mechanisms** in preeclampsia including placental ischemia, the role of angiogenic factors and maternal inflammatory and immune response
- **Predictors** of worst outcome and the role of serological markers
- New **preventive** therapies

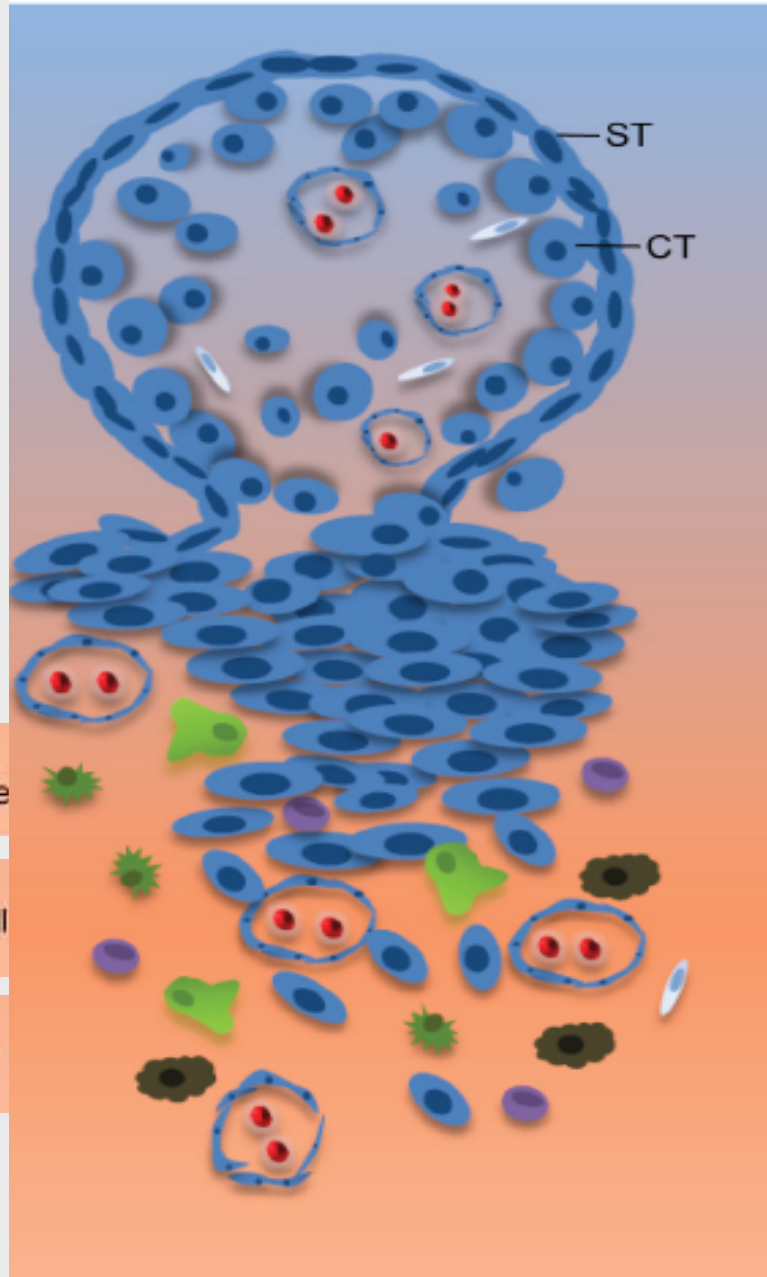
PLAN

- Normal placentation
- Placentation in Preeclampsia
- Markers
 - Best
 - Future
- Preventive therapies
 - Actual
 - Future



Normal pregnancy

Fetal side



blood vessel with erythrocyte

dendritic cell

stroma cell

Maternal side

Maternal-fetal recognition

KIRS



natural killer cell

Fetal HLA-C



macrophage

Apoptotic bodies



T-cell

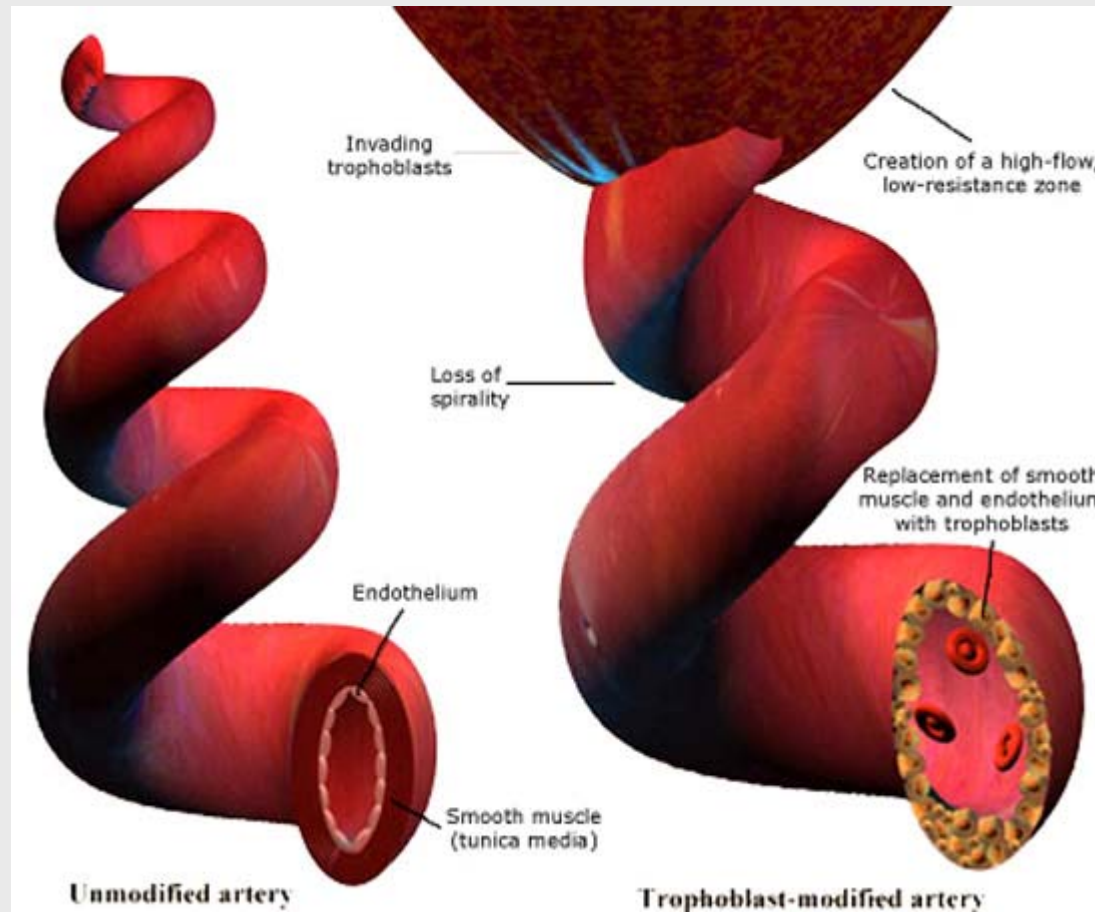
Inflammation

Oxidative stress

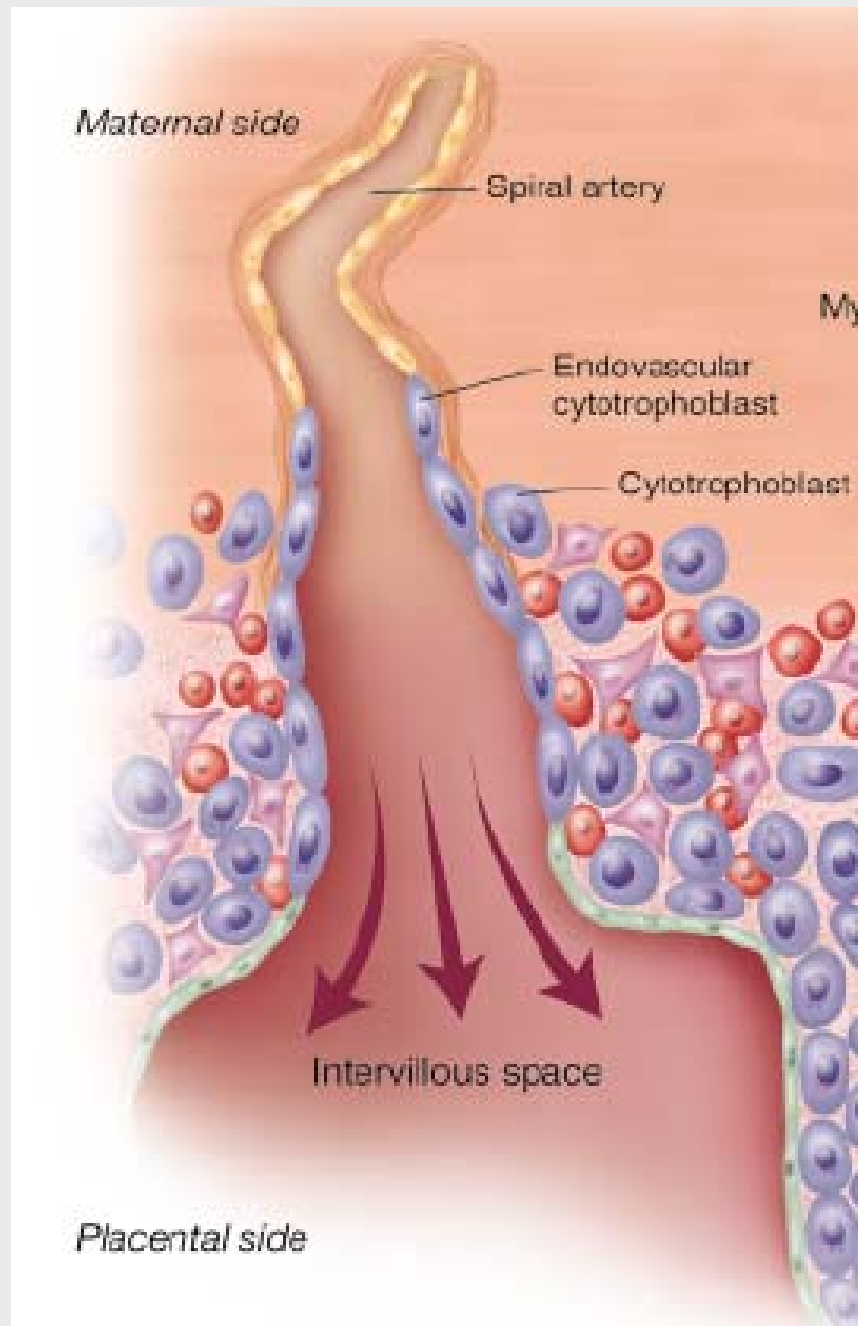
Angiogenic factors

3-8w

Adapted from Louwen 2012



Remodeling of the spiral arteries



18w

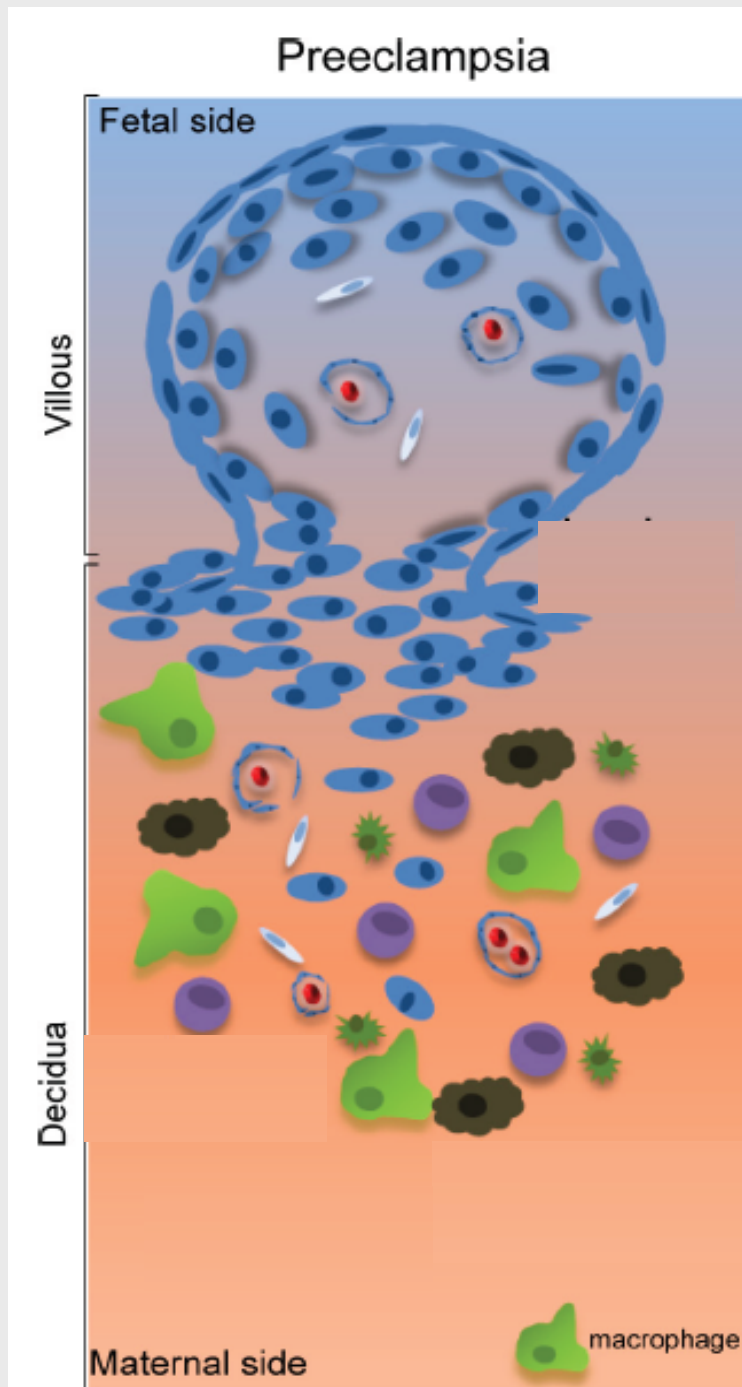
Adapted from Redman 2005

PREECLAMPSIA

- Abnormal placentation
- Relative insufficiency: ↑ mass (DB, twin)
- Deteriorating placenta (hydrops, post-term)

STAGE 1

Abnormal MATERNAL tolerance to
FETAL cells



Insufficient activation of the NK

Autoantibodies agonists of
Angiotensin receptors

↓ Heme oxygenase-1

↑ Apoptotic bodies



↑ Inflammatory response

↑ Oxidative stress

Anti-angiogenics factors

Adapted from Louwen 2012

STAGE 2

Abnormal trophoblast growth and
differentiation

PLACENTAL DYSFUNCTION

- ↓PP13 *
- ↓PAPP-A *
- ↓ADAM12
- ↓Metastin
- ↓β-hCG

- ↑Activin-A
- ↑Inhibin-A *

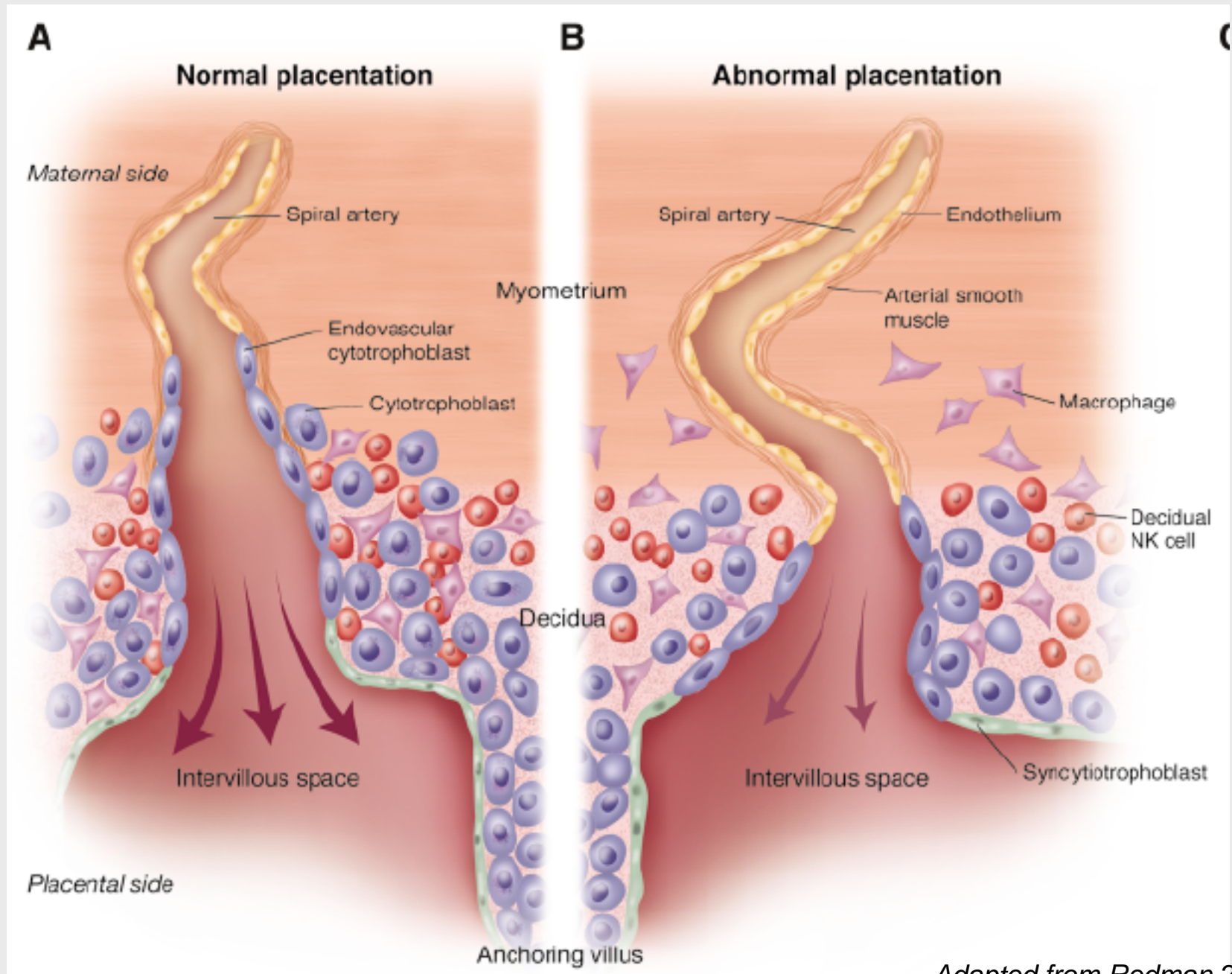
ANGIO- ANTIANGIOGENICS FACTORS

Angiogenic F.

- ↓ VEGF
- ↓ PIGF*

Anti-Angiogenic F.

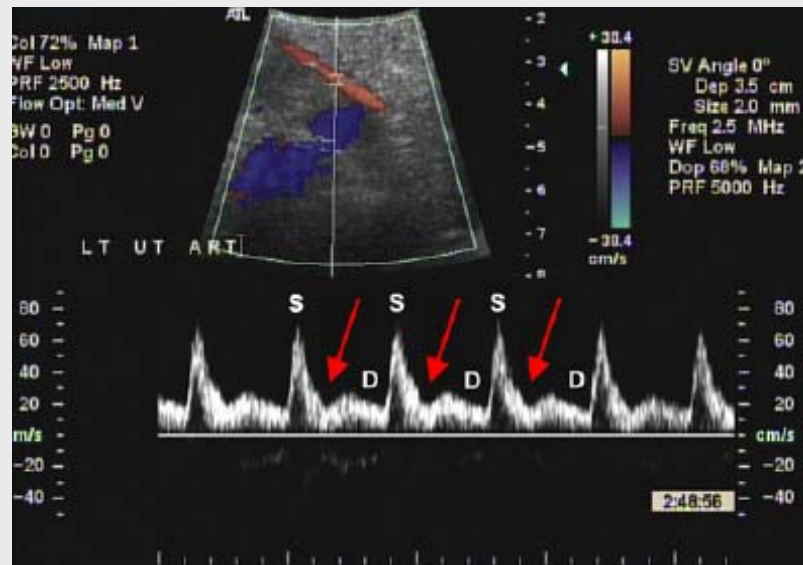
- ↑ sFlt-1
- ↑ sEndoglin*
- ↑ sFlt-1/PIGF



Adapted from Redman 2005

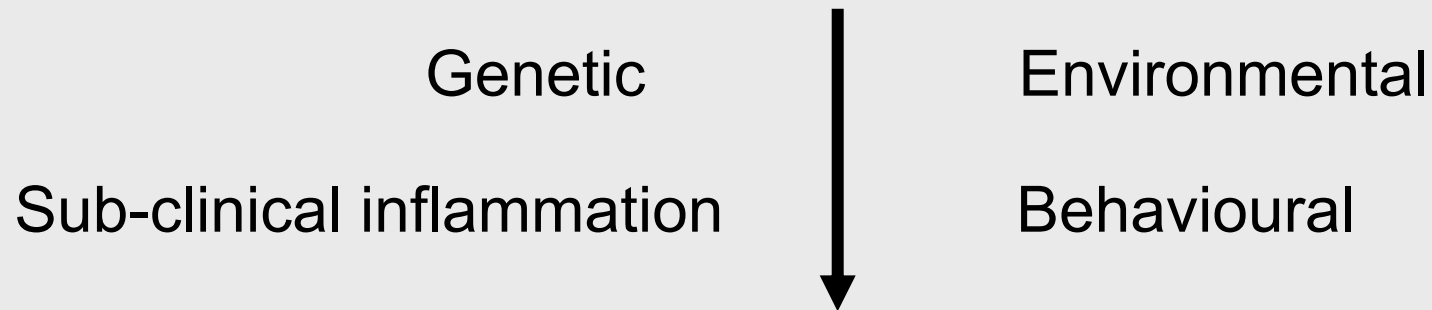
HEMODYNAMICS

- UA Doppler velocimetry
- Better 2nd T



STAGE 3

Maternal response



ENDOTHELIAL DYSFUNCTION

SYNDROME OF PREECLAMPSIA

MATERNAL RESPONSE (1)

- ↑ROS
- ↑8-isoprostane
- ↑MDA*
- ↑ PGF2 α
- ↑Oxidized LDL*
- ↓PON1
- ↓superoxide dismutase

- ↑fibronectin*
- ↑PTX3*
- ↑chitotriodidase*
- ↑TNF- α
- ↑IL-6, IL-8, IL-2
- ↑IFN- γ
- ↑Th1/Th2
- ↓IL-10
- ↑CA-125

MATERNAL RESPONSE(2)

- ↑PAI-1
- ↑thrombomoduline
- ↑thrombine consom.
- ↓fibrinolyse

- ↑Angiotensin II
- ↑Endotheline-1
- ↑Serotonine
- ↑PDGF
- ↓PGI₂
- ↓EDRF
- ↑ApoCIII/ApoCII

BEST PREDICTOR

- Clinical factors
- +
- Biomarkers

11-14w

- Clinical factors
- UA PI
- PAPP-A
- PIGF

Sensitivity

- **93%** *Poon 2009*
- **75%** *Audibert 2010*

Same + PP-13 +
Inhibin A +Activin A +
sEndoglin +PTX3 +
P-selectin

Sensitivity **91%**

– *Akolekar 2011*

ONGOING

- Improvement of biomarkers
- Podocytopathia/ Nephrin
- Cell-free fetal DNA
- Proteomics markers
- Metabolomics markers

PREVENTION

EXERCICE

HOW	↓ Inflammation, insulin resistance
EFFECT <i>Cochrane 2006</i>	Vs normal activity OR 0.31 (0.01-7.09) 2 studies. 45 W
<i>Yeo 2008</i>	Stretching vs. walking RR 5.6
Comment	Ongoing study in China

CALCIUM

HOW	↓ Vasoconstriction
DOSE	At least 1g/d
EFFECT <i>Cochrane 2010</i>	↓ PE OR 0.45 (0.31-0.65) ↓ PE in low intake OR 0.36 (0.20-0.65) ↓ PE in high risk OR 0.22 (0.12-0.42)
Comment	↑ HELLP OR 2.67 (1.05-6.82)
	High risk = 2/3: Roll-over test +, ≥ 28w; 2g/d; no chronic conditions

MULTIVITAMINS

HOW	↓ Endothelial dysf and oxidative stress
DOSE	Pregnancy dose
EFFECT <i>Merchant 2005</i>	↓ hypertension RR 0.62(0.40-0.94)
Comment	Tanzania; HIV+

MULTIVITAMINS

Observational studies: ↓ PE if N BMI

Pittsburgh OR 0.29(0.12-0.65) < 16w

Danemark HR 0.78(0.60-0.99) 4w before to 8w after

HR 0.63(0.42-0.93) ad 12w

Canada aOR 0.37(0.18-0.75) 12-20w

ANTIOXYDANTS

HOW	↓ Oxidative stress
	Selenium, V E and/or V C, Lycopene, L-arginine+ Vitamins
EFFECT <i>Salles 2012</i>	PE OR 0.92 (0.82-1.04) Severe PE OR 1.03 (0.87-1.22)

VITAMINES C AND E

HOW	Antioxydants
DOSE	V C:1000mg; V E 400 IU
EFFECT <i>Conde-Agudelo 2011</i>	High risk OR 0.95 (0.85-1.06) cHT OR 1.00 (0.84-1.19) DB OR 0.84 (0.65-1.10)
Comment	↑ PROM, ↑ low birthweight

L-ARGININE

HOW	Antioxydant; precursor of NO
DOSE	4-6.6g/d
EFFECT	<i>Neri 2010</i> cHT: ↓ need of RX 24% vs. 45% <i>Vadillo-Ortega 2011</i> ↓ PE L-Arg+V: RR 0.42 (0.28-0.62)
Comment	Vitamins: C,E,B2,B6,B12,FA 0.4 PH and/or FH of PE L-arginine↑ in PE

NEAR FUTURE

FACT

- cHT, DB, twin, PH PE, BMI \geq 35
- FA 4mg vs. placebo
- 8-16w

VITAMINE D

HOW	Ca; ↓ immune, inflammation dysfct
DOSE	1200IU+375mg Ca
EFFECT <i>Cochrane 2012</i>	RR 0.67 (0.33-1.35)
Comment	1 trial 10 ongoing trials

STATINS

- Non lipid-lowering effects: improvement of endothelial function
- Simvastatine: ↓ sFlt-1 and endoglin in vitro
- Pravastatine: Mice: ↑ VEGF in PE and ↓ PE symptoms

BUT

STATINS (2)

- HMG-CoA reductase activity required for normal placentation
- Effect may be \neq according to dose
- Malformation?

- Ongoing study: on established PE

FUTURE

- VEGF administration
- Manipulation of the heme-oxygenase-1 pathway
- Manipulation of the Endothelin pathway

2012:WHAT DO I DO?

- Before pregnancy:
 - Healthy life, milk products, multivitamins, exercise, ↓ stress
 - Good control of chronic conditions
 - Interpregnancy interval
- Pregnancy: + Calcium, multivitamins
- Aspirin and LMWH
- Research projects