The Role of Endothelial Dysfunction in
Preeclampsia

PUFFINESS OF FACE
PITTING EDEMA

Preeclampsia

It is one of the most frequent complications of pregnancy affecting about 3-10% of all pregnancy.

It constitutes a major cause of maternal & perinatal morbidity & mortality in the developed & developing countries.

Fetal
syndrome
(IUGR, IUD, prematurity)

Maternal
syndrome
(HTN, renal, CNS)

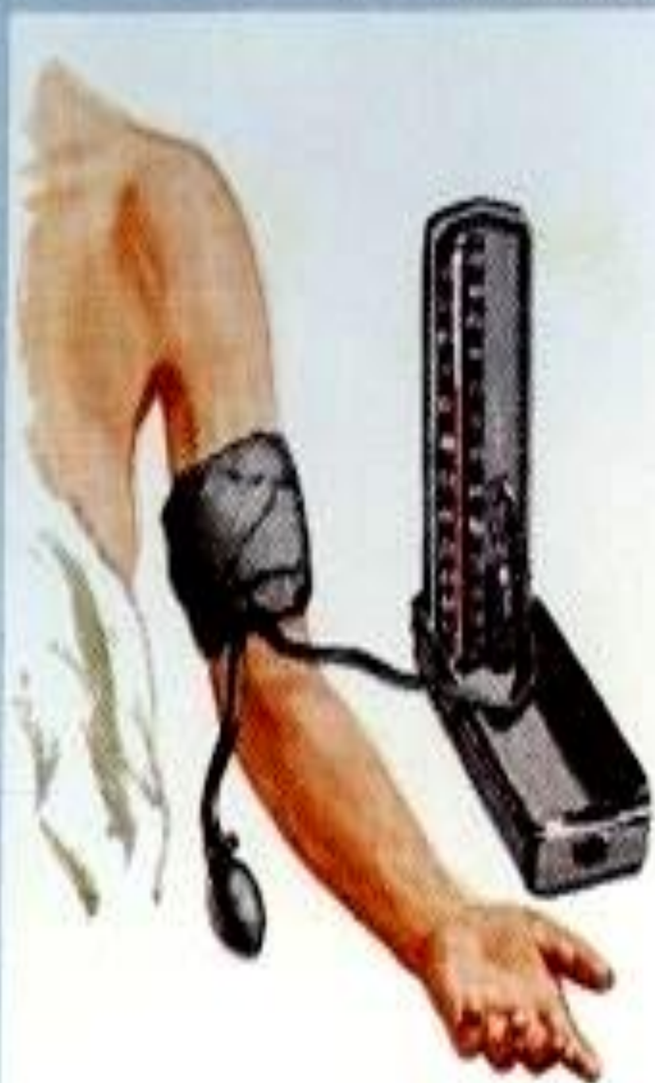
Placental disease
Abdominal implantation
Placental vascular lesions
Maternal disease
Vasoplasm
Intravascular coagulation
Endothelial dysfunction

Genetic susceptibility
(maternal x fetal)

Definition

It is defined as the development of new onset hypertension & proteinuria after 20 weeks of gestation in a woman who previously normotensive & non protein uric.

CLINICAL TRIAD



ELEVATED BLOOD PRESSURE

EXCESSIVE WEIGHT GAIN

ALBUMINURIA

The diagnostic criteria of preeclampsia

Blood pressure is ≥ 140 mmHg systolic & 90 mmHg diastolic on two occasions at least six hours apart, in women who were normotensive before 20 weeks gestation.

Or Hypertension in pregnancy is diagnosed by:

1. blood pressure: Diastolic BP ≥ 110 mmHg on any one occasion.

2. Proteinuria: Is described as 300mg =3+ of urinary protein/24 hours urine collection or persistent 30mg /dl =1+ dipstick in random urine samples.

Classification of hypertension during pregnancy

1.Gestational hypertension.

2.Chronic hypertension

3.Unclassified hypertension &/or proteinuria.

4. Eclampsia

Endothelins

Endothelins (ET) are a family of peptide produced by the endothelial & vascular smooth muscle cells.

They act locally to modulate vasomotor tone, cell proliferation & hormone production.

The Endothelins family consist of three distinct 21-aminoacid peptides (ET-1, 2 & 3) all with very similar peptide structure.

Only one of the three members identified, the only one produced by the endothelium is endothelin-1.

Endothelin-1

Endothelin-1 is liberated by the endothelial cells & it is the most potent endogenous vasoconstrictor known & its efficacy has been shown to be potentiated in arteries with loss of endothelium.

The stimuli for the endothelin-1 release are hypoxia, thrombin, angiotensin II, bradykinin 4, & transforming growth factors B1.

Endothelin-1 play an important role in the pathophysiology of preeclampsia, either by acting on vascular smooth muscle directly to induce contraction or by increasing the formation of angiotensin II, to which there is an increased vasopressor response in preeclampsia .

Beside the abilities of ET-1 to change vascular tone, it also induce hypertrophy in smooth muscle cells & function as mito-genes as well, structural alterations of the vessels wall, such as an increase in vessel wall thickness (vascular hypertrophy due to ET mitogenic effect), could play a role.

Pathophysiology of Preeclampsia

Preeclampsia has been dubbed the "disease of theories" because of the multiple hypothesis that have been proposed to explain its occurrence however, the mechanisms responsible for preeclampsia are unclear .

Several pathophysiological mechanisms have been implicated in the development of preeclampsia , these include :

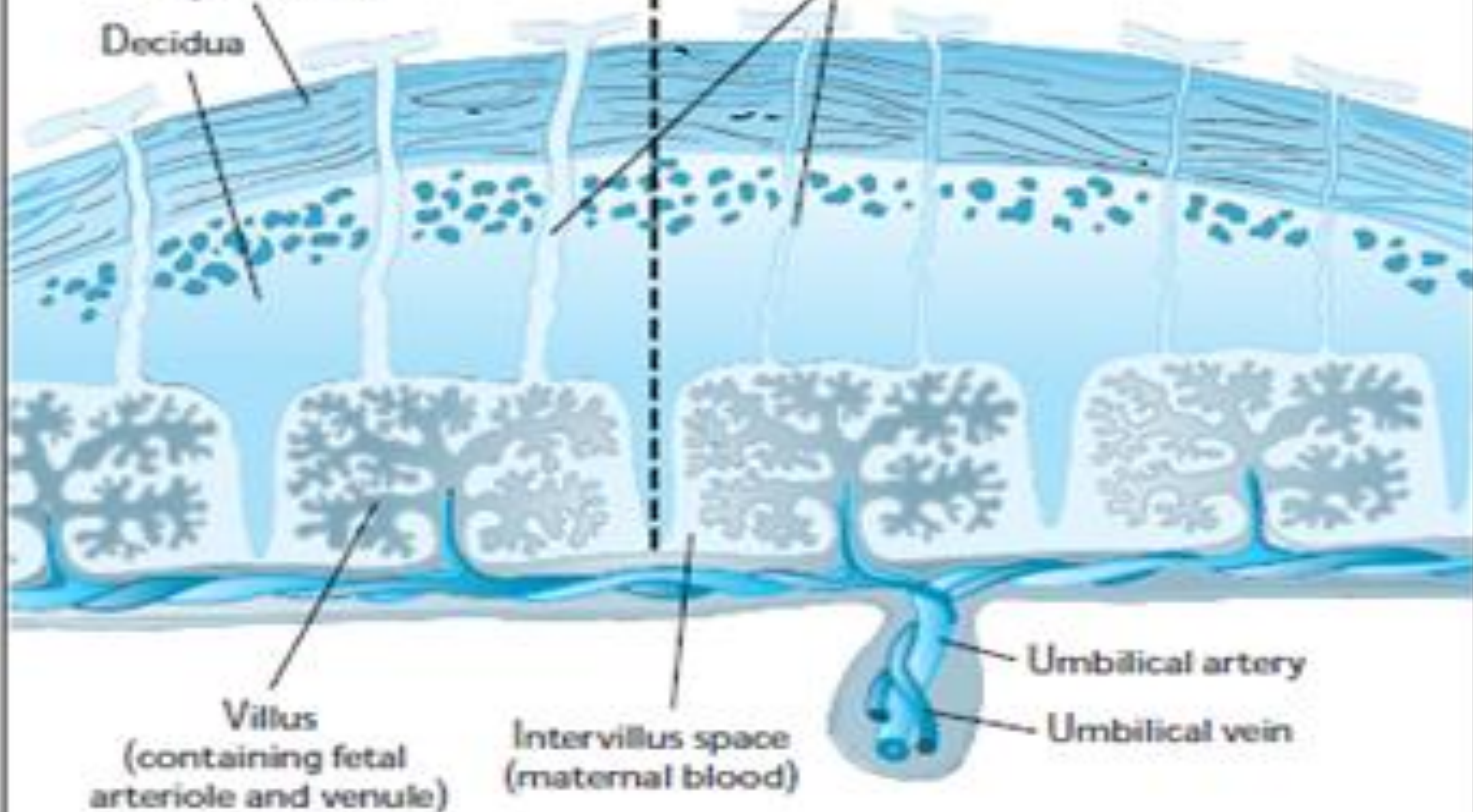
1. ***Endothelial dysfunction***
2. ***Oxidative stress***
3. ***Inflammatory pathway***
4. ***Rennin-angiotensin aldosterone system***
5. ***Dyslipidemia***

Many consider the placenta as the pathogenic focus for all manifestations of preeclampsia because delivery is the only definitive cure of this disease.

Ischemia, or hypoxia appears to be central to the development of the disease.

Normal

Preeclampsia

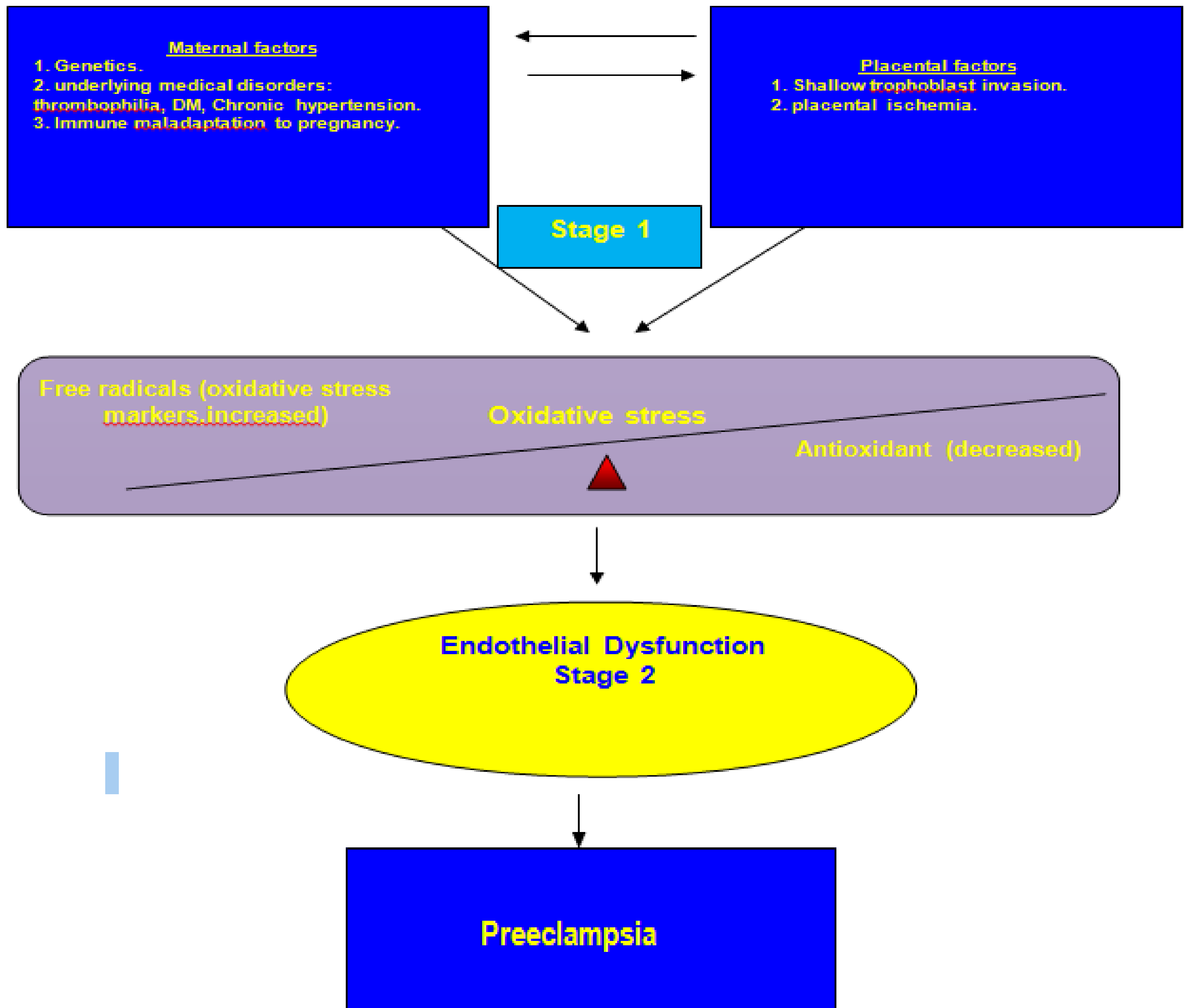


Normal pregnancy
Preeclampsia
A
B
Spiral arteries
Myometrium
Decidua
Umbilical artery
Umbilical vein
Villus
(containing fetal
arteriole and venule)
Intervillus space
(maternal blood)

During early pregnancy incomplete trophoblast invasions leads to failure of conversion of thick walled tortuous spiral arteries to low resistance flaccid sinusoidal vessels, which results in impaired placental perfusion.

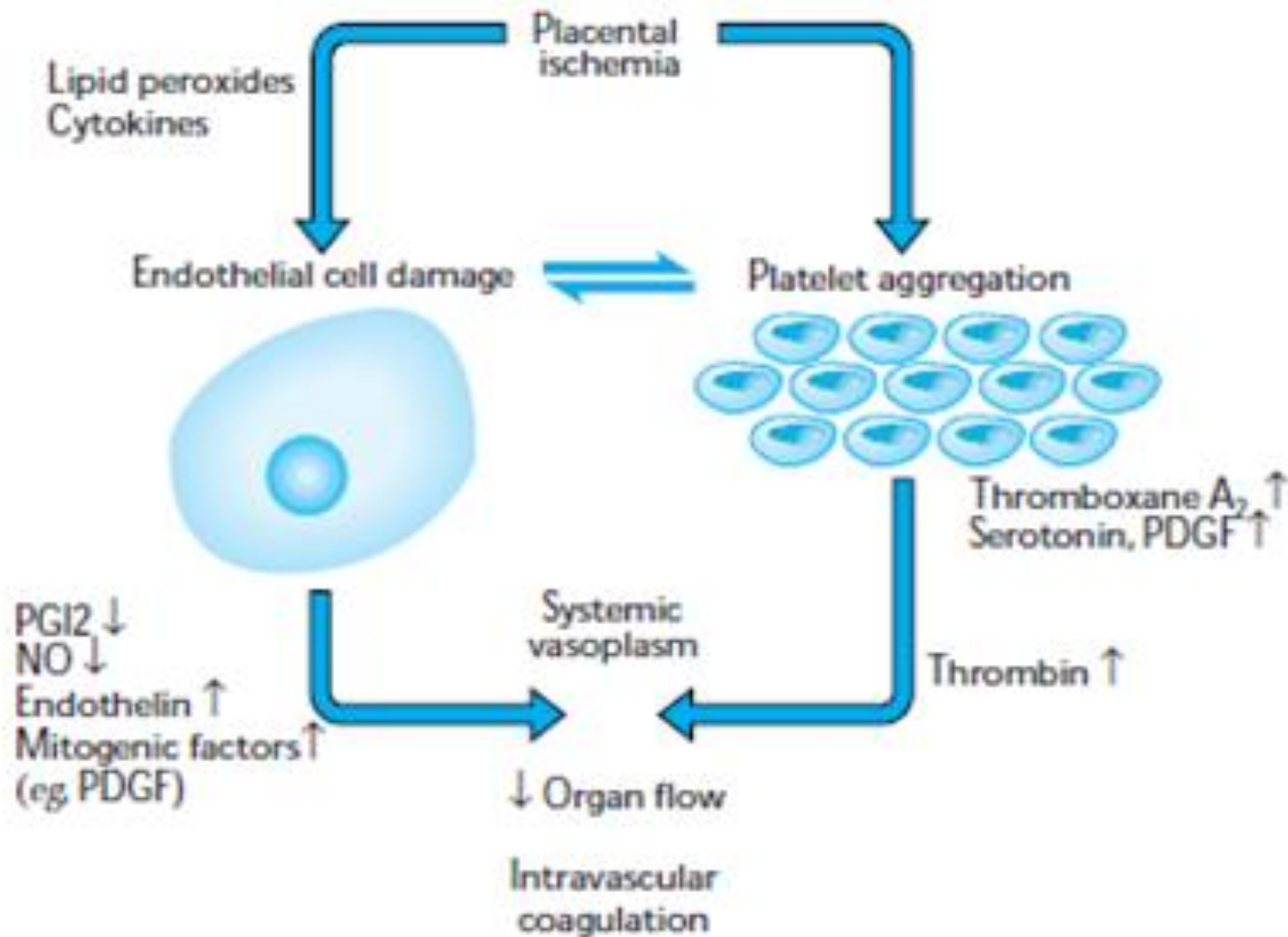
The hypoxia/reperfusion injury leads to increase generation of toxins including oxygen free radicals & lipid peroxides tilts the balance in favor of **oxidation stress**.

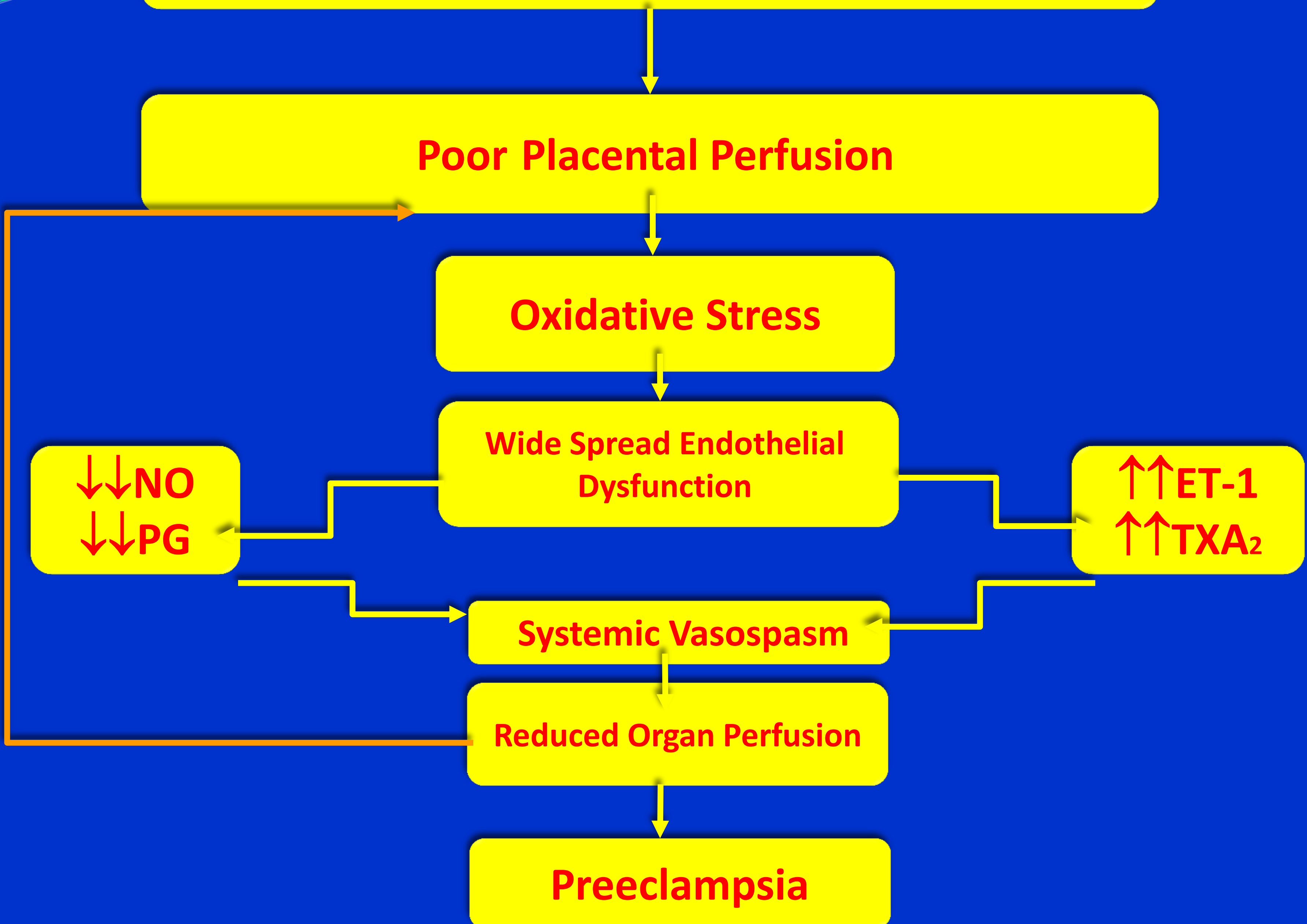
These toxins enter the circulation & cause a **widespread endothelial dysfunction** which cause an alteration in the ratio of the vasoconstrictors to the vasodilators


Maternal factors
1. Genetics.
2. underlying medical disorders:
thrombophilia, DM, Chronic hypertension.
3. Immune maladaptation to pregnancy.
Placental factors
1. Shallow trophoblast invasion.
2. placental ischemia.
Stage 1
Free radicals (oxidative stress
markers.increased)
Oxidative stress
Antioxidant (decreased)
Endothelial Dysfunction
Stage 2
Preeclampsia

The markers of endothelial dysfunction are:

1. Increase endothelin-1 level.
2. Decrease nitric oxide synthesis.
3. Increase thromboxane A2 to prostaglandin I2 ratio.
4. Decrease prostacyclin synthesis.


Placental ischemia
Lipid peroxides
Cytokines
Endothelial cell damage
Platelet aggregation
Thromboxane A2 ↑
Serotonin, PDGF ↑
PGI2 ↓
NO ↓
Endothelin ↑
Mitogenic factors ↑
(e.g. PDGF)
Systemic vasoplasm
Thrombin ↑
↓ Organ flow
Intravascular coagulation



Abnormal Trophoblastic Invasion
Poor Placental Perfusion
Oxidative Stress
Wide Spread Endothelial Dysfunction
↓↓NO
↓↓PG
↑↑ET-1
↑↑TXA2
Systemic Vasospasm
Reduced Organ Perfusion
Preeclampsia

Endothelial dysfunction & Preeclampsia

Endothelial cell activation explains the wide spread manifestations of the disease ,as the vascular endothelium supplies all organ systems involved

The net effect of these processes would be widespread vasoconstriction leading to hypoxia & ischemic damage in different vascular beds.

Many investigators found a higher plasma concentrations of ET-1 of approximately two to threefold in women with preeclampsia

The elevated endothelin-converting-enzyme activity postpartum may indicate an inherent endothelial dysfunction predisposing to preeclampsia or that preeclampsia may cause irreversible changes in endothelial function.

It has been shown that maternal plasma ET-1 levels increase in PE & correlate with the severity of preeclampsia.

Typically, plasma levels of endothelin-1 are highest during the latter stage of the disease, suggesting that endothelin-1 may not be involved in the initiation of preeclampsia but rather in the progression of disease into a severe form.

Also it was reported that significant differences in endothelial morphology between arteries from normal pregnant women & those women with preeclampsia.

THANK YOU FOR ATTENTION