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# New perspectives of diagnosis and treatment for preeclampsia

## 子癲前症新觀點：診斷及治療

蘇美慈

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2023.08.12

# Declaration of Conflict Interest

- I have no commercial disclosure

# Outline

- Current
  - Diagnosis and Practice Guidelines of Preeclampsia (ACOG)
  - Pathoetiology: Two-stage disease
- New perspectives
  - Pathoetiology
    - Decidualization resistance
    - Dysbiosis
    - Environment- PM 2.5, nano-particles, nano-plastics
  - Diagnostic markers
  - Treatment targets

# Definition, Clinical Presentations and Managements of Preeclampsia

# Definition for preeclampsia



## ISSHP 2018

- New onset of hypertension with one or more the following conditions after GA 20 wks
  - Proteinuria
  - Maternal organ dysfunction
    - Renal insufficiency
    - Liver involvement
    - Neurological complications
    - Hematological complications
  - Uteroplacental dysfunction

Pregnancy Hypertension 19 (2020) 206–211

## ACOG 2020

- new onset of hypertension after GA 20 wks
  - Proteinuria
  - Significant end-organ dysfunction
    - PLT < 100,000/uL
    - Crea >1.1 mg/dL
    - Liver enzymes > 2* normal limits
    - Pulmonary edema
    - Visual symptoms (blurred vision)
    - Headache (new onset)

ACOG Practice Bulletin No. 222;
Obstet Gynecol 2020; 135:e237.

# Preeclampsia screening and prediction model



- **First trimester (11-14 wks)** Fetal Medicine Foundation (FMF triple test)
  - Maternal factors (MF)
  - Mean arterial pressure (mAP)
    Uterine artery pulsatility index (UtA-PI)
    Serum placental growth factor (PlGF) or PAPP-A
  - Detection rates of 90% and 75% for the prediction of very early (< GA 32 wks) and preterm preeclampsia, respectively, with a 10% false-positive rate
- **Second to third trimester**
  - sFLT1 and placental growth factor (PlGF): a sens of 80% and a speci of 92%
  - sFLT1/ PlGF of 38
    - Diagnosis of PE within 4 weeks: a sens of 66.2% and a spec of 83.1%
    - To rule out the disease within 1 week with a NPV of 99.9%

Am J Obstet Gynecol. 2022 Feb;226(2S):S1071-S1097.e2.
Poon et al., Prenat Diagn 2010;30:216–23.

# Practice Guidelines from ACOG and SMFM

(2018 and reaffirmed Oct 2022)



- One high risk factor or two moderate risk factors for PE
  - Low-dose aspirin therapy (81 mg/d) should be started between GA 12 and 28 wks (optimally before 16 weeks)
  - Continued daily until delivery
- Any patient with PE or gestational HTN
  - GA ≥37 wks→ delivery.
- Patients with PE or gestational HTN with **severe features**
  - GA ≥34 wks→ delivery
  - GA< 34 wks→ consider expectant management

Obstet Gynecol 2018;132:e44-52; JAMA 2021;326:1186-91.

**Clinical Risk Factors for Preeclampsia**

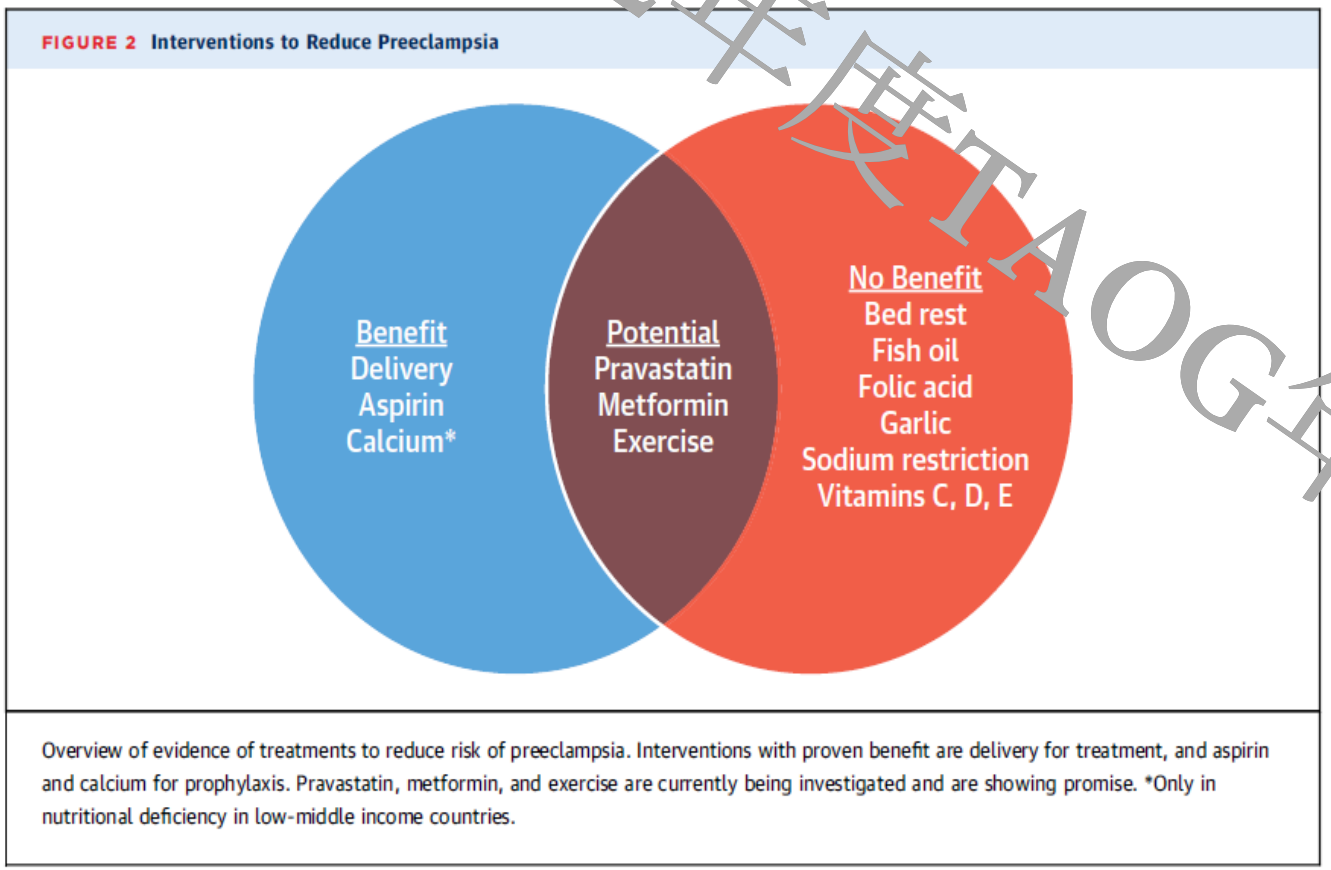
| Risk level | Risk factors |
|---|---|
| High (1) | Autoimmune disease (e.g., systemic lupus erythematosus, antiphospholipid syndrome) |
| | Chronic hypertension |
| | Diabetes mellitus – type 1 or type 2 |
| | History of preeclampsia |
| | Multifetal gestation |
| | Renal disease |
| Moderate (2) | Age 35 years or older |
| | Black race or low socioeconomic status |
| | Family history of preeclampsia (mother or sister) |
| | History of low-birth-weight infant, adverse pregnancy outcome, or more than 10 years between pregnancies |
| | Obesity (body mass index > 30 kg per $m^2$) |
| | Nulliparity |

+ in vitro conception

# Interventions to reduce Preeclampsia

American College of Cardiology (2020)





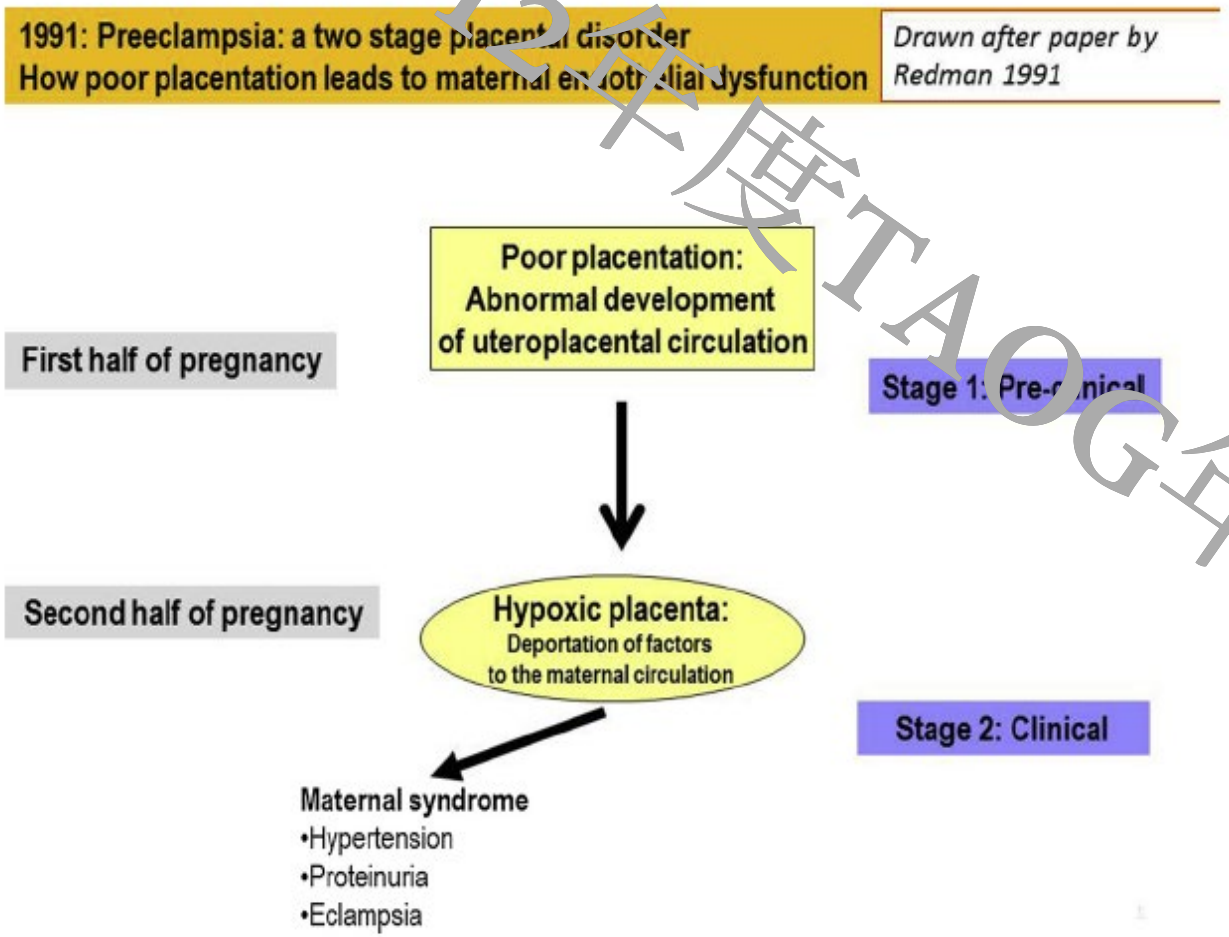

J Am Coll Cardiol. 2020 Oct 6;76(14):1690-1702.

- **Benefit**
  - Delivery
  - Aspirin
  - Calcium *: only in nutritional def. countries
- **Potential**
  - Pravastatin
  - Metformin
  - Exercise
- **No benefit**
  - Bed rest, Sodium restriction
  - Fish oil, Folic acid, Garlic
  - Vit C, D, E

# Patho-etiology of Preeclampsia

## Two-stage model

# Two-stage placental model of preeclampsia (1991)




- Redman C.W. 1991
- **Stage 1**
  - Pre-clinical
  - Placental dysfunction
  - “poor placentation” with unremodelling of spiral arteries
- **Stage 2**
  - Clinical signs

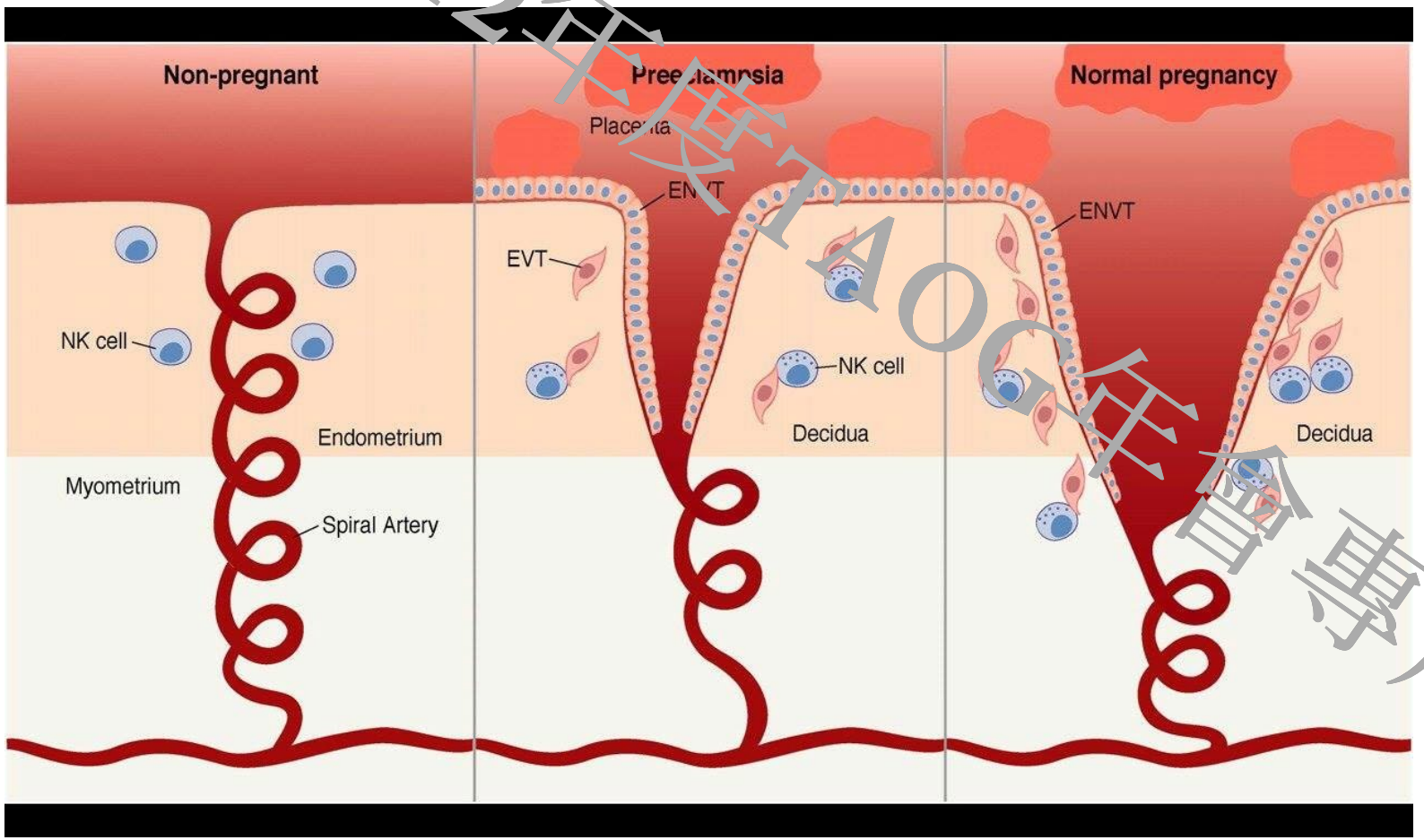


Placenta. 1991;12(4):301-308.

Journal of Reproductive Immunology 2019;134–135,1–10

# Stage 1. Poor placental development

## Abnormal trophoblast invasion and spiral artery remodeling

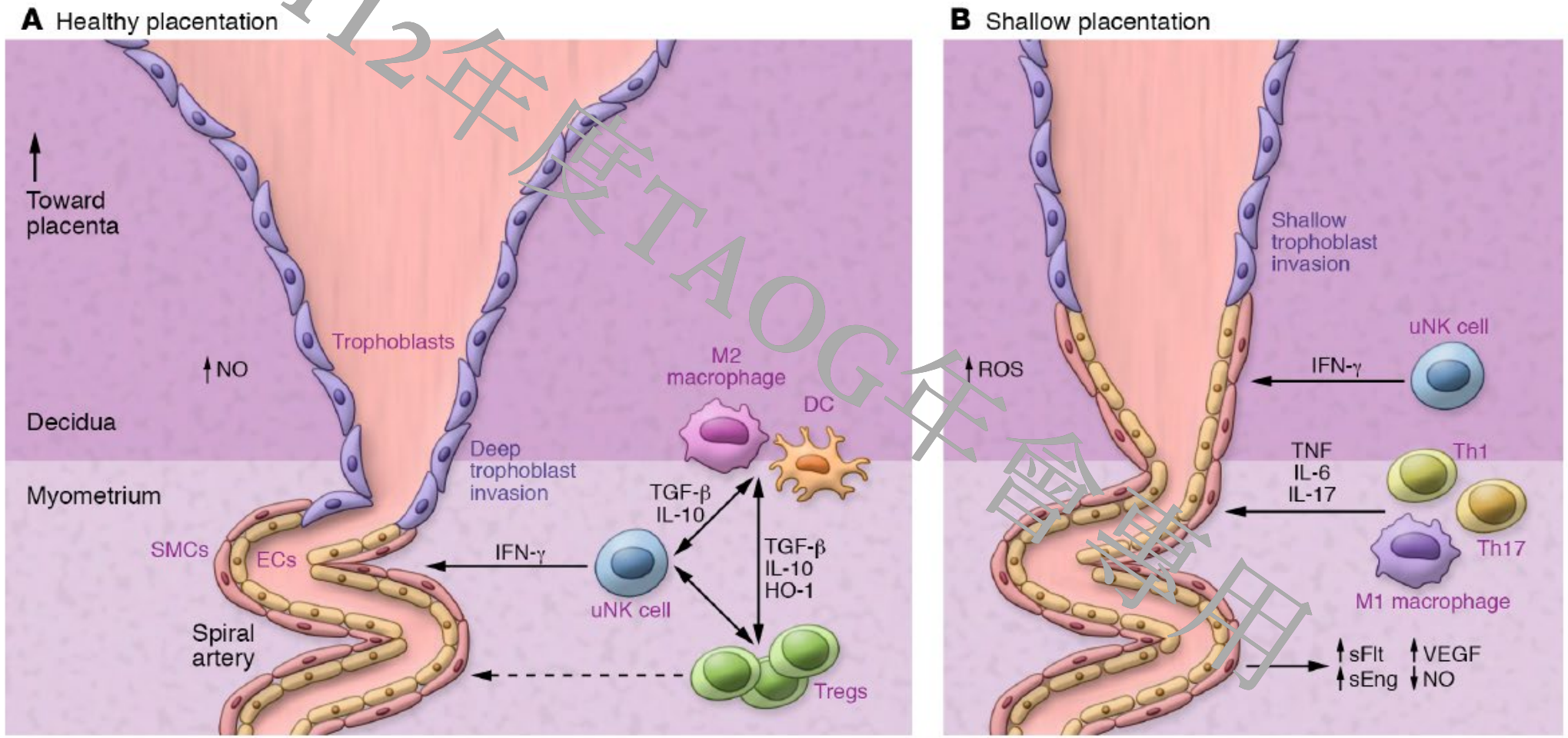




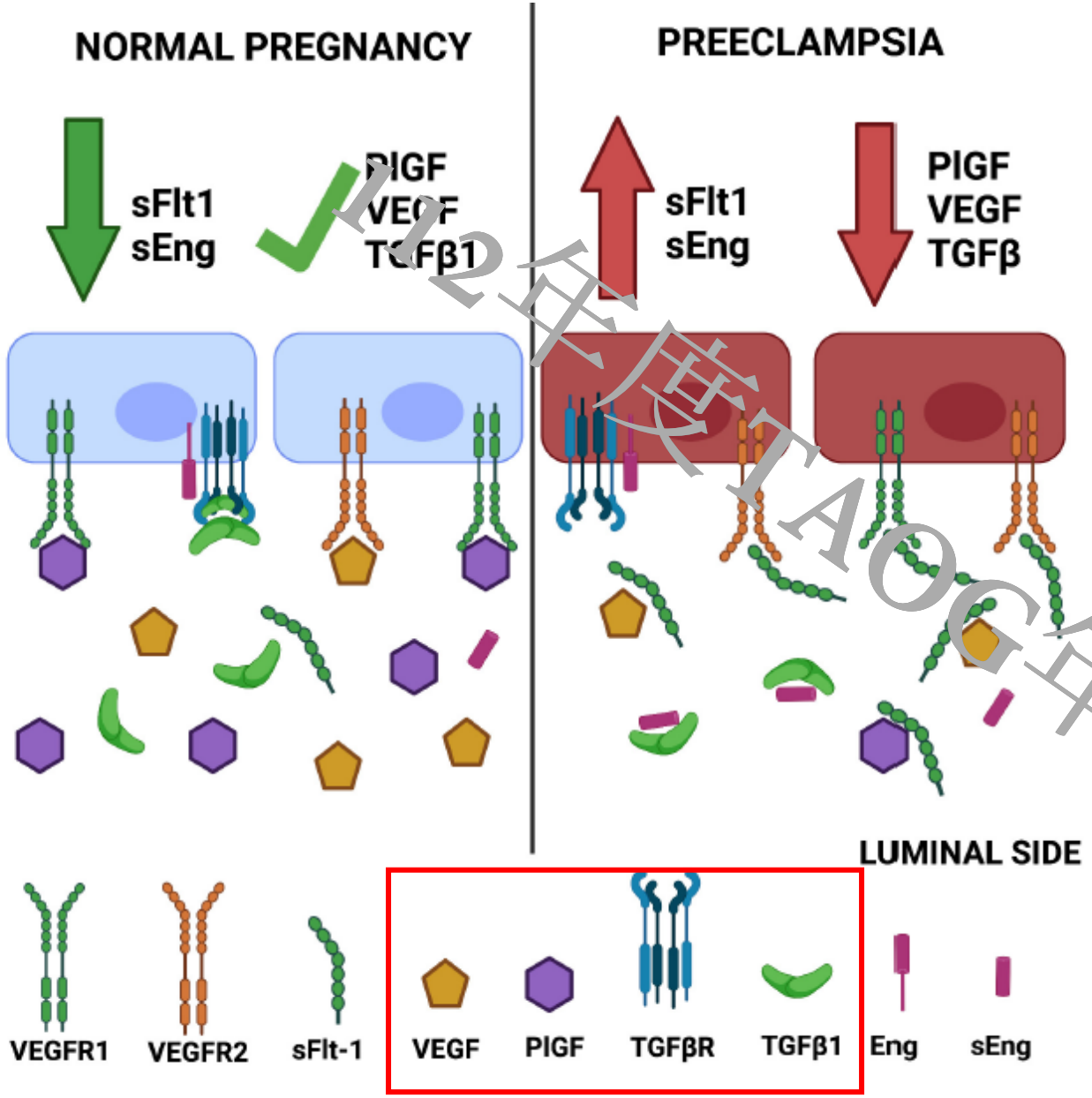

Toxicol Pathol. 2014;42(2):327-38.

# Decidual Tregs, M2 macrophage, DC, uNK cells facilitate spiral arteries remodeling and placental development





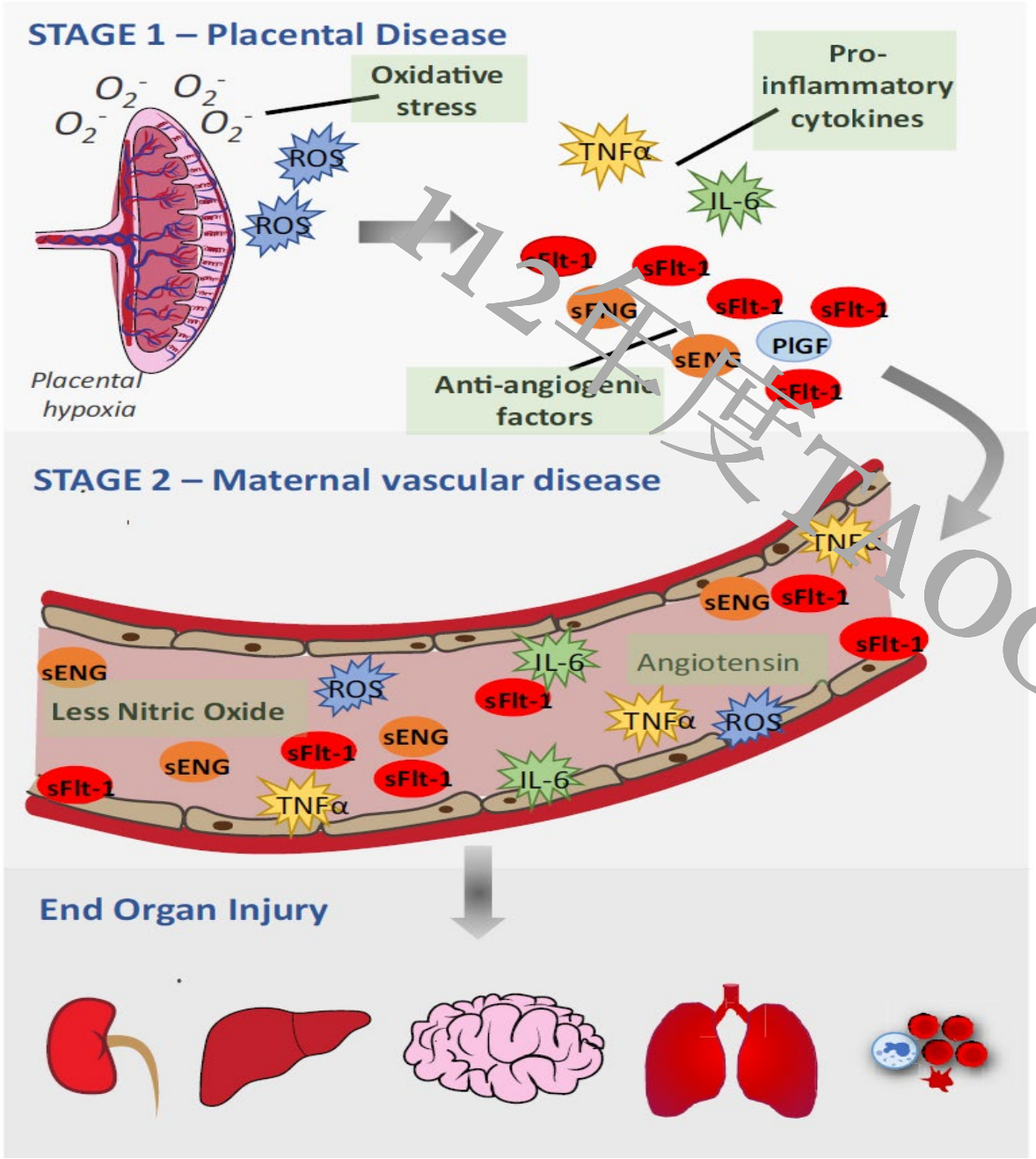

J Clin Invest. 2018; 128(10):4224-4235.




# Stage 2

- **Placenta ischemia**
- **Maternal vascular disease**
  - High levels of **sFlt-1 and sEng**
    - Endothelial dysfunction
    - Vasoconstriction
    - Immune dysregulation
  - Negatively impact maternal end organ system and the fetus

Front Physiol. 2022 Feb 8;12:805082.




# Preeclampsia: a two-stage process

- **Stage 1: poor placentation**
  - Trophoblast invasion, spiral a. remodeling
  - Oxidative stress
  - Proinflammatory cytokines
- **Stage 2: Placenta ischemia & maternal vascular disease**
  - Anti-angiogenic factors (**sFLT-1, sEng**)
  - Inflammatory response (**TNF-α, IL-1**)

Am J Obstet Gynecol. 2022 Feb;226(2S):S1157-S1170.

# New perspectives of pathoetiology in preeclampsia

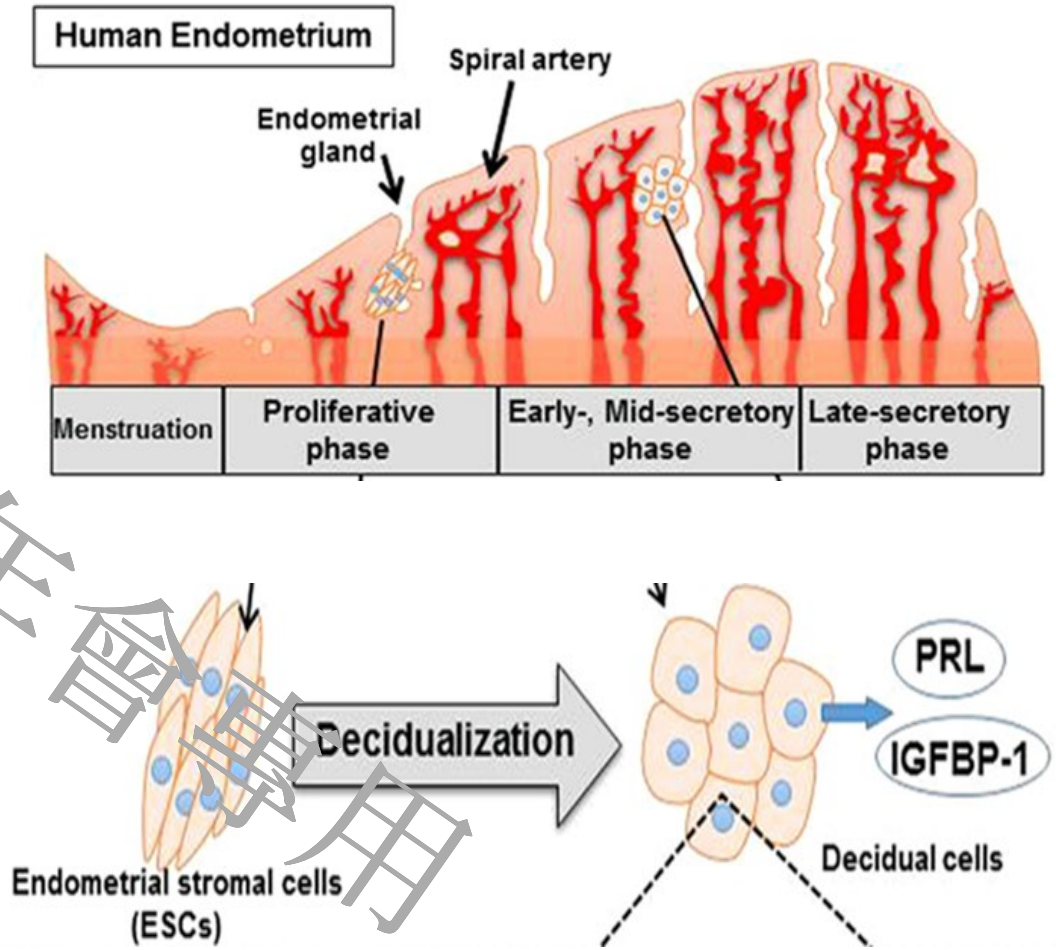
Decidualization resistance

Microbiota (gut, uterine, oral)

# Decidualization resistance and preeclampsia

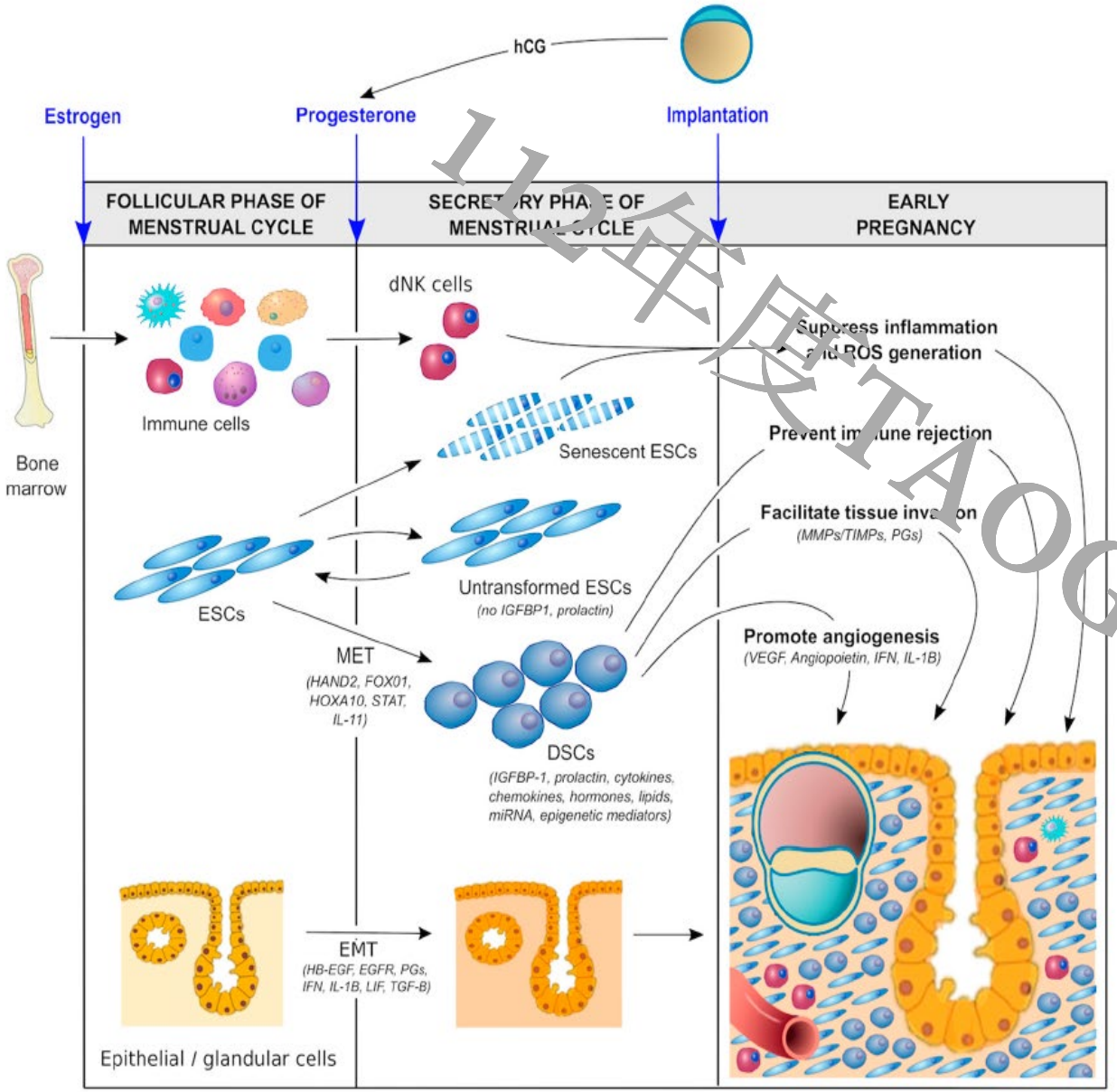
# Endometrial decidualization

- From secretory phase → early pregnancy
  - (1) Morphological transformation
    endometrial stromal cells (ESCs)→ decidual stromal cells (DSCs)
  - (2) Biochemical change
    Decidualized hESCs secrete prolactin & insulin-like growth factor binding protein 1 (IGFBP-1)
- Driven by progesterone and local cAMP
- Functions
  - Embryonic implantation, placentation, and pregnancy maintenance.
- **Deficient decidualization**
  - Implantation failures, age-related decline in reproductive capacity
  - Preeclampsia, miscarriage, premature labor, IUGR




Maternal-Fetal Medicine (2021) 4;1

# Molecular pathways involved in decidualization




- **Dramatic changes** occur in the **gene expression profiles** during decidualization
  - Steroid hormones
  - Growth factors
  - molecular and epigenetic mechanisms.
- **Endometrial immune system**
  - Increased in uNK cells, Treg
- MET
- Epigenetic modifications
  - DNA methylation, histone modification, and nc-RNAs

Int J Mol Sci. 2020 Jun; 21(11): 4092.

# Association between deficient decidualization and preeclampsia

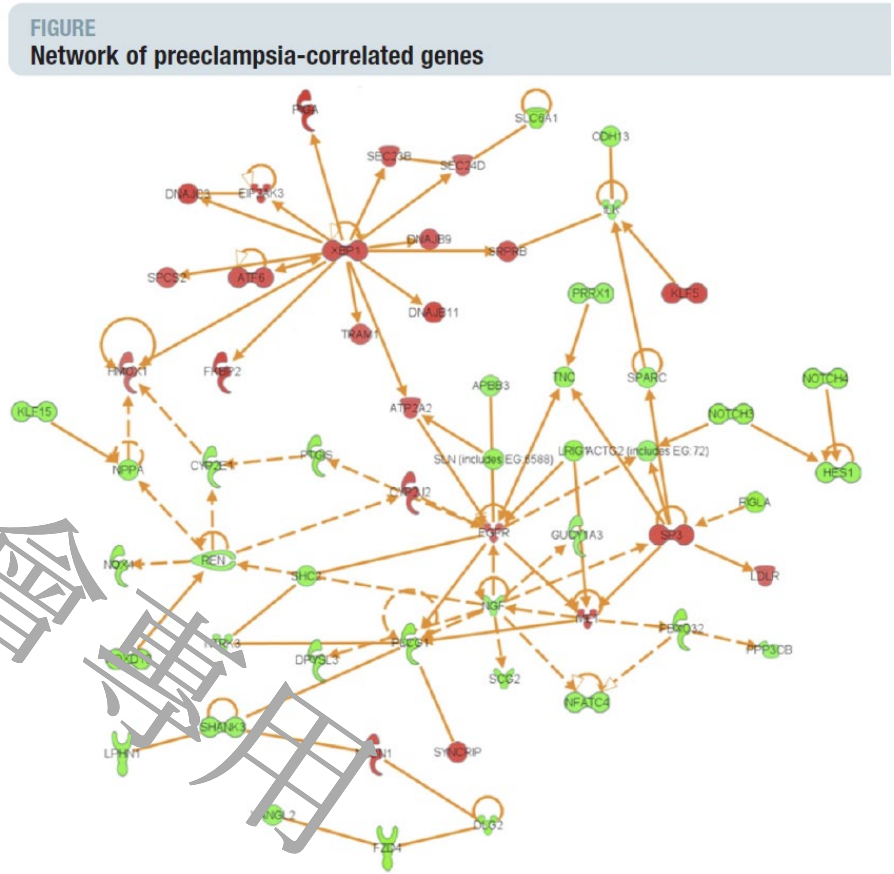
- Suboptimal endometrial maturation and uNK cells present in the decidua **before** preeclampsia development
- Removing the decidua in the immediate postpartum period by uterine curettage accelerates the speed of recovery in patients with PE (1993, 2013)
- Isolated human ESCs from nonpregnant participants with a previous severe PE history
  - Cultured cells fail to be decidualized by analyzing PRL and IGFBP1
  - The deficient decidualization of PE **exist 5 years**, and **the impairment of decidualization might begin before pregnancy**



PNAS 2017;114(40):E8468–E8477.
Am J Obstet Gynecol 2020;S0002-9378(20):31130-311333.
Am J Obstet Gynecol. 2022 Feb;226(2S):S886-S894.

# Decidualization Resistance in Severe Preeclampsia

- A transcriptional profile of the decidua in preeclampsia (**RNA array**)
  - 455 differentially expressed genes (DEGs) in the pathogenesis of PE
    - chorionic villous samples identified 396 DEGs at 11.5 weeks' gestation in patients who developed sPE symptoms 6 months later
    - >200 dysregulated genes in sPE related to decidual dysfunctionality.
  - The conditioned medium from sPE patient cells did not support CTB invasion
    - Decidualization resistance is associated with shallow CTB invasion



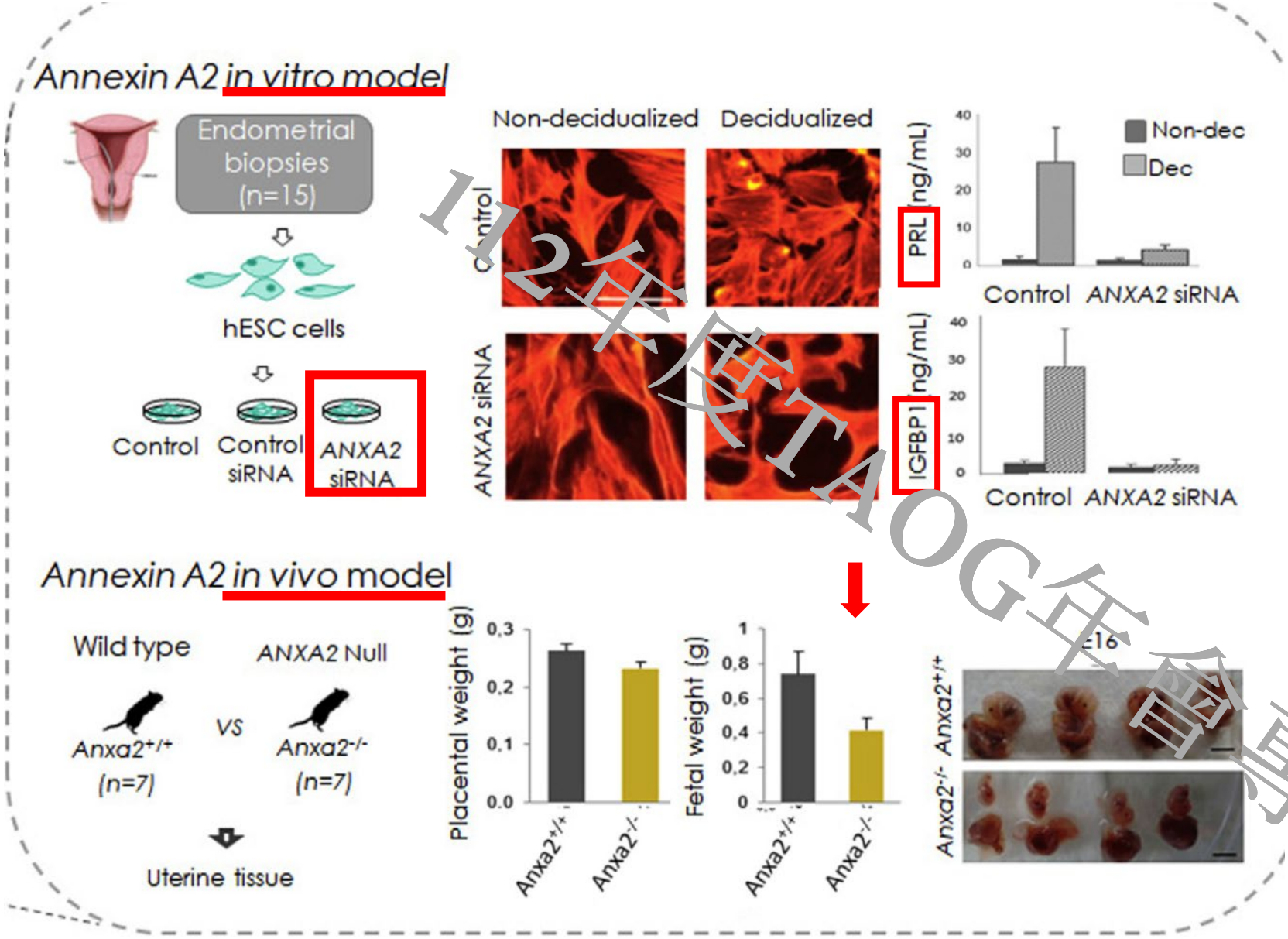

Am J Obstet Gynecol 2011;204:84.e1–27.

# Annexin A2 (ANXA2) as a putative preconception maternal biomarker

- Global transcriptional profiling
  - Alterations in gene expression during in vitro decidualization of hESCs from former patients with sPE.
  - Annexin A2 (ANXA2) expression was lower.
- **ANXA2**
  - ANXA2 is abundantly expressed in the placental villous and decidua basalis
    - Initial steps of embryo adhesion to endometrium during implantation
  - Its impaired activity could cause fibrinolytic deficiency associated with increased thrombosis, predisposing to PE
    - **A putative preconception maternal biomarker** for sPE risk prediction



PNAS. 2017;114(40):E8468-E8477.
Am J Obstet Gynecol. 2020;222(4):376.e1-376.e17.
Am J Obstet Gynecol. 2022 Feb;226(2S):S886-S894.






## In vitro and in vivo models of Annexin A2

- ANXA2 was silenced in hESCs
  - Unable to decidualize
- an ANXA2-null mouse model
  - defects in placentation and fetal growth restriction
- **A deficiency in ANXA2 is associated with the decidualization resistance observed in preeclamptic patients**

Am J Obstet Gynecol. 2020;222(4):376.e1-376.e17.

# **Decidualization deficiency** as a contributor to the pathogenesis of severe preeclampsia

- The pathogenesis of sPE begins **before implantation**
  - followed by shallow CTB invasion resulting in abnormal spiral remodeling, aberrant placentation, and impaired blood flow to the placenta
  - causing the placenta to release inflammatory factors resulting in systemic endothelial dysfunction.
- Clinical translation of the maternal contribution to the pathogenesis of sPE could provide novel strategies to prevent the disease



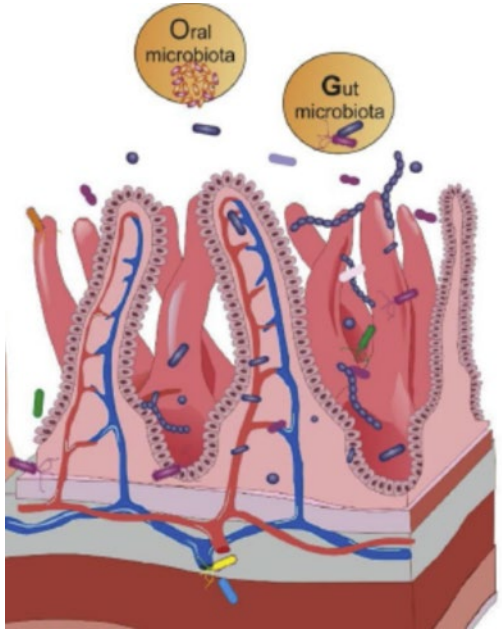
Expert Review ajog.org

**Decidualization resistance in the origin of preeclampsia**



Tamara Garrido-Gómez, PhD[1]; Nerea Castillo-Marco, MSc[1]; Teresa Cordero, MSc; Carlos Simón, MD, PhD

Am J Obstet Gynecol. 2022 Feb;226(2S):S886-S894.

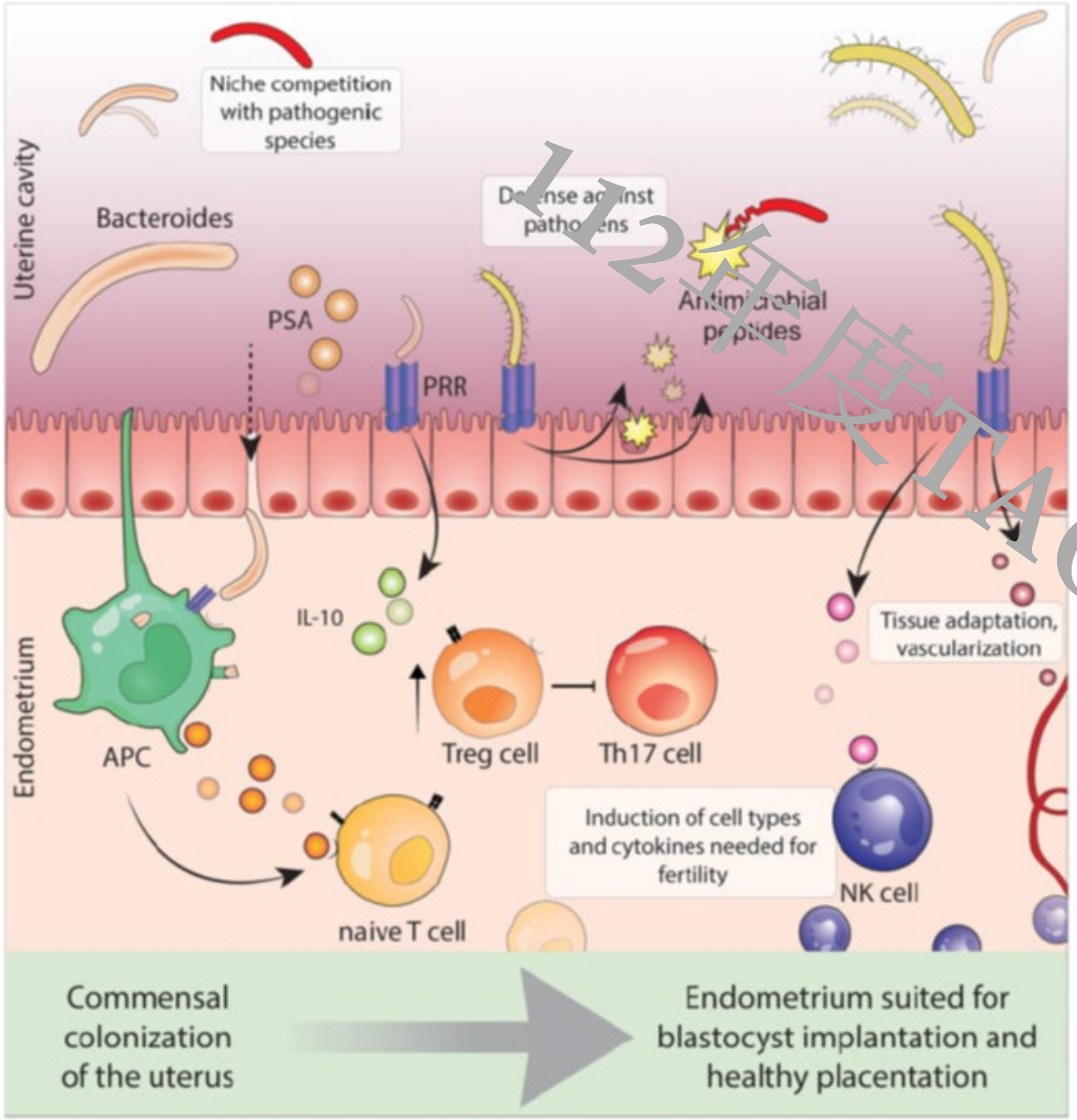





# Microbiota and Preeclampsia

Gut microbiota

Uterine/Placental microbiota

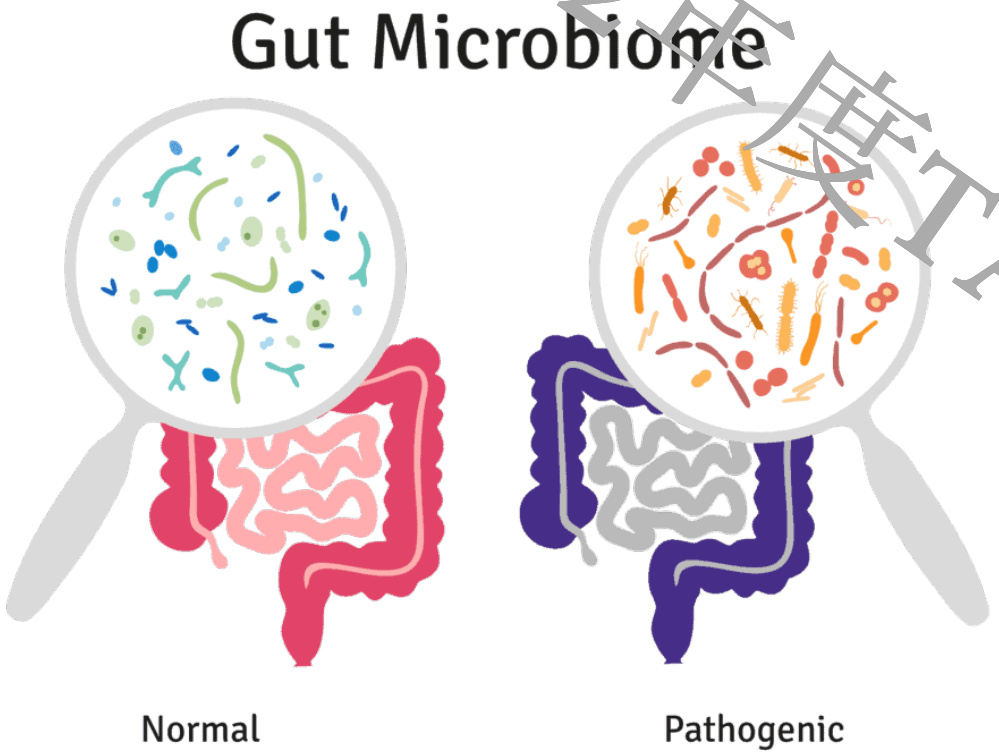



# Uterine microbiota on a fertile endometrium

- Uterine microbiota may contribute to healthy endometrium physiology
- **Local lymphocytes could sense microbes**, thereby initiating a signaling cascade
  - mucosal T cell balance
  - Cytokines
  - Th17, Treg, uNK cells
- an effect on the local immune environment

Hum Reprod Update. 2018 Jul 1;24(4):393-415.

# Probiotics may have a protective effect on preeclampsia




- Genome-wide association study **(GWAS) from MiBioGen and FinnGen** consortiums, the causal association between gut microbiota and PE
  - *Bifidobacterium* had a protective effect on preeclampsia-eclampsia (OR = 0.76, 95% CI: 0.64–0.89)
- However, the results of published studies are not consistent



Canadian Digestive Health Foundation

BMC Medicine (2022) 20:443

# Inflammatory cytokines

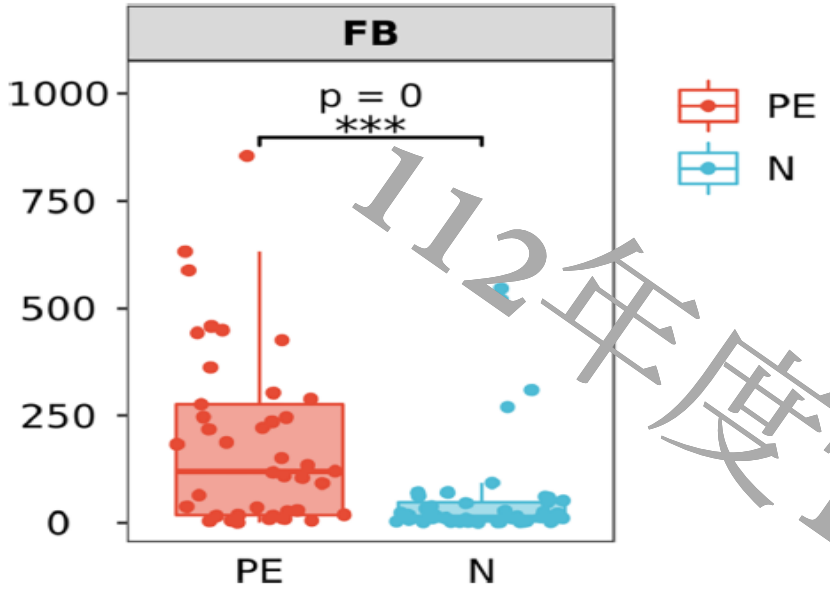
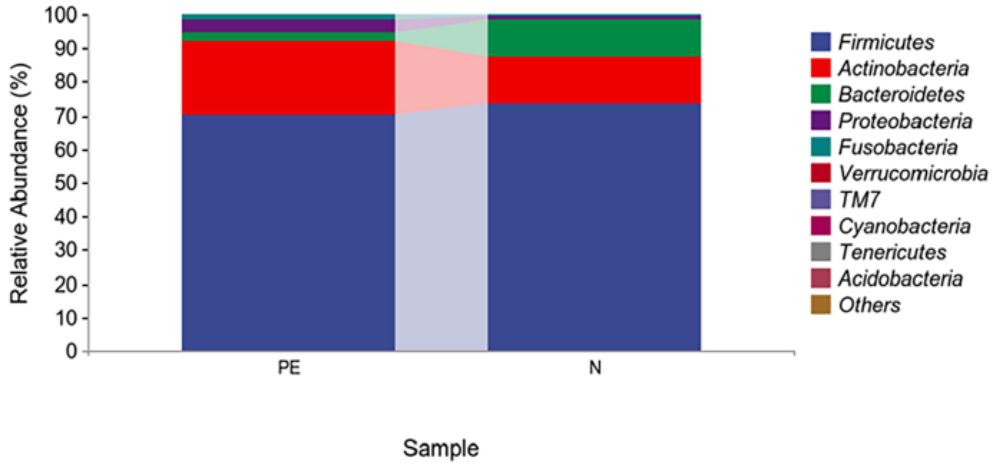



FIGURE 5
Varying ratios of Firmicutes and Bacteroidetes (F/B) at the phylum level between the two groups. F/B at the phylum level in the PE group is significantly higher than that in the normal group. PE, preeclampsia; N, the healthy normal group. ***$P < 0.001$.



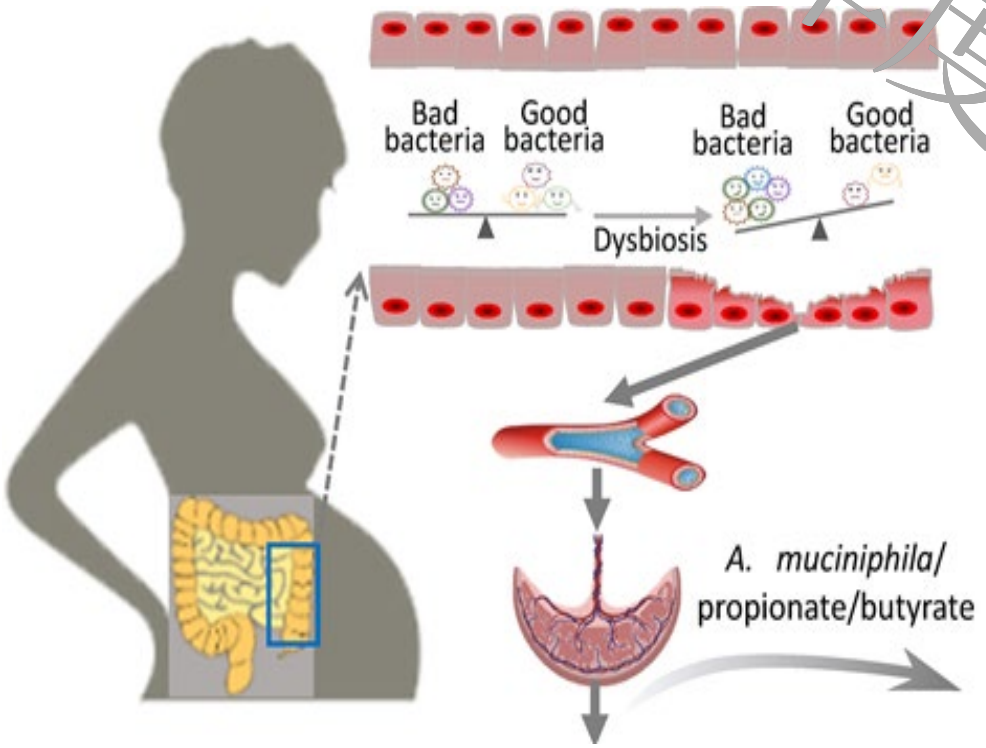

- PE patients
  - Gut microbiota disturbances
  - Serum proinflammatory factors
    - Firmicutes and Bacteroidetes (F/B) ratio
    - Higher serum TNF-α and IL-6

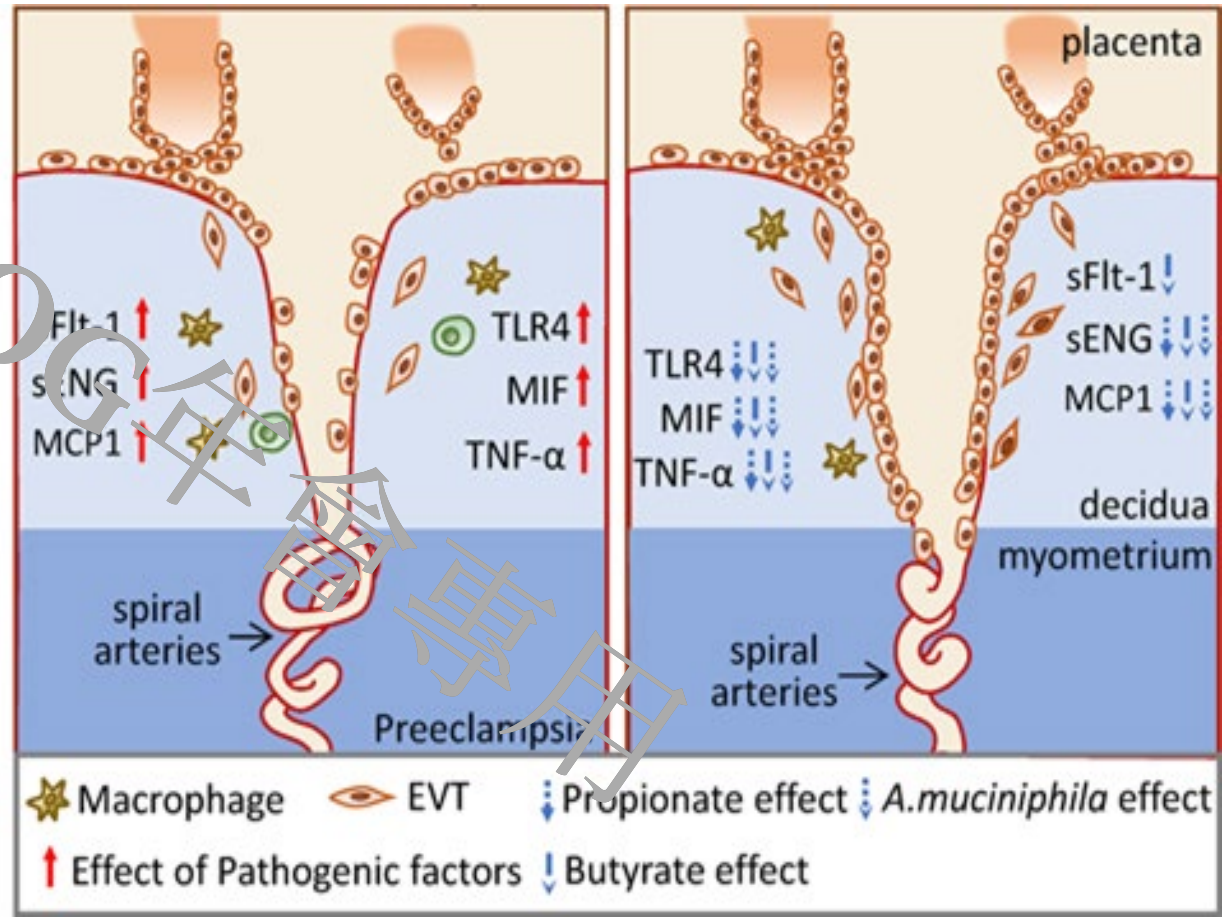
Front Cell Infect Microbiol. 2023 Jan 4;12:1022857.

# Gut Dysbiosis Promotes Preeclampsia by Regulating Macrophages and Trophoblasts

Jiajia Jin,* Liaomei Gao,* Xiuli Zou,* Yan Zhang, Zhijian Zheng, Xinjie Zhang, Jiaxuan Li, Zhenyu Tian, Xiaowei Wang, Junfei Gu, Cheng Zhang, Tiejun Wu, Zhe Wang, Qunye Zhang*

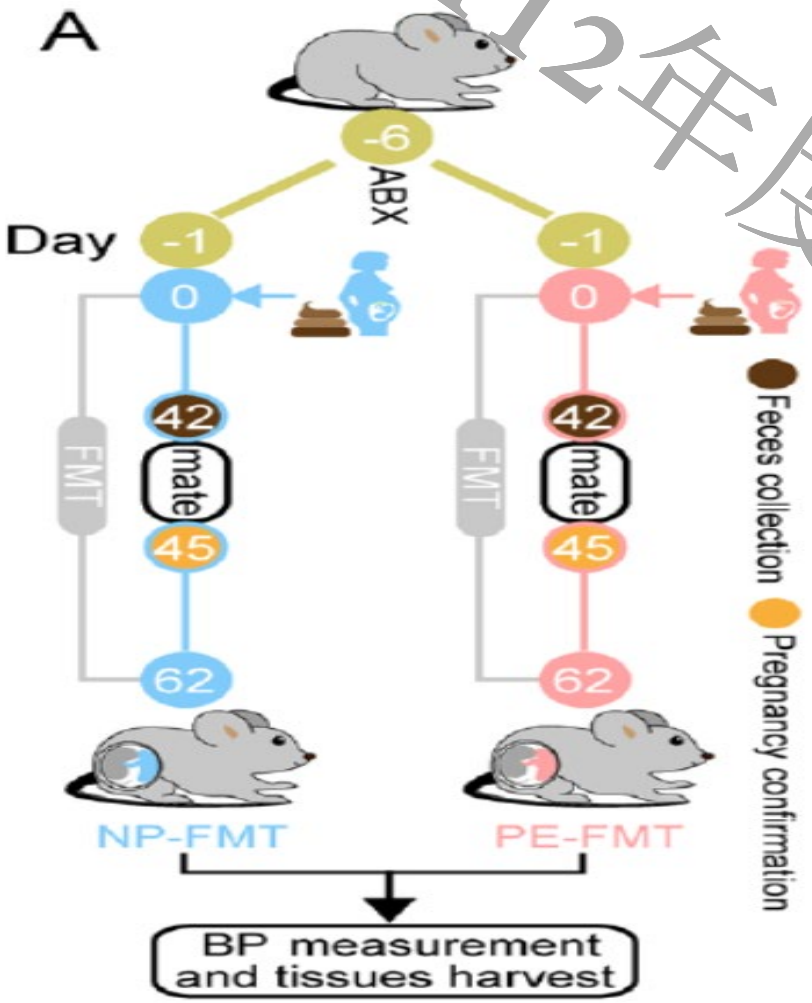





Circulation Research. 2022;131:492–506

# ‘Gut–placenta’ axis can have an essential role in the etiology of PE




- Gut dysbiosis can provoke pre-eclamptic symptoms and impact the host’s blood pressure in women with PE
  - Inoculation of the gut microbiome from pts with PE
    - Trigger higher blood pressure before pregnancy
    - PE-like phenotypes during pregnancy, including worsened hypertension, proteinuria and IUGR
  - Induced immune imbalances related to T cells and intestinal barrier dysfunction
- **Gut microbiota screening** shows potential for **predicting PE onset** and provides a new approach for the **prevention and treatment** of this disease

Gut 69 (2020) 513–522

# New horizons for the prevention or treatment of preeclampsia

Am J Obstet Gynecol. 2022 Feb;226(2S):S1157-S1170.



# Pravastatin, proton-pump inhibitors, metformin, micronutrients, and biologics: new horizons for the prevention or treatment of preeclampsia

Stephen Tong, PhD, FRANZCOG; Tu'uhevaha J. Kaitu'u-Lino, PhD; Roxanne Hastie, PhD; Fiona Brownfoot, PhD, FRANZCOG; Catherine Cluver, PhD; Natalie Hannan, PhD





- There are a dearth of drugs to treat preeclampsia. **Only 1 drug, aspirin, clearly prevents the condition**
  - Reduction of preterm PE: 18- 67% (Cochrane)

- 2015-2020 systemic search (trials)
- **Prevention and treatment**
  - **Pravastatin**
  - **Metformin**
  - **Esomeprazole**

Cochrane Database Syst Rev 2019;2019:CD004659.

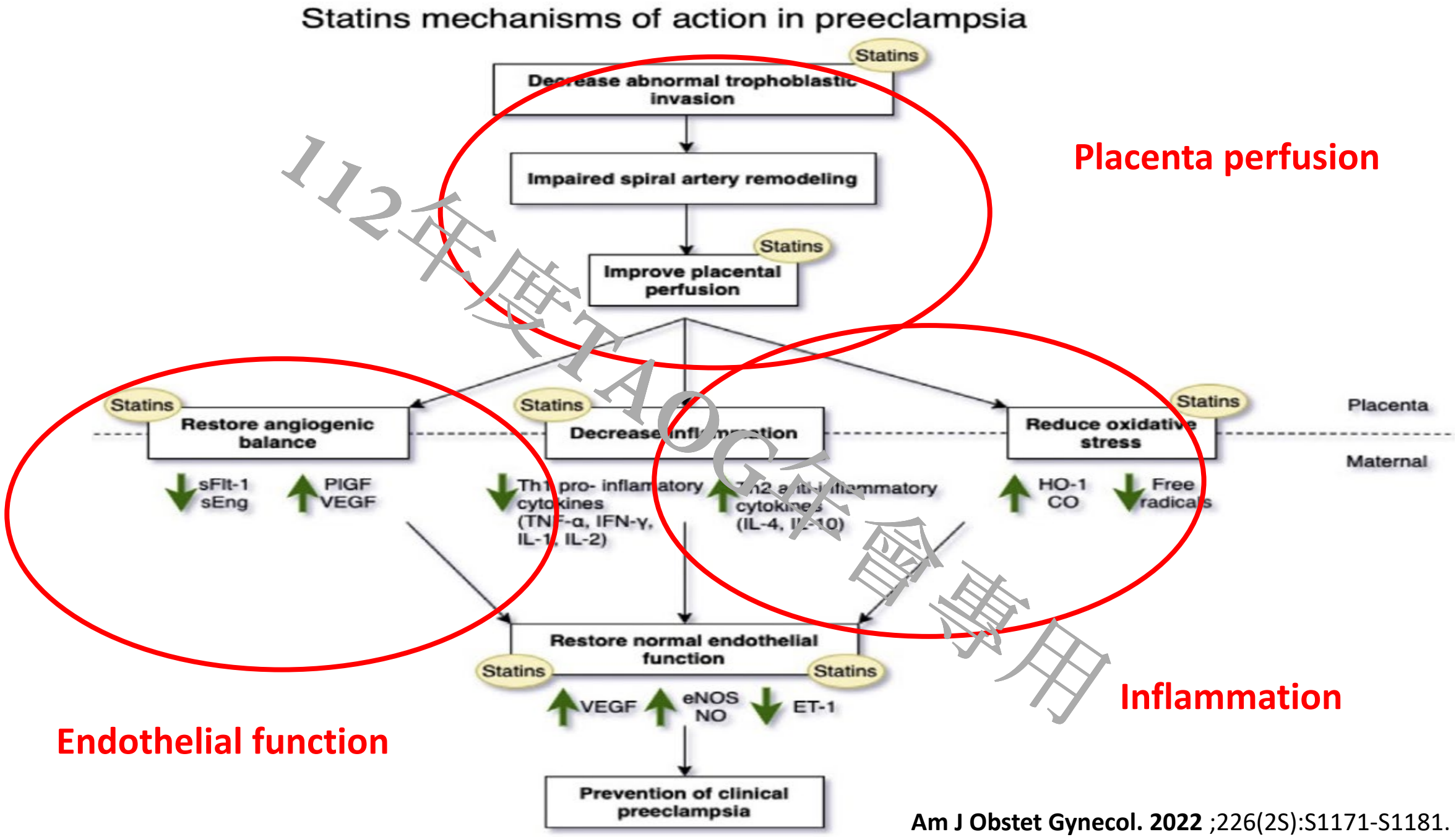
# Pravastatin


- It has pleiotropic actions and can resolve a preeclampsia phenotype in many animal models.
  - beneficial actions on both placental and maternal vascular diseases
- Some early phase clinical trials suggest that it may have therapeutic activity.
  - Several large prevention trials are planned or ongoing
- All of the following change shortly after beginning therapy (6 months)
  - Reversal of endothelial dysfunction
  - Decreased inflammation
  - Thrombogenicity and plaque stabilization



Am J Obstet Gynecol. 2022 Feb;226(2S):S1171-S1181.

Am J Obstet Gynecol. 2022 Feb;226(2S):S1157-S1170.






**Am J Obstet Gynecol. 2022** ;226(2S):S1171-S1181.

# Effects of statins by cell types

**TABLE 1**
**Mechanisms and effects of statins by cell type**

| Cell types | Mechanisms | Effects |
|---|---|---|
| Placental trophoblast cells[41–43] | Increased VEGF and PlGF<br>Increased HO-1<br>Decreased sFlt-1 and sEng | Decreased inflammation<br>Improved vascular reactivity |
| Platelets[15,26] | Inhibition of platelet adhesion<br>Decreased $TXA_2$ | Decreased thrombosis |
| Monocytes and macrophages[15,26,31] | Inhibition of T-cell adhesion, activation, and release of proinflammatory cytokines | Decreased inflammation |
| Endothelial progenitor cells[15,26] | Increased mobilization of stem cells | Improved neovascularization and reendothelialization |
| Endothelial cells[15,39,40] | Increased eNOS<br>Decreased ET-1<br>Increased VEGF<br>Decreased PAI-1<br>Decreased ROS | Improved endothelial function<br>Decreased oxidative stress<br>Decreased vasoconstriction<br>Decreased inflammation<br>Improved angiogenesis |
| Vascular smooth muscle cells[47] | Decreased AT1 receptor expression<br>Decreased ROS | Decreased vasoconstriction |



- Trophoblasts
- Monocytes/ macrophages
- Endothelial cells
- Vascular smooth m. cells
- Platelets

Am J Obstet Gynecol. 2022 Feb;226(2S):S1171-S1181.

**TABLE 3**
**Summary of human studies evaluating pravastatin for preeclampsia**

| Study | Author | Year | Country | Design | Sample size | Dose | Primary outcome | Major findings |
|---|---|---|---|---|---|---|---|---|
| Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial | Costantine et al[57] | 2016 | United States | Pilot randomized placebo-controlled trial | 20 | 10 mg | Maternal-fetal safety and pharmacokinetic parameters of pravastatin during pregnancy | Pravastatin group found reduced rates of preeclampsia (0% vs 40%), severe features of preeclampsia, and indicated preterm delivery before 37 wk (10% vs 50%) |
| Pravastatin improves pregnancy outcomes in obstetrical antiphospholipid syndrome refractory to antithrombotic therapy | Lefkou et al[58] | 2016 | Greece | Nonrandomized control trial | 21 | 20 mg | Uteroplacental blood hemodynamics, progression of preeclampsia features, and fetal or neonatal outcomes | Pravastatin group found improved uterine artery Doppler velocimetry, lower blood pressure (130/89 mm Hg vs 160/98 mm Hg), higher birthweight (2390 g vs 900 g), later delivery (36 wk vs 26.5 wk) |
| Pravastatin for early-onset preeclampsia: a randomized, blinded, placebo-controlled trial | Ahmed et al[59] | 2020 | United Kingdom | Proof of principle randomized placebo-controlled trial | 56 | 40 mg | Difference in mean plasma sFlt-1 levels over the first 3 days following randomization | Pravastatin use was not associated with reduction in maternal plasma sFlt-1 levels (difference of 292 pg/mL [95% CI, 175–592; P=0]), prolongation of pregnancy or other pregnancy outcomes |
| Evaluating the effect of pravastatin in early-onset fetal growth restriction: a nonrandomized and historically controlled pilot study | Mendoza et al[61] | 2020 | Spain | Pilot nonrandomized controlled trial | 38 | 40 mg | Doppler progression, sFlt-1 and PlGF values, and pregnancy outcomes | Pravastatin group found improvement in angiogenic profile, greater gestational latency (by 16.5 d), greater birthweight (by 260 g), and decreased rates of preeclampsia (31.6% vs 47.4%) |



# Clinical studies of pravastatin

- **Clinical improvem't**
  - **Small sample size (20-56)**

- Preeclampsia rate
- Uterine artery flow
- Maternal BP
- Plasma sFlt-1 level
- Infant BW
- Later delivery

Am J Obstet Gynecol. 2022 Feb;226(2S):S1171-S1181.

# The role of **metformin** in Preeclampsia


- Metformin
  - Readily crosses the placenta. Safe during pregnancy
  - Treatment of prediabetes mellitus, GDM, and PCOS
  - From observations in randomized clinical trials: a possible treatment or prevention of preeclampsia (secondary endpoints of a clinical trial evaluating of LGA)
- Mechanism
  - a reduction in the production of antiangiogenic factors (sFlt-1 and sEng)
  - reduce inflammation and insulin resistance
  - modify cellular homeostasis and energy disposition, mediated by rapamycin, a mechanistic target (AMPK-mTOR pathway)
    - This has also been implicated in the pathogenesis of preeclampsia

Am J Obstet Gynecol. 2017 Sep;217(3):282-302.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus

Argyro Syngelaki, Ph.D., Kypros H. Nicolaides, M.D., Jyoti Balani, M.D.,



Table 2. Pregnancy Outcomes, According to Study Group.*

| Outcome | Metformin (N=202) | Placebo (N=198) | Odds Ratio (95% CI) | P Value |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Median birth-weight z score (IQR) | 0.05 (−0.71 to 0.92) | 0.17 (−0.62 to 0.89) | — | 0.66 |
| **Maternal outcomes** | | | | |
| Median weight gain (IQR) — kg | 4.6 (1.3 to 7.2) | 6.3 (2.9 to 9.2) | — | <0.001 |
| Gestational diabetes mellitus — no./total no. (%) | 25/202 (12.4) | 22/195 (11.3) | 1.11 (0.60 to 2.04) | 0.74 |
| Preeclampsia — no./total no. (%) | 6/202 (3.0) | 22/195 (11.3) | 0.24 (0.10 to 0.61) | 0.001 |

## Metformin in obese pregnant women without DM

- Reduced maternal weight gain (4.6 vs. 6.3 Kg)
- Incidence of preeclampsia (3.0% vs. 11.3%)

N Engl J Med. 2016 Feb 4;374(5):434-43.

# Metformin

- The incidence of pre-eclampsia increased by **insulin-resistant disorders**
  - GDM, Type 2 DM, PCOS and obesity
  - Four-fold risk
- **Meta-analysis** of Metformin on **lowering PE risk in insulin-resistant** pregnant women (RR=0.68)
- Metformin with and without insulin treatment is associated with a lower incidence of pre-eclampsia than insulin treatment alone in GDM or type 2 DM women
  - probably linked to reduced weight gain
  - In other high-risk pregnancies, metformin does not appear to be beneficial

Diabet Med. 2018 Feb;35(2):160-172.

# Proton pump inhibitors

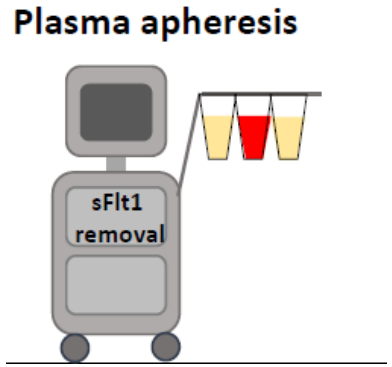
- **Preclinical studies** suggests a plausible preventive effect
  - Reduction in sFlt1, sEng and proinflammatory cytokine in placental endothelial cells
  - esomeprazole has been shown to resolve the hypertensive phenotype in 2 animal models of preeclampsia (PE)
- **Prospective cohort study** (2017)
  - lower levels of sFLT-1 and sEng were noticed among pregnant PPI users with preeclampsia
- **Controversial results from large cohort databases**
  - A large cohort study from the US using the Truven Health Market Scan database → No association of PPIs with a decreased risk of preeclampsia or severe preterm PE
  - A Swedish population register-based cohort study found reduced preterm and early preeclampsia risk in women who used PPIs in the third trimester
  - Meta-analysis: a trivial increase in the risk of PE, RR of 1.27 (95% CI: 1.23–1.31)
- **Conclusion**:
  - There is no evidence supporting that PPI use decreases the risk of PE or preterm PE

Hypertension **2017**, 70, 594–600
J Clin Med. 2022 Aug 10;11(16):4675.
Am J Perinatol 2021; 38(14): 1519-1525
Hypertension2019, 73, 1097–1103.

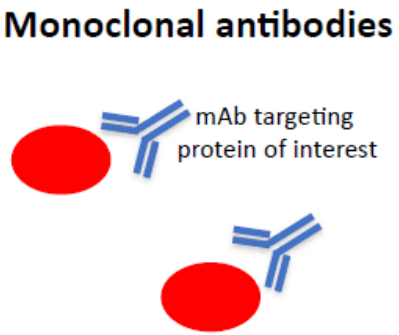
# Classes of therapeutic strategies

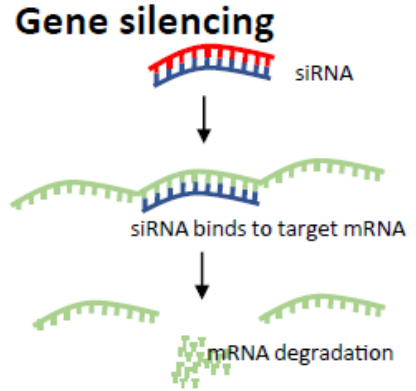


- **Repurposed drugs**
  - Pravastatin
  - Metformin
  - Esomeprazole (PPI)
- **Plasma apheresis**
  - Small trials have shown it can remove circulating sFlt-1 (transiently)




- **Monoclonal Abs**
  - Etenercept (anti-TNFα )
  - Eculizumab (complement inhibitor)
    - highly specific
    - Expensive and safety
- **Gene silencing**
  - siRNAs targeting sFlt-1 or angiotensinogen
  - Specific but lack trials




Am J Obstet Gynecol.
2022 Feb;226(2S):S1157-S1170.

# Take Home Message

Interventions to reduce Preeclampsia: ACC 2020



- **Benefit**
  - Delivery
  - Aspirin
  - Calcium *
    - only in nutritional def. countries
- **Potential**
  - Pravastatin
    - Clinical outcomes (decreased PE rates, prolong delivery
    - Parameters (mBP, UtPI, sFlt-1)
    - Small sample size
  - Metformin
    - Decreased maternal BW gain
  - Exercise

J Am Coll Cardiol. 2020 Oct 6;76(14):1690-1702.

# Prevention of preeclampsia before pregnancy?



- **Current Prediction Strategies**
  - **ACOG and SMFM : 1 high risk or 2 moderate risk factors**
  - **FMF triple tests : maternal factors + MBP, UtPI, PlGF**
  - **sFLT1/ PlGF of 38**
- **New diagnostic or treatment strategies**
  - **Decidualization resistance**
    - Annexin 2 deficiency
  - **Probiotics** to restore gut /uterine microbiota
- Provide **aspirin** from 1st trimester in women without history of PE (no risk factors)

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# Thank you for attention !