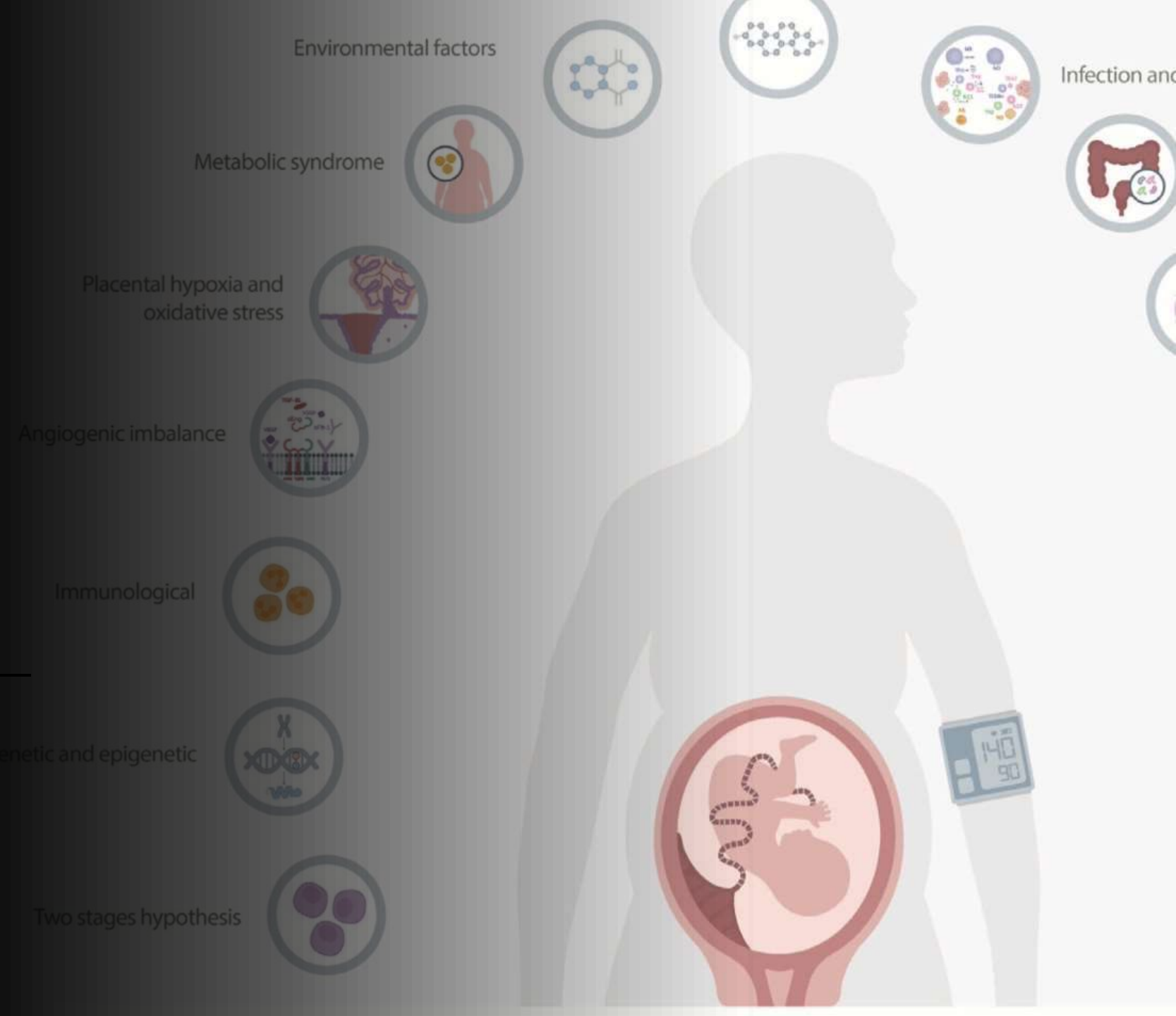
Targeting oxidative stress in preeclampsia

Rully Ayu Nirmalasari

Feto Meeting, July 29th 2025

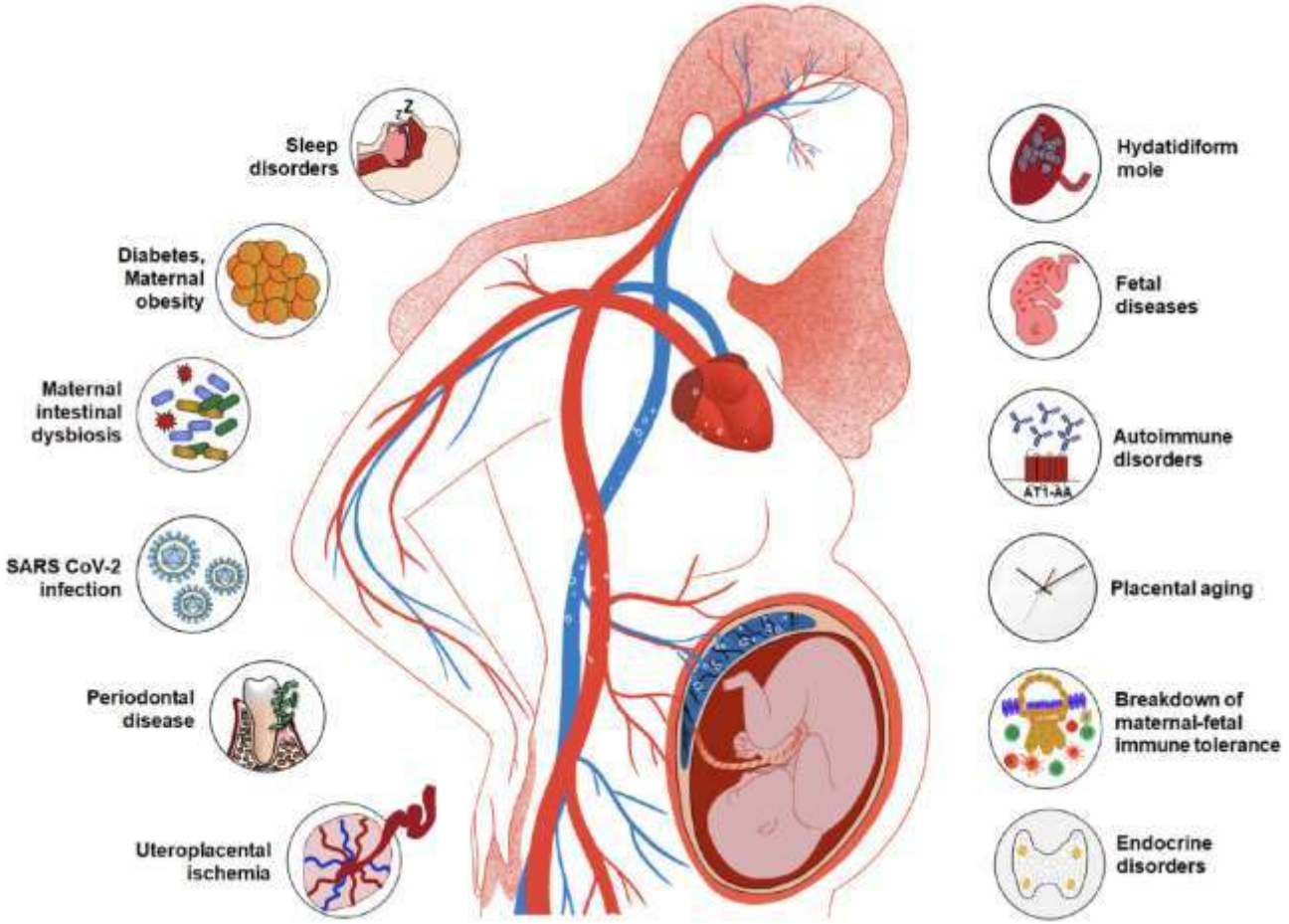


Introduction to Preeclampsia (PE)

- A multifactorial pregnancy disorder characterized by **new-onset hypertension (onset after 20th week of gestation)** and often accompanied by proteinuria or other organ dysfunction (e.g., kidneys, liver, blood, brain, placenta)
- Complicates approximately **2%–8% of all pregnancies globally**
- Accounting for **16% of maternal deaths worldwide**
- **Long-term risks for mothers:** chronic hypertension, cardiovascular disease, stroke, metabolic syndrome, cognitive impairment, end-stage renal disease
- **Long-term risks for infants:** more susceptible to neurodevelopmental impairments, diabetes mellitus, coronary heart disease, and hypertension

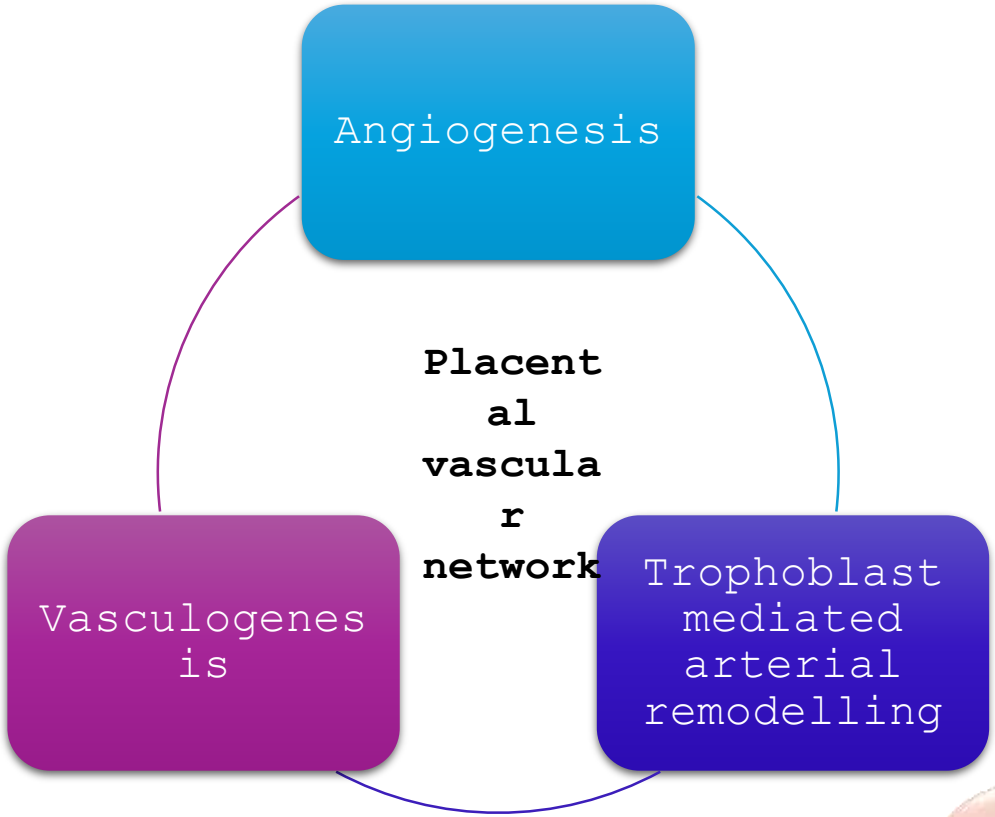
Int. J. Mol. Sci. 2024, 25, 7569. https://doi.org/10.3390/ijms25147

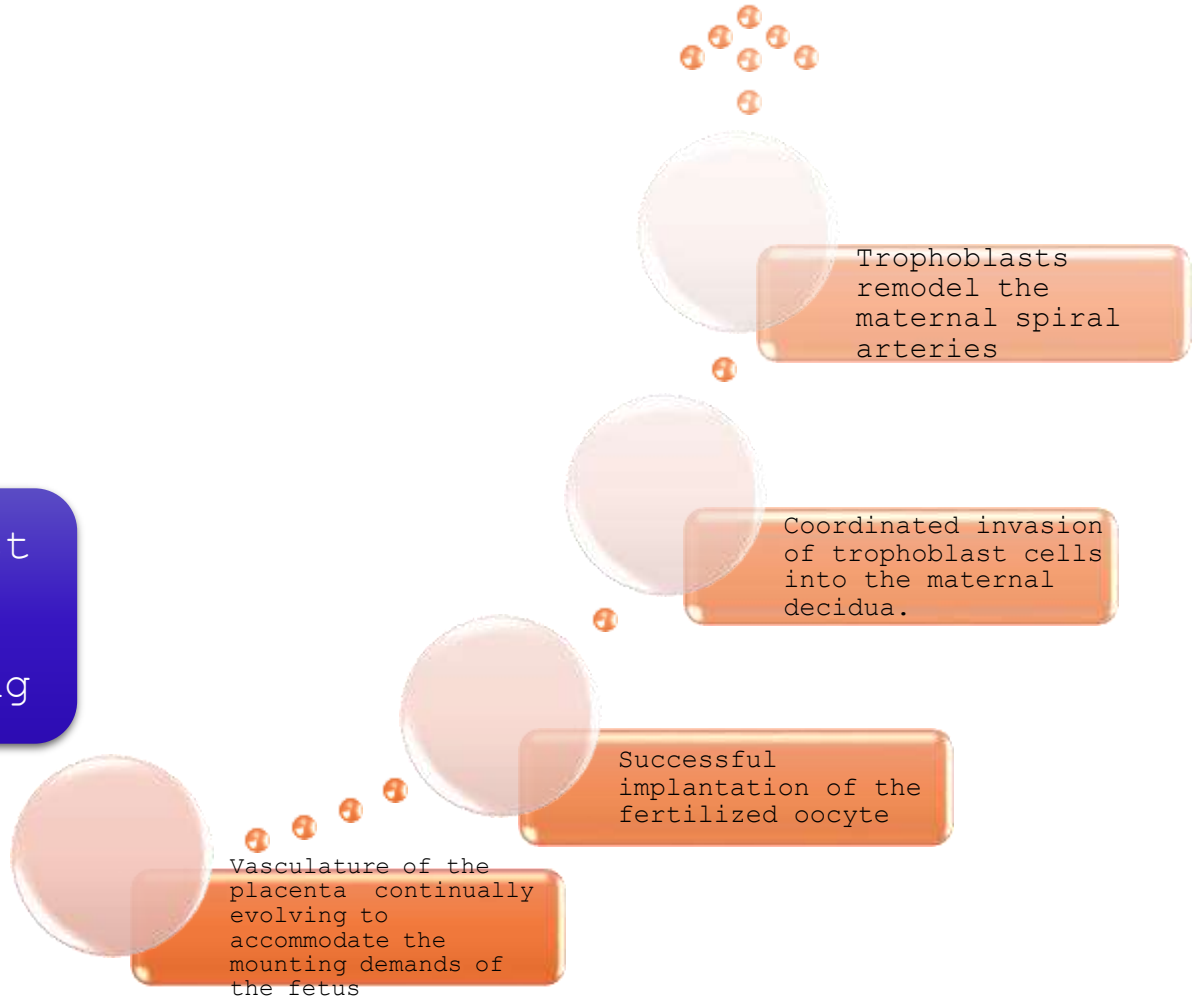
Multiple etiologies implicated in preeclampsia



Am J Obstet Gynecol . Author manuscript; available in PMC 2023 Februa

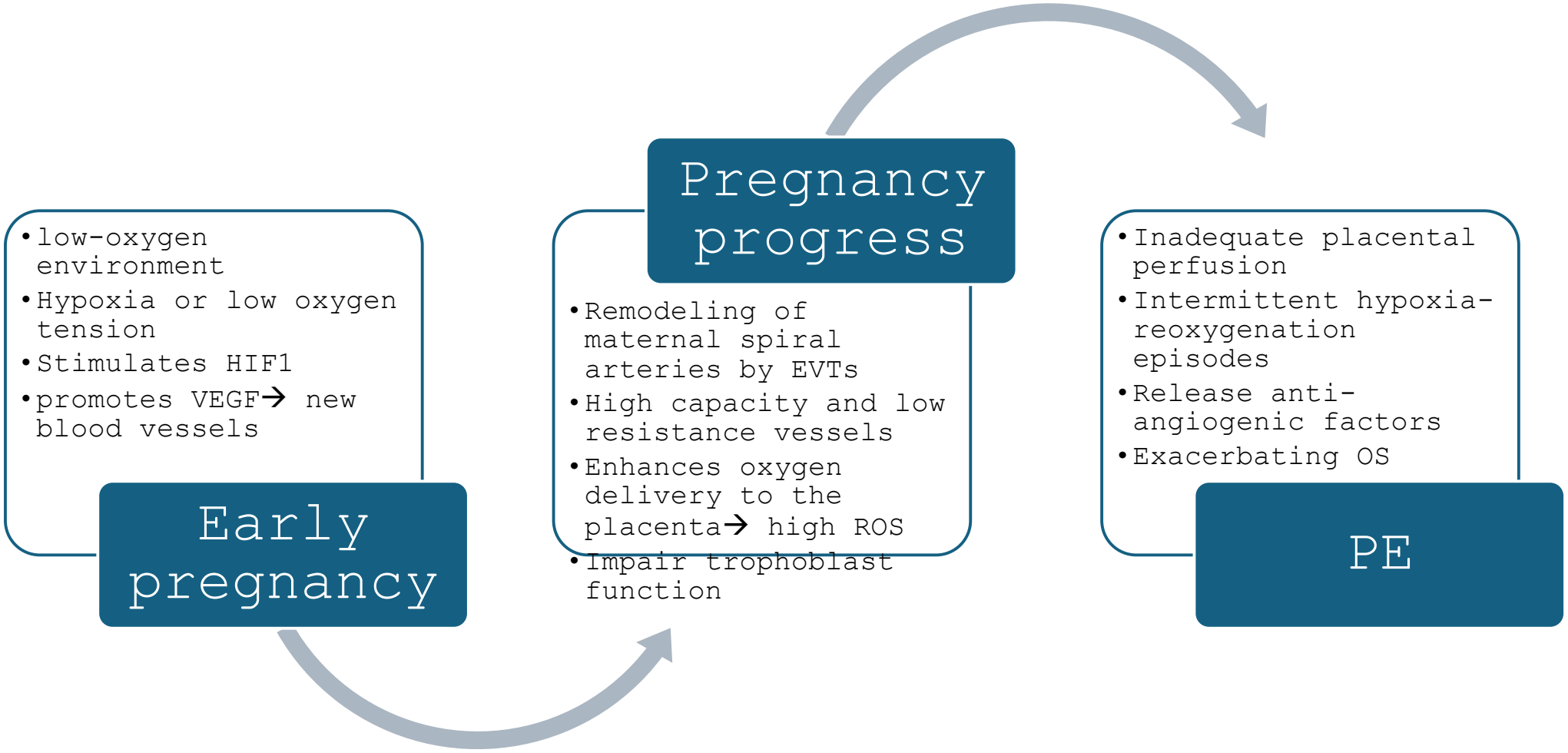
The establishment of proper placental function





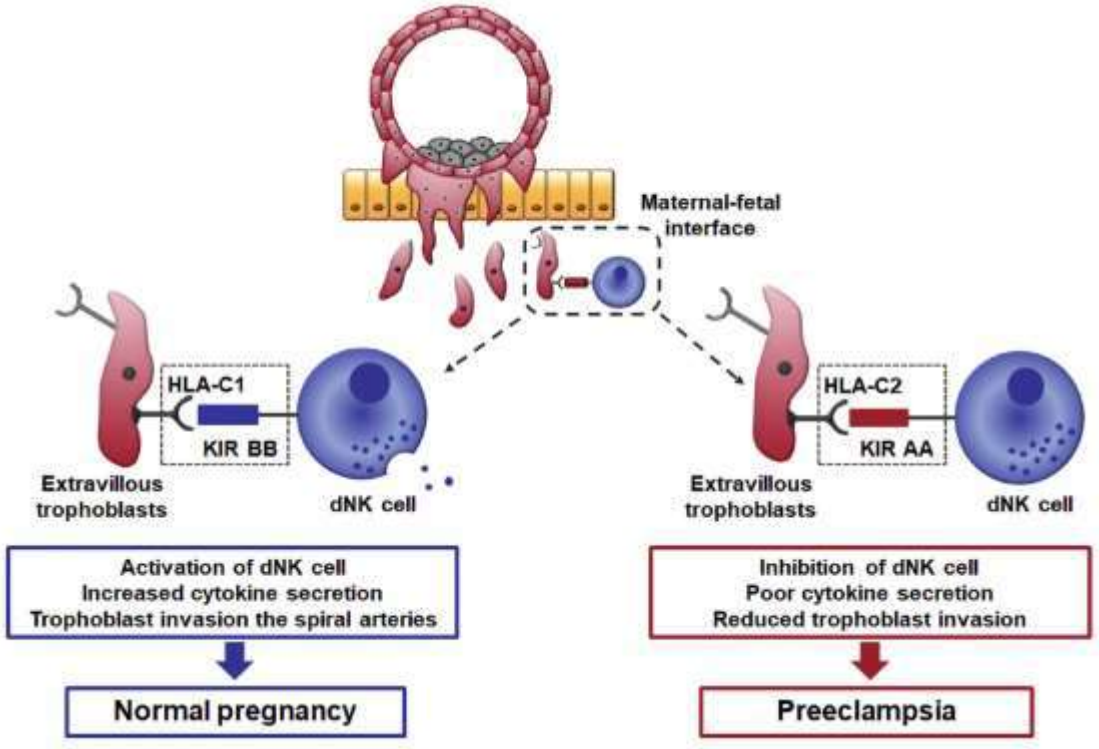
Pereira RD. Angiogenesis in the Placenta: The Role of Reactive Oxygen Species Signaling. http://dx.doi.org

After Apposition, adhesion and invasion:

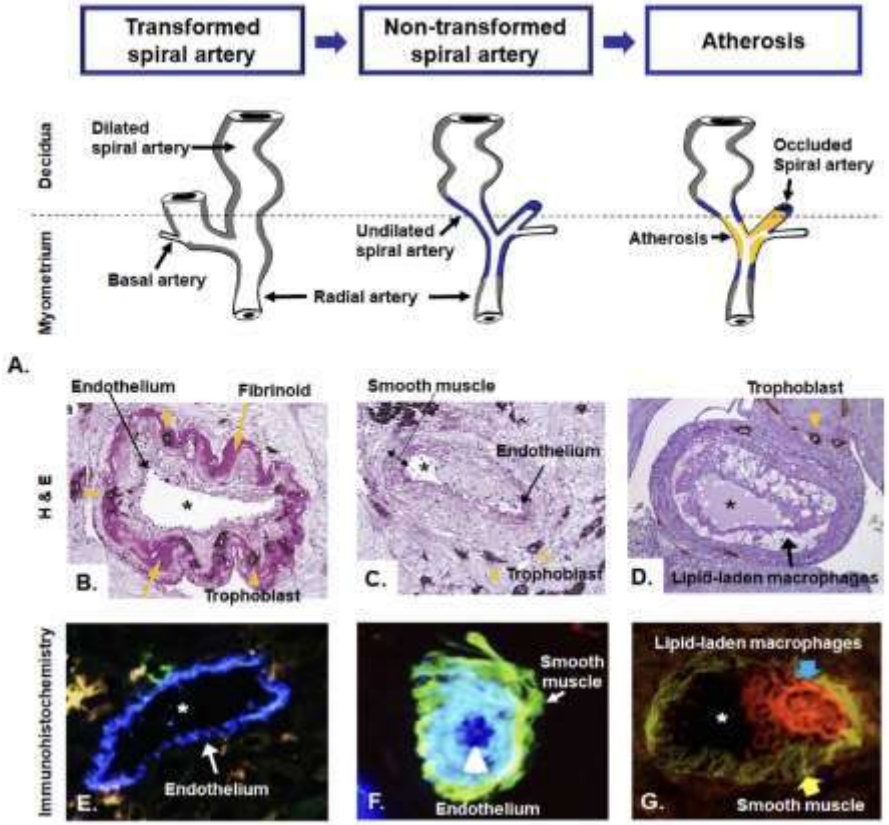


Int. J. Mol. Sci. 2024, 25, 12195. https://doi.org/10.3390/ijms2522

Interactions between maternal KIR and fetal HLA-C at the site of placentation



Non-transformed spiral arteries are prone to atherosis

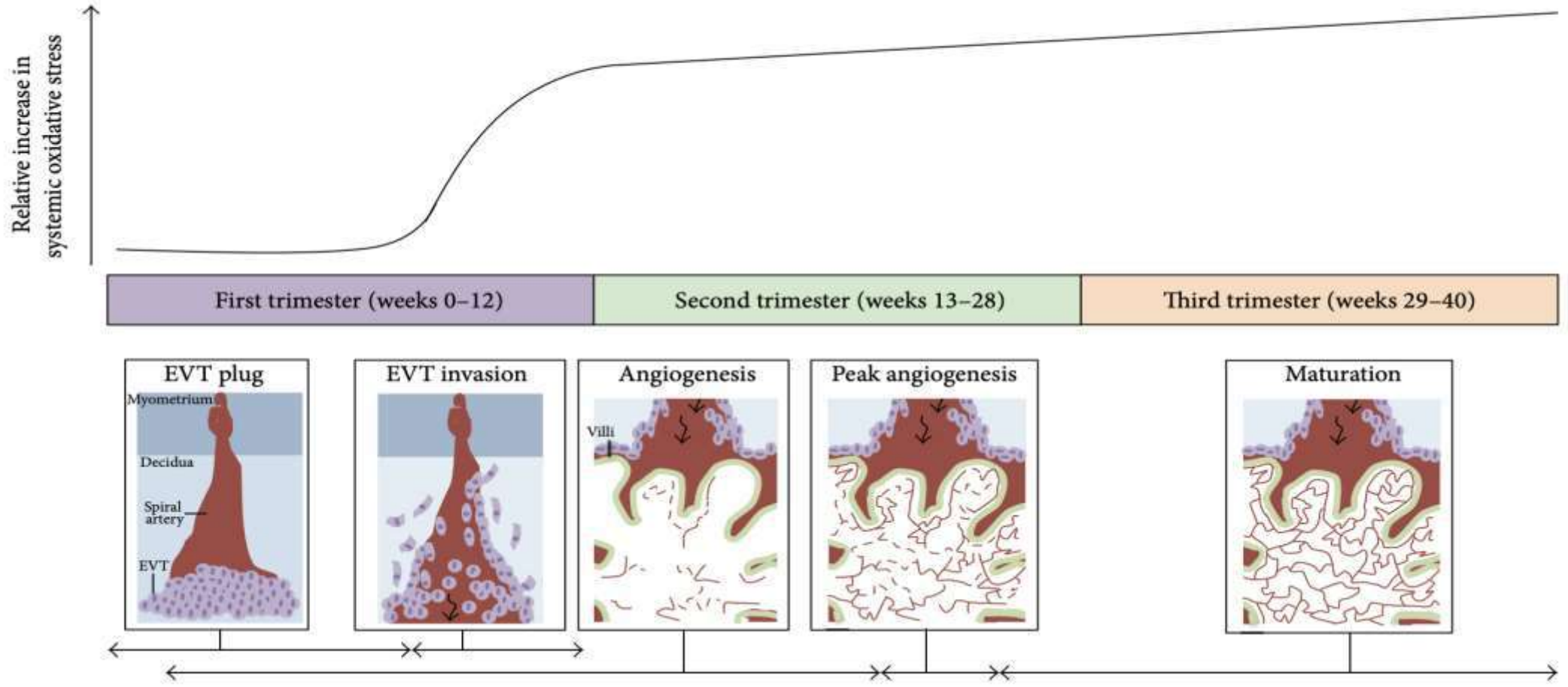


A key factor influencing placental development and function is the delicate **balance between** reactive oxygen species (**ROS**) and reactive nitrogen species (**RNS**) production **and the antioxidant** defense mechanisms **that neutralize** these reactive molecules

An imbalance leads to oxidative stress (OS), which can damage lipids, proteins, and DNA, disrupt cellular functions, and trigger cell death pathways such as apoptosis and autophagy

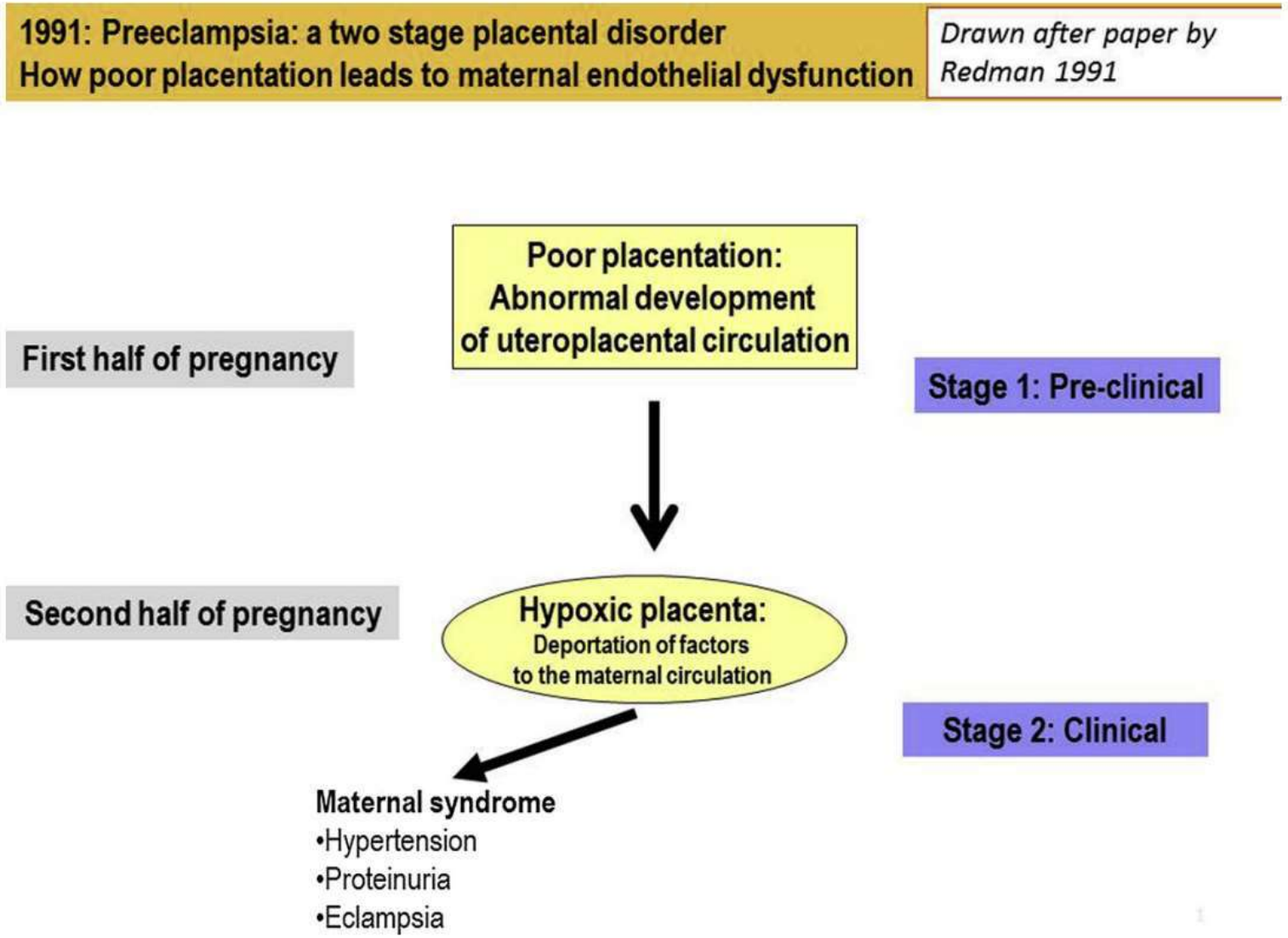
Int. J. Mol. Sci. 2024, 25, 12195. https://doi.org/10.3390/ijms25221219

Oxidative stress throughout human pregnancy and its relation to placental angiogenesis



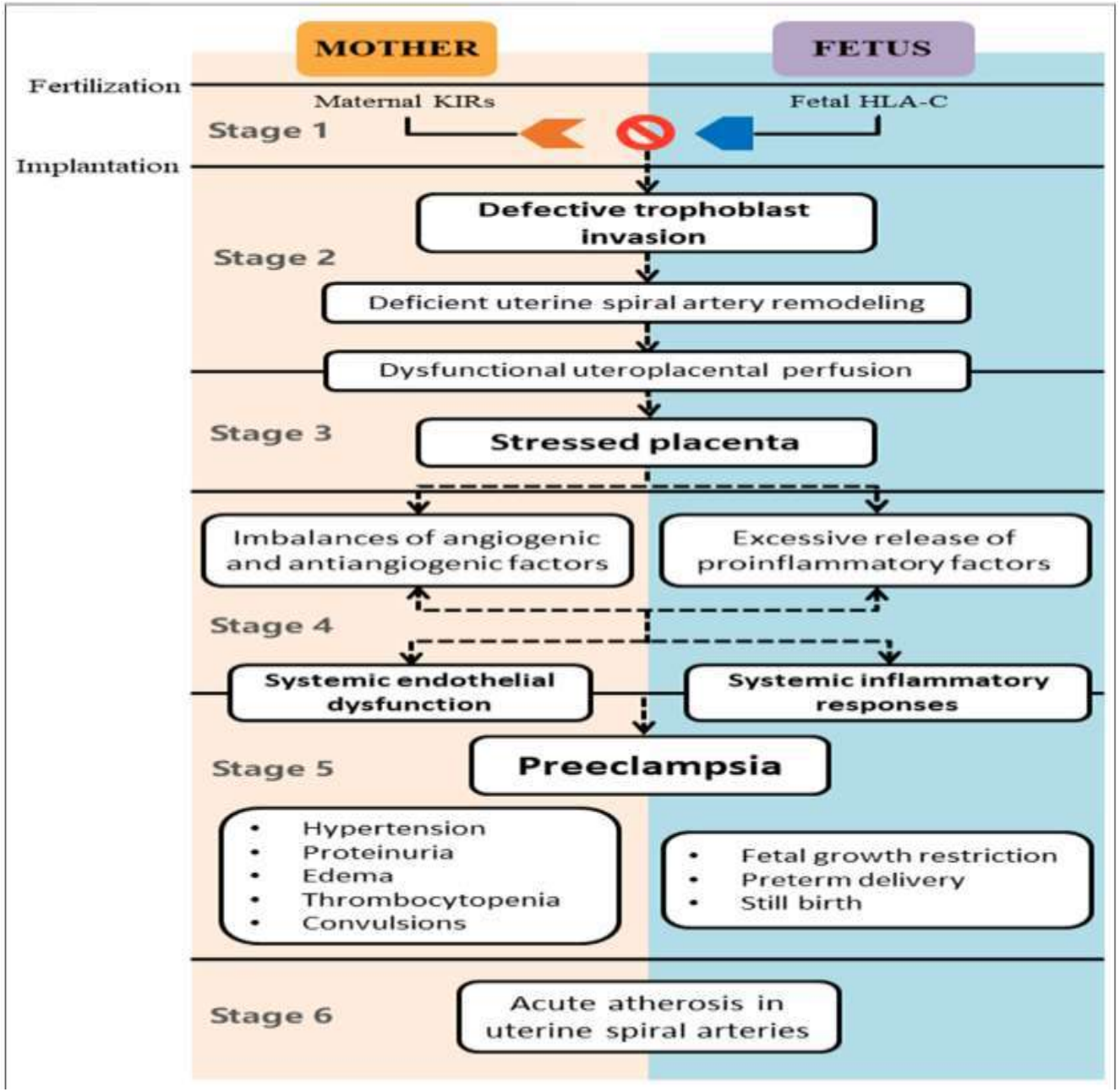
Pereira RD. Angiogenesis in the Placenta: The Role of Reactive Oxygen Species Signaling. http://dx.doi

Redman 1991 Two Stage Placental Disorder

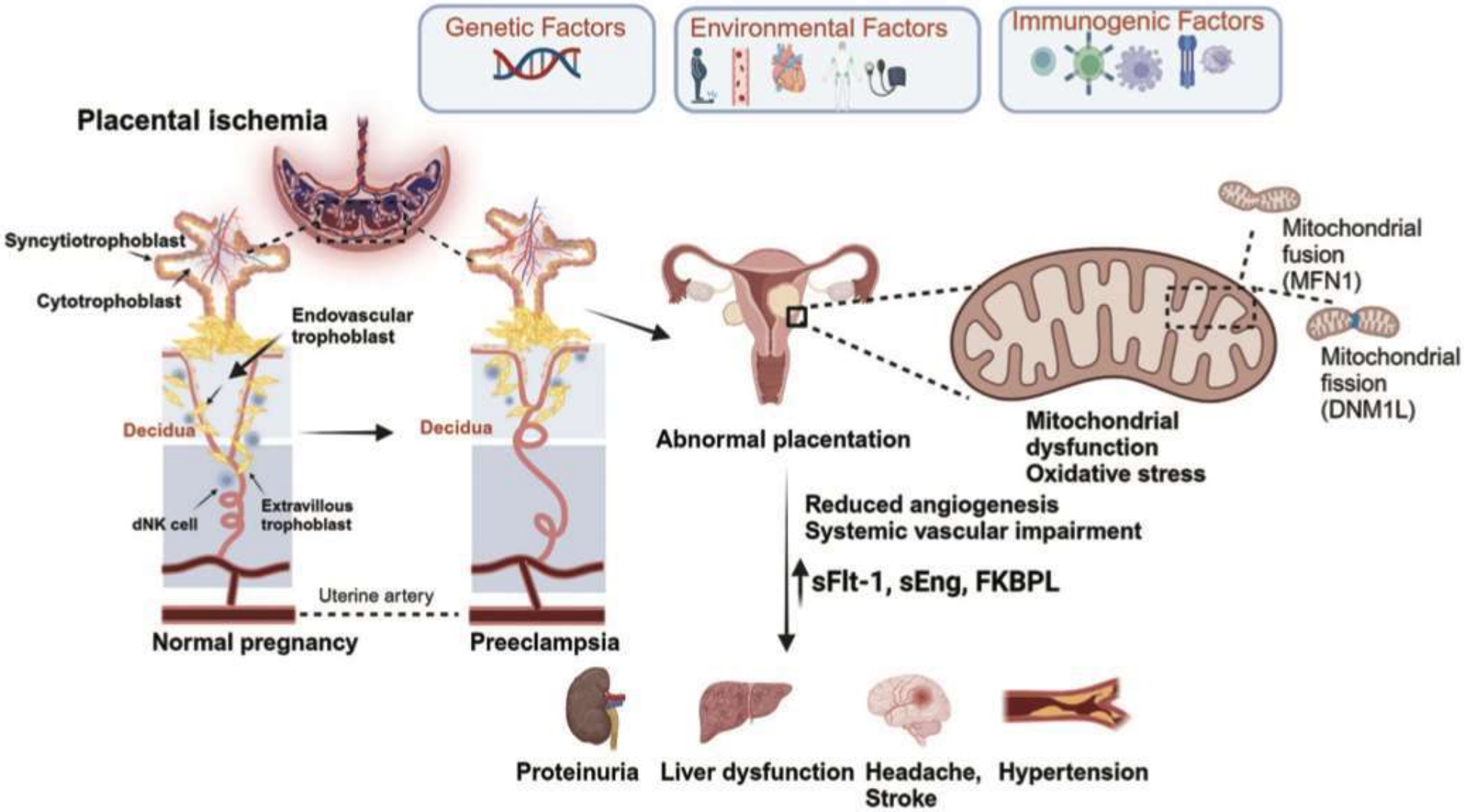


Journal of Reproductive Immunology 134–135 (2019) 1–10. https://doi.org/10.1016/j.jri.2019.07.004

Redman et al, Six-stage theory of PE pathogenesis.



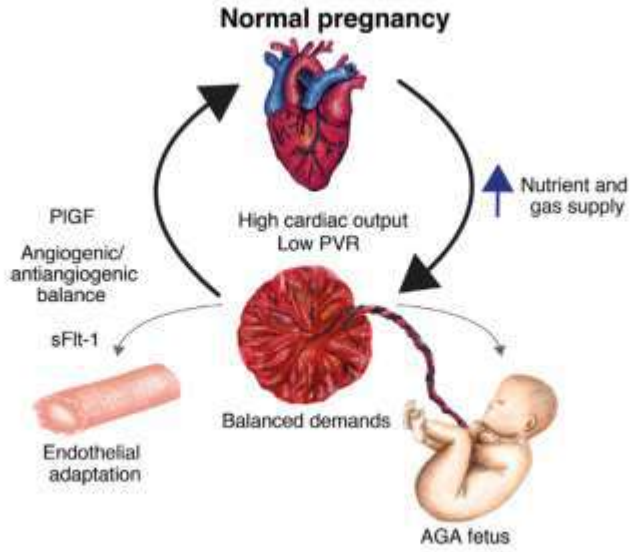
Schematic diagram of preeclampsia pathogenesis

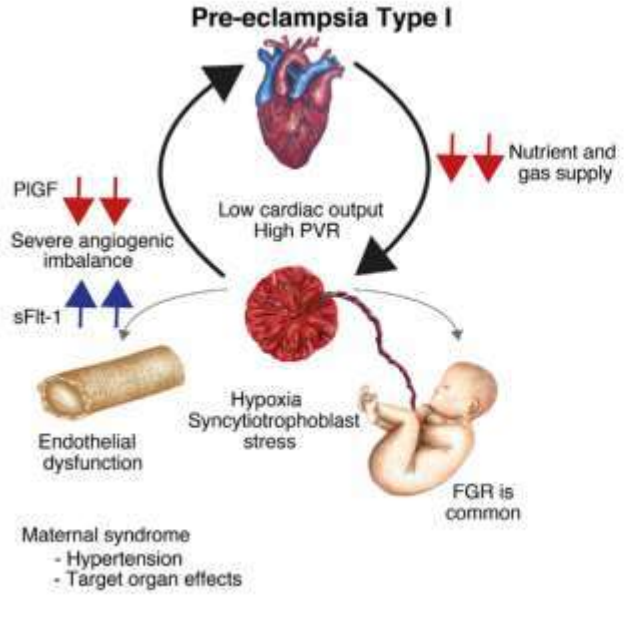


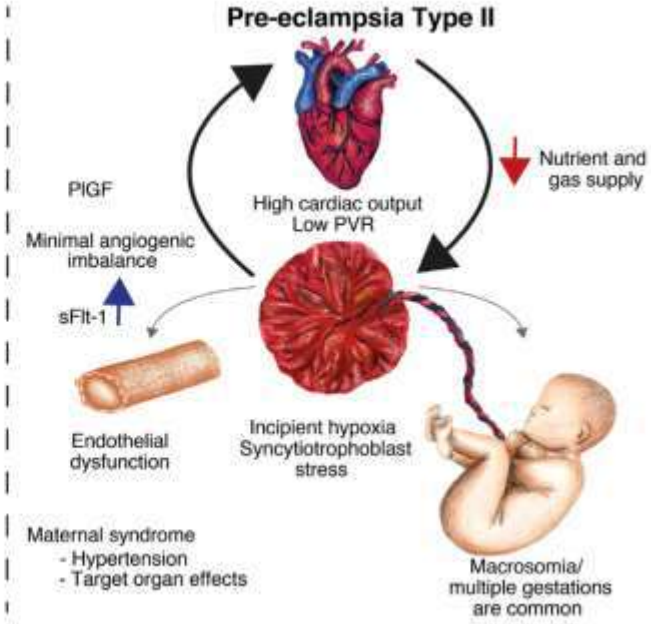
Targeting oxidative stress in preeclampsia, Hypertension in Pregnancy, 44:1, 2445556, DOI:10.1080/10641955.2024.2445556

An integrated model of the maternal cardiac–placental–fetal array (the development of preeclampsia placenta-dominant or maternal cardiovascular system-dominant)

contribute to the development of
risk-reduction strategies
and long-term follow-up







Yagel S, Cohen SM, Admati I, et al. Expert review: preeclampsia Type I and Type II. Am JObstet Gynecol MFM 2023;5:101203.

Proposed classification of preeclampsia Types I and II

Clinical parameter	Type I: placental dysfunction	Type II: maternal cardiovascular maladaptation
Most common characteristics and laboratory results	Usually presents earlier (<34 wk) FGR sFlt-1/PlGF ↑↑↑ Cardiac output ↓ Peripheral vascular resistance ↑	Usually presents later (>34 wk) Macrosomia/twins and multiples sFlt-1/PlGF ↑ Cardiac output ↑ Peripheral vascular resistance ↓
Risk factors	Nulliparity Previous preeclampsia Diabetes IVF without corpus luteum[96,97] IVF with donor eggs[98] Antiphospholipid syndrome[99] Molar pregnancy Fetal conditions[a]	Nulliparity Previous preeclampsia Diabetes IVF without corpus luteum[96,97] IVF with donor eggs[98] Obesity Chronic hypertension Chronic kidney disease
Screening	Maternal factors, mean arterial pressure, uterine artery Doppler, and PlGF[100]	
Preventative measures	Exercise (~140 min/wk) Aspirin Aspirin+low-molecular-weight heparin (APLA) Calcium administration Progesterone support in IVF pregnancy?	Exercise (~140 min/wk) Glycemic control Weight control and reduction Prevention of multiple pregnancy
Pregnancy surveillance	Clinical parameters Laboratory studies (including sFlt-1/PlGF) Doppler studies EFW Maternal cardiac studies	Clinical parameters Laboratory studies (including sFlt-1/PlGF) EFW Maternal cardiac studies?
Treatments	Exercise NO donors, calcium channel blockers, fluid support aimed at vasodilation Timed delivery	Exercise Alpha/beta blockers Timed delivery
Future treatments	sFlt-1 ligands siRNA-based therapy Plasmapheresis Antioxidants	Timed delivery
Postpartum and long-term follow-up	Cardiac studies	Cardiac studies?

APLA, antiphospholipid antibody; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *IVF*, in vitro fertilization; *NO*, nitric oxide; *siRNA*, small interfering RNA.

[a] Fetal conditions include, for example, trisomy 13 and abdominal ectopic pregnancy.; Modified from Yagel et al.[38]

Yagel. Preeclampsia Type I and Type II. Am J Obstet Gynecol MFM 2023.

The role of mitochondrial function in placental development and growth

- Responsible for nutrient transport and metabolism
- Mitochondrial enzymes including pyruvate dehydrogenase complex (PDHC) and carnitine palmitoyl transferase (CPT), facilitate the conversion of glucose and fatty acids, respectively, into acetyl-CoA, leading to energy production
- Mitochondria participate in apoptosis and regulate oxidative stress within trophoblast cells
- Mitochondrial dysfunction can lead to excessive ROS generation, resulting in oxidative stress

Prediction and diagnosis of preeclampsia

Has been challenging due to inter-patient variability in symptoms and features

Uterine artery Doppler ultrasound has demonstrated promise as a noninvasive imaging technique for predicting preeclampsia.

An **sFlt-1: PlGF ratio** with a cut-off of > 38 was found to be an important predictor of preeclampsia with positive predictive value of 36.7% with 66.2% sensitivity and 83.1% specificity for preeclampsia within 4 weeks, which informed its use as a rule-out than rule-on test

Low plasma PlGF concentrations had high sensitivity (96%), negative predictive value (98%), and specificity (55%). A low PlGF plasma concentration with 0.87 area under the receiver operating characteristic (ROC) curve for predicting preeclampsia within 14 days

vascular cell adhesion molecules **(VCAM-1) > 450 ng/ml** was associated with a sensitivity of 79% and a specificity of 90% for the detection of severe pre-eclampsia and eclampsia

Combining demographic information, imaging parameters from uterine Doppler ultrasound, and biomarkers related to angiogenesis, endothelial dysfunction, inflammation, and metabolic alterations can enhance the accuracy of prediction and diagnosis of preeclampsia.

The role of oxidative stress in preeclampsia

- Oxidative stress, defined by an excess of ROS over antioxidant defenses, is increasingly recognized as a key driver of **cellular senescence in the placenta** → Elevated markers of oxidative stress and senescence, p21 and p53
- Senescence: a process characterized by permanent cell cycle arrest and the secretion of pro-inflammatory factors collectively termed the senescence-associated secretory phenotype (SASP)
- Excessive oxidative stress (ROS → NO, superoxide, hydrogen peroxide, hydroxyl radicals, and peroxynitrite) contributes directly to impaired trophoblast invasion and endothelial dysfunction

The role of oxidative stress in preeclampsia

- NADPH oxidase catalyzes the production of free radicals, and it is found to be upregulated in placental tissues from individual with preeclampsia
- Dysfunctional HDL particles → increased levels of oxidized LDL and ROS to accumulate, which exacerbates endothelial dysfunction and inflammation

Targeting oxidative stress in preeclampsia, Hypertension in Pregnancy, 44:1, 2445556,
DOI: 10.1080/10641955.2024.2445556

Current treatments for preeclampsia

- The only current curative treatment is the removal of the placenta and delivery of the fetus.
- Antihypertensive agents (labetalol, methyldopa and/or nifedipine
- Some prevention strategies include low dose aspirin (80 -150 mg/day) before 16 weeks of gestation→ reduce risk 62%
- Calcium and vitamin D supplements
- Muscle resistance, exercises (2.5-5 hours a week), and weight loss for overweight/obese mothers
- a three-fold increased risk of developing preeclampsia when pregnant women have a high body mass index (BMI >30kg/m2)

Potential treatments for preeclampsia

- Small human trial evaluating **pravastatin (40 mg/day)** showed a promise in **reducing rates of preterm preeclampsia**
- The primary rationale for considering statins in preeclampsia lies in their pleiotropic effects, which include antioxidant, anti-inflammatory, and general improvement in vascular health, with a potential to abrogate oxidative stress central to preeclampsia pathophysiology

Potential treatments for preeclampsia

- **Metformin**, has been shown to reduce weight gain and the risk of preeclampsia in women with a BMI >35 kg/m2 and to prolong gestation in women with preterm preeclampsia by almost a week without causing serious side effects

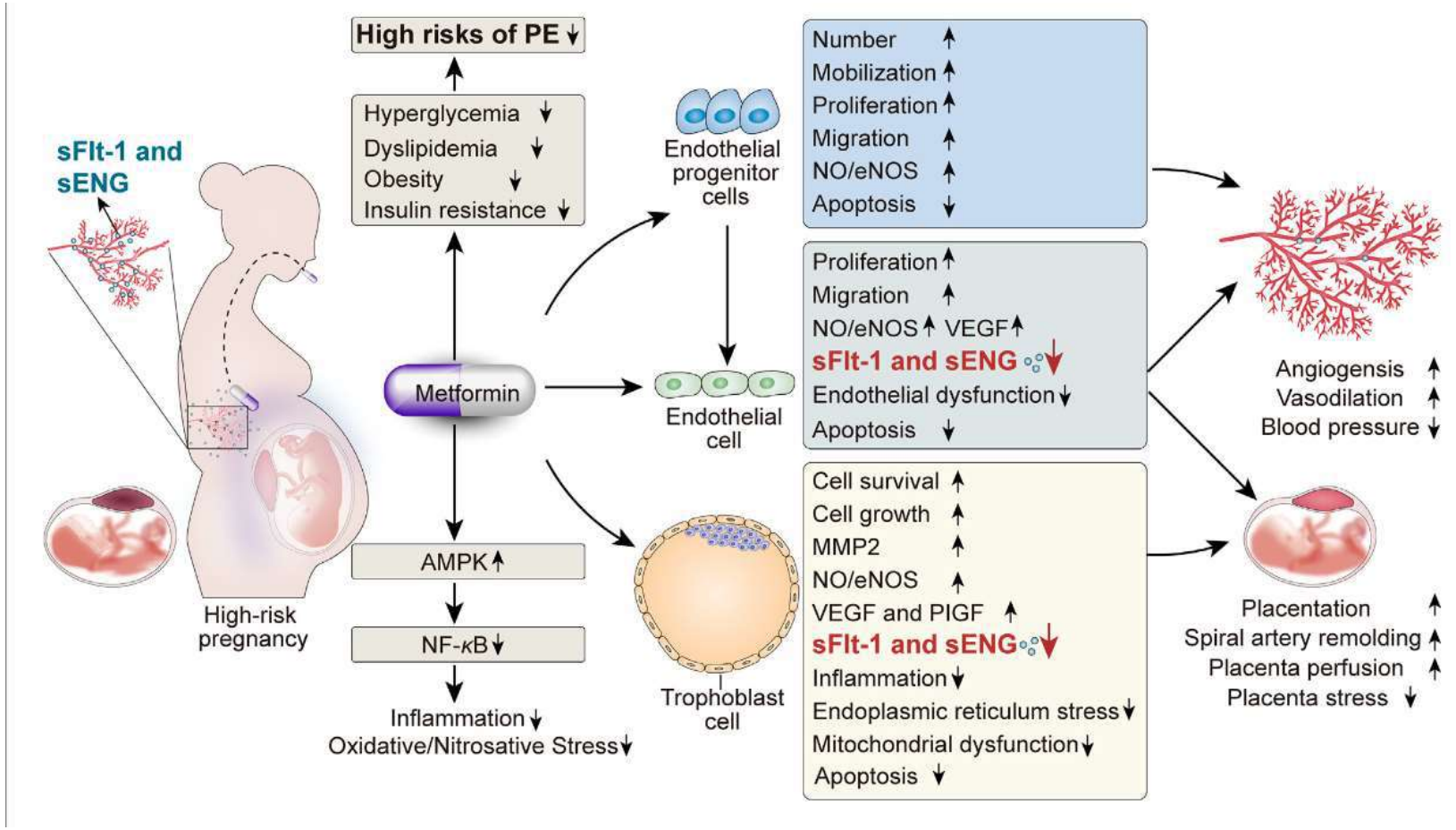
Potential treatments for preeclampsia

- Other studies have also suggested the use of **glycerol trinitrate**, its precursors, or **L-arginine** → restore nitric oxide levels and angiogenesis within the placenta, reduce oxidative stress

Drugs	Study Types	Findings
Metformin	Clinical trials Meta-analyses RCTs	• In obese pregnant women without type 2 diabetes mellitus, metformin reduced preeclampsia by 75% • Extended gestational age of delivery in early-onset preeclampsia by an average of 7 days. • Metformin ± insulin reduces gestational weight gain and risk of preeclampsia by 30% compared to insulin only • Metformin + esomeprazole reduces endothelial dysfunction and sFlt-1 secretion
Low dose aspirin	*In vitro* studies Meta-analyses Clinical trials RCTs	• Prophylactic treatment for preeclampsia • Reduces incidence of preterm preeclampsia and IUGR • Non-steroid, anti-inflammatory, antiplatelet properties • Improves placental function and abrogates cytokines upregulation, apoptosis and premature trophoblast differentiation • Restores syncytiotrophoblast dysfunction
Resveratrol	*In vitro* studies Clinical trials *In vivo* studies	• Anti-oxidant, anti-inflammatory properties • Upregulates SIRT expression • Inhibits sFlt-1 and sEng secretion by primary trophoblasts and HUVECs • Reduces secretion of pro-inflammatory molecules and increases antioxidant molecule expression • Resveratrol inhibited pigment epithelium-derived factor (PEDF) by upregulating miR-363-3p expression, thereby further elevating the expression of VEGF in a rat model of preeclampsia. Furthermore, resveratrol was found to improve the viability, migration, and angiogenesis of Cocl2-induced hypoxic trophoblasts *in vitro*. • Resveratrol increases the velocity of blood flow in the uterine arteries and fetal weight in $COMT^{-/-}$ mice • Resveratrol + nifedipine therapy could be beneficial for preeclampsia management by attenuating hypertensive symptoms .

PPIs	Clinical trials *In vitro* studies	• Reduce inflammatory cytokine levels in the placenta and blood vessels • Inhibit sFlt-1, sEng and ET-1 secretion in women with confirmed or suspected preeclampsia • Higher dose of intravenous administration may be effective in pre-term preeclampsia • Good safety profile and no teratogenic reports
Sulfasalazine	Clinical trials *In vitro* studies	• Anti-inflammatory and antioxidant properties • Inhibits sFlt-1, sEng and PlGF secretion in primary trophoblast cells • Mitigates vascular dysfunction in primary endothelial cells and omental vessel • Inhibits anti-angiogenic factors, stimulates angiogenic factors, inhibits HO-1 and VCAM, and induces vasodilation • Sulfasalazine + Metformin at low dose significantly increase VEGFα expression and reduce ET-1 expression in primary endothelial cells
Pravastatin	Clinical trials *In vitro* studies *In vivo* studies	• Promising preventative treatment when used in early gestation in pregnancy • Early administration of pravastatin is associated with lower IUGR • Favorable safety profile compared to other statins • In a murine model of preeclampsia, pravastatin increased VEGF and PlGF expression in placenta and ameliorated symptoms of preeclampsia • In primary human tissue studies (purified cytotrophoblast cells and placental explants), pravastatin inhibits sFlt-1 and sEng production • Prevents vascular dysfunction by increasing eNOS within aortic endothelial cells in a mouse model of preeclampsia

Beneficial pleiotropic effects of MET on PE and the potential mechanisms



Mitochondria targeting therapies

- Daily oral administration of 200mg CoQ10 from 20 weeks of gestation until delivery was associated with reduced preeclampsia risks.
- Some evidence suggests that CoQ10 could increase the total antioxidant capacity, which could decrease ROS and reactive nitrogen species (RNS) levels in preeclampsia
- Other: MitoTEMPO (mimics SOD), AP39 (a mitochondria-targeted hydrogen sulfide (H2S) donor)

Micronutrients supplements as a therapy for preeclampsia

- The inflammatory and oxidative stress state of pregnancy may be worsened by the deficiencies in folate, selenium, vitamin C, and vitamin E
- Vitamin D’s active form calcitriol, has been shown to inhibit ROS production and improve antioxidant defenses
- antioxidant properties of vitamins C and E help scavenge free radicals and reduce cellular damage caused by ROS

Thank you