

IN SUMMARY
PREGNANCY INDUCED HYPERTENSION

Classification of Hypertensive Disorders of Pregnancy

- Gestational hypertension (6-7%)
 - Onset of HTN without proteinuria after 20wks of gestation with resolution to baseline by 12wks postpartum
- Preeclampsia (5-8%)
 - Hypertension plus proteinuria
 - 140/90 on two occasions six hours apart
 - 0.3 gm/dl in 24hrs or 1+ on urine analysis
- Chronic hypertension (3-5%)
 - HTN prior to pregnancy
 - Gestational HTN which does not resolve within 12 wks of delivery
- Superimposed preeclampsia (25% of CHTN)
 - Chronic HTN plus new onset proteinuria or other signs or symptoms of preeclampsia

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Berg, C. J., H. K. Atrash, L. M. Koonin, and M. Tucker. "Pregnancy-Related Mortality in the United States, 1987-1990." *Obstet Gynecol.* 88, no. 2 (August 1996): 161-7.

Classification of Preeclampsia

- Mild preeclampsia
 - BP 140/90
 - 300mg of proteinuria in 24hrs
- Severe preeclampsia (any of these)
 - BP 160/110
 - 5gm of proteinuria in 24hrs
 - Oliguria or <500 ml in 24hrs
 - Cerebral or visual disturbances
 - Pulmonary edema or cyanosis
 - RUQ tenderness
 - Fetal growth restriction
 - Thrombocytopenia
 - Impaired liver function
- Eclampsia
 - Presence of new-onset grand mal seizures in a woman with preeclampsia

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RISK FACTORS

Nulliparity	3:1
Age >40 y.o.	3:1
African-American race	1.5:1
Family history	5:1
Chronic Renal disease	20:1
Chronic hypertension	10:1
Antiphospholipid syndrome	10:1
Diabetes mellitus	2:1
Twin gestation	4:1
High body mass index	3:1
Angiotensinogen gene T235	
Homozygous	20:1
Heterozygous	4:1

Adopted from ACOG Technical Bulletin 219, Washington, DC 1996

Measurement of Blood Pressure

- Comfortable sitting position
- Korotkoff V th sound should be used
- If the V th sound is not present, use the IV th but should note as such
- Some automated BP cuffs use the IV th sound
- In serial readings use the higher set of values
- Relative BP change of 30mmHg/15mmHg is no longer used as hypertension

Clinical Predictors of Eclampsia

- 254 Women with Eclampsia
- No edema: 80 (32%)
- No HTN: 58(23%)
- No proteinuria: 49 (19%)

Sibai 1990

- 383 Eclampsia collected from 279 Hospitals in UK
 - ✓ No proteinuria: 71 (22%)
 - ✓ No proteinuria or HTN: 36 (11%)
 - ✓ No hypertension: 32 (10%)
 - ✓ Headaches: 188 (50%)
 - ✓ Visual disturbance: 72 (19%)
 - ✓ Epigastric pain: 71 (19%)

Douglass, 1994

“A disease of theories that have not stood the test of time”

1000 BC: First description of eclampsia is found in Kahun papyrus from Egypt

1800: An association between onset of hypertension and proteinuria and seizure during pregnancy was recognized

1950: A distinction between primary renal disease, chronic hypertension, epilepsy and preeclampsia/eclampsia became widely accepted

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EVIDENCE FOR TROPHOBLASTIC INVASION

Clinical

Predisposing factors include

Vascular disease (SLE, diabetes, chronic HBP)

Multiple gestation

Hydatidiform mole

Animal Studies

Most successful models have induced utero-placental ischemia in rabbits, dogs and primates

Human Studies

Histopathology of the placental bed

Doppler of uterine artery

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Adhesion Molecules Expressed by Cytotrophoblasts

Villous Cytos

$\alpha 6 / \beta 4$

E-cadherin

Invasive Cytos

$\alpha 1 / \beta 1$

$\alpha v / \beta 3, \beta 6$

VE-cadherins

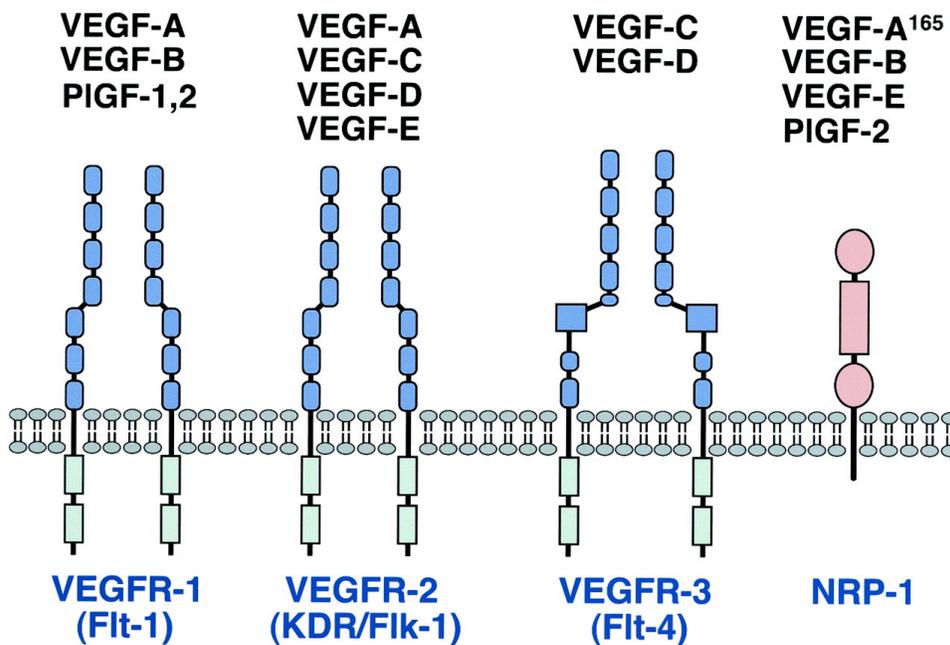
PECAM

VCAM

Figures removed due to copyright restrictions. Please see:
Lim, K. H., Y. Zhou, M. Janatpour, M. McMaster, K. Bass, S. H. Chun, and S. J. Fisher.
"Human Cytotrophoblast Differentiation/Invasion is Abnormal in Pre-eclampsia."
Am J Pathol. 151, no. 6 (December 1997): 1809-18.

CIRCULATING TOXIC FACTORS

- Cytokines
- IL-1
- IL-6
- TNF-alpha
- Free fatty acid
- Antioxidants
- Angiogenic factors



VEGF

- Promotes angiogenesis
- Induces nitric oxide and prostacyclin
- Glomerular healing

Anti-VEGF

- Increases apoptosis
- Impairs glomerular capillary repair
- Increases proteinuria in rat model of mesangio-proliferative nephritis
- Increases proteinuria in experimental thrombotic microangiopathy

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[Structure of sVEGFR-1 (sFlt-1).]

First described by Kendall et al.(1993) and has been localized to trophoblast by Clark et al.1998.

Has been shown to be produced in greater amount in trophoblasts isolated from preeclampsia (Zhou et al. 2002)

Its role in distal organs and in various pathologic state is unknown

Hypoxia may increase its production in trophoblast

Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia

See the related Commentary beginning on page 600.

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See the related articles beginning on pages 649 and 707.

Soluble VEGF receptor Flt1: the elusive preeclampsia factor discovered?

Aernout Luttun and Peter Carmeliet

The Center for Transgene Technology and Gene Therapy, Flanders Interuniversity Institute for Biotechnology, Katholieke Universiteit Leuven, Leuven, Belgium

J. Clin. Invest. 111:600–602 (2003). doi:10.1172/JCI200318015.

Figure removed due to copyright restrictions. Please see:

Figure 1 in Luttun, A., P. Carmeliet. "Soluble VEGF receptor Flt1: The Elusive Preeclampsia Factor Discovered?" *J Clin Invest.* 111, no. 5 (March, 2003): 600-2.

Serum Levels of sFlt-1 Prior to onset of Preeclampsia

Figures removed due to copyright restrictions.

Serum Levels of PlGF Prior to onset of Preeclampsia

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Parenteral Antihypertensive Agents in Pregnancy

Drug	Dose	Onset	Duration	Side Effects
Hydralazine	5-10 mg IV	10-20 min	3-6 hrs	Tachycardia Headache, flushing, angina
Labetalol	20-80 mg IV	5-10 min	3-6 hrs	Scalp tingling, vomiting, heart block
Sodium Nitroprusside	.25-10 ug/kg/min	Immediate	1-2 min	N/V, thiocyanate toxicity
Nicardpine	5015 mg/h IV	5-10 min	1-4 hrs	Tachycardia, headaches, phlebitis

Magnesium Sulfate

- Seizure Prophylaxis
 - Intravenous
 - Loading dose: 4-6 g in 100ml over 15-20 min
 - Maintenance: 2 g per hr. (target 4-8 mEq/L)
 - Intramuscular
 - Loading dose: 10 g MgSO₄ as 50% sol
 - For severe PE and eclampsia: 4g in 20% solution at 1g/hr (IV)
 - Maintenance: 5g MgSO₄ in 50% sol. Q4hr

Eclampsia

- Reversible posterior leukoencephalopathy
 - Renal insufficiency and hypertension
 - Immunosuppressive therapy
 - Eclampsia
 - Subcortical edema in the posterior circulation
 - Presents with blurred vision, cortical blindness, headaches, vomiting, confusion and seizures
 - Resolution of neurologic deficits in 2wks
 - Anterior circulation may be more protective
- MRI findings
 - Cerebral ischemia
 - Cerebral edema
 - Local hemorrhagic infarcts
- Pathophysiology
 - Local cerebral vasoconstriction--cytotoxic edema
 - Loss of autoregulation--over perfusion -- vasogenic cerebral edema

Pulmonary Edema

- Cardiogenic
 - Systolic dysfunction
 - Diastolic dysfunction
 - Combined
- Noncardiogenic
 - Increased capillary permeability
 - Narrowed COP-wedge pressure gradient
 - Decreased COP
 - Delayed mobilization of extravascular fluid
 - Iatrogenic fluid overload

FUNDAMENTAL QUESTIONS

1. What happens to blood pressure as pregnancy advances?
2. What happens to blood volume in pre-eclampsia?
3. When does one typically develop pre-eclampsia?
4. List 5 risk factors for pre-eclampsia?
5. What are the clinical manifestations of pre-eclampsia?
6. What happens in eclampsia? What are the changes one may see in the CNS?
7. What is VEGF?
8. What is sFlt1? What role might it play in pre-eclampsia?
9. Describe the alterations in trophoblastic invasion in pre-eclampsia.
10. What is the most effective therapy for pre-eclampsia?
11. Name some drugs used to control blood pressure in pre-eclampsia.

