The Role of Endothelial Dysfunction in Preeclampsia
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

Genetic susceptibility (maternal x fetal)

Maternal disease
- Vasoplasam
- Intravascular coagulation
- Endothelial dysfunction
**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.
The diagnostic criteria of preeclampsia

Blood pressure is $\geq 140$ 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 $\geq 110$ 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 (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.
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 an increase in the generation of toxins including oxygen free radicals and lipid peroxides, which tilts the balance in favor of oxidation stress.

These toxins enter the circulation and cause widespread endothelial dysfunction, which results in an alteration in the ratio of the vasoconstrictors to the vasodilators.
Maternal factors
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.
Abnormal Trophoblastic Invasion

Poor Placental Perfusion

Oxidative Stress

Wide Spread Endothelial Dysfunction

Systemic Vasospasm

Reduced Organ Perfusion

Preeclampsia

↓↓NO

↓↓PG

↑↑ET-1

↑↑TXA₂
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