Cardiovascular disease during pregnancy

- Preeclampsia -

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Hypertensive disorders in Pregnancy

Gestational Hypertension

- SBP ≥140 or DBP ≥90 mmHg for first time during pregnancy
- No proteinuria

Preeclampsia

- Hypertension; BP ≥ 140/90 mmHg after 20 weeks' gestation
- Proteinuria; ≥ 300 mg/24 hrs or ≥ 1+dipstick

Eclampsia

- Seizures in a woman with preeclampsia without other causes

Superimposed Preeclampsia on chronic hypertension

- New-onset proteinuria ≥ 300mg/24hrs in hypertensive women but no proteinuria before 20 weeks of gestation
- A sudden increase in proteinuria or blood pressure in women with hypertension

Chronic hypertension

- BP ≥ 140/90 mmHg before pregnancy or diagnosed before 20 weeks gestation
- Hypertension first diagnosed after 20 weeks gestation and persist after 12 week postpartum

Preeclampsia

" a ***pregnancy-specific syndrome*** ***that can affect virtually every organ system***"

secondary to <u>vasospasm</u> and <u>endothelial activation</u>

- **Diagnosis**

<u>Mininum criteria</u>

Hypertension; BP ≥ 140/90 mmHg after 20 weeks' gestation

Proteinuria; ≥ 300 mg/24 hrs or persistent ≥ 1+dipstick

Adopted by Working group of the NHBPEP (2000)

Preeclampsia

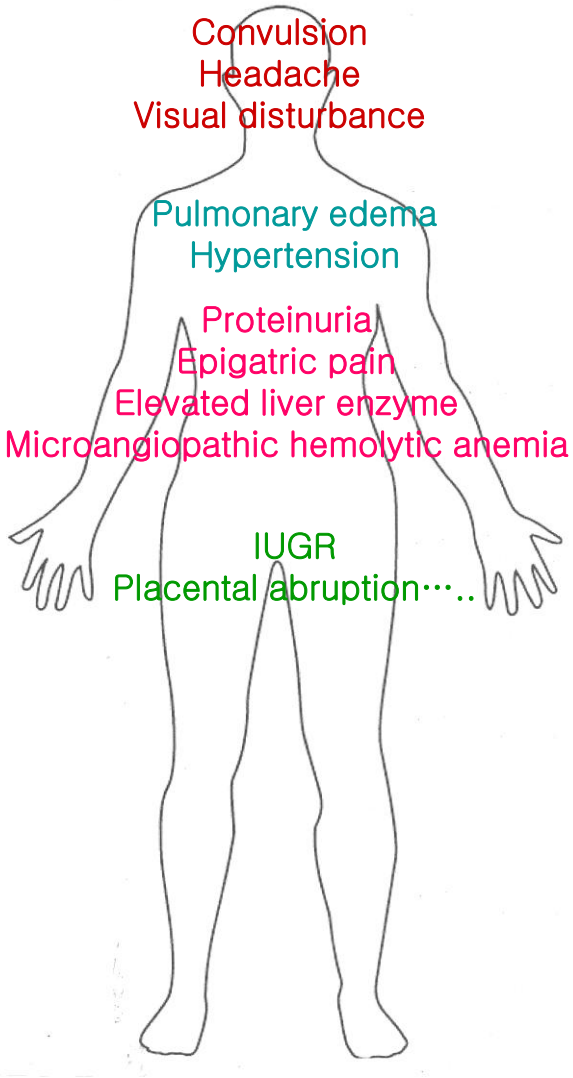
- **Incidence**; 3-5% of all pregnancies

- **Risk factors**
  - Young & nulliparous women
    - Cf. Older women – risk factor for chronic hypertension with superimposed preeclampsia
  - Race / ethnicity – genetic predisposition
  - Environmental, socioeconomic, seasonal influences
  - Obesity, multifetal gestation

Cf. Smoking / Placental previa – reducing the risk

Preeclampsia

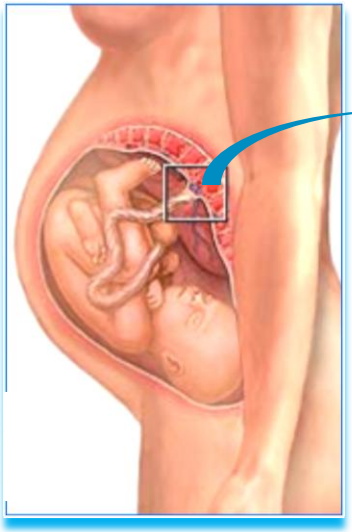
Clinical Manifestation ; multiorgan disorders / failure

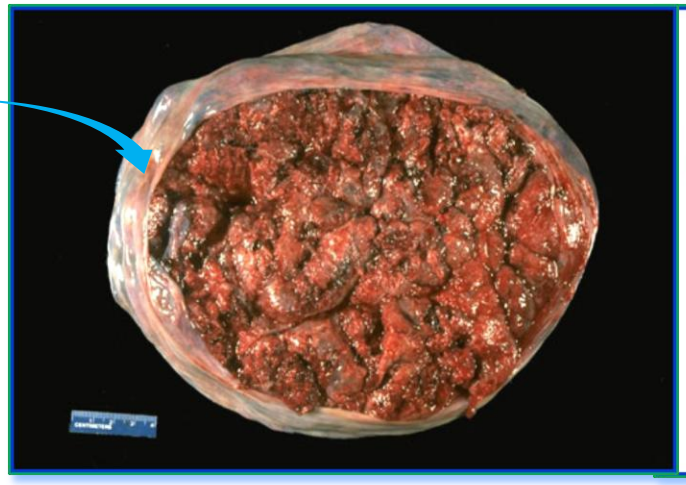


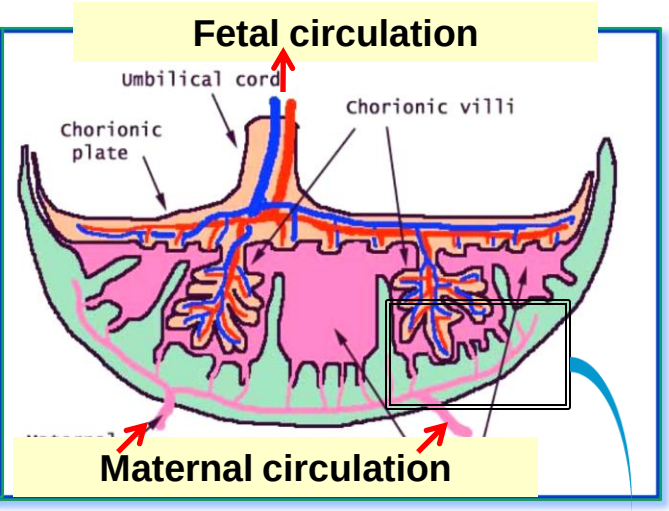
Preeclampsia

- **Clinical significances of preeclampsia**
  - **High maternal mortality & morbidity**
    - **Hyperetension, renal failure, hepatic failure, coagulopathy, cardiac failure, HELLP syndrome, seizure etc.**
  - **High perinatal mortality & morbidity**
    - **Fetal Death in Uterus (FDIU), Fetal growth restriction, Prematurity, Fetal distress etc.**

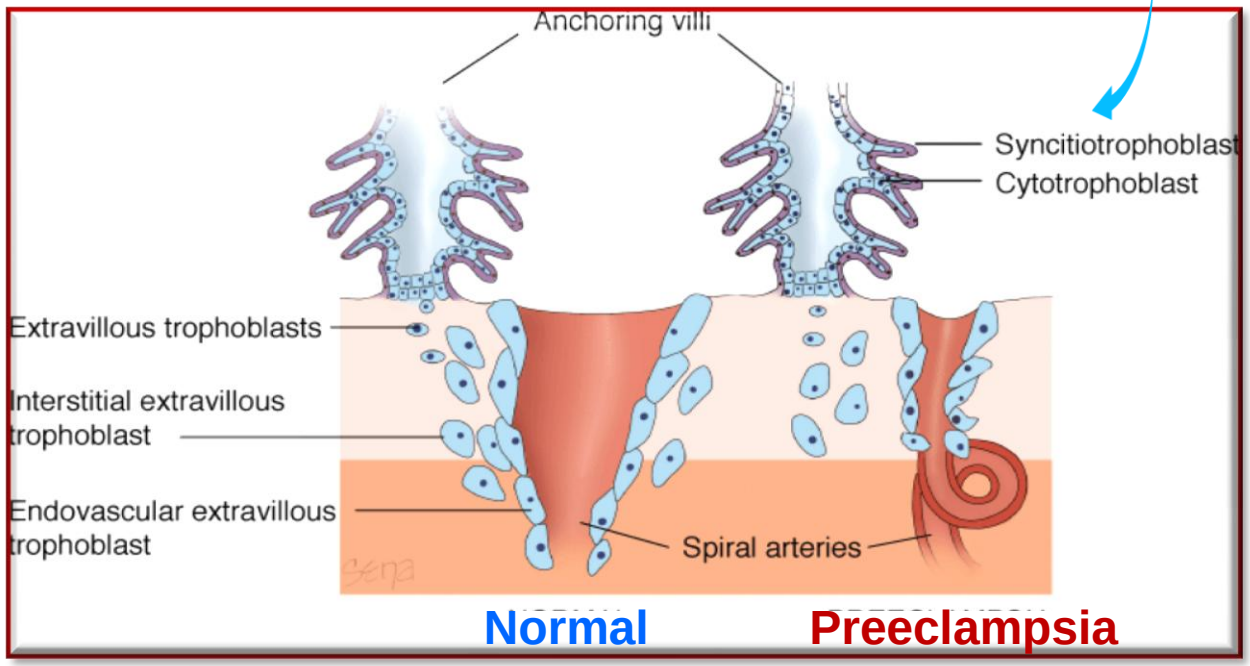
Etiology & Pathogenesis of Preeclampsia ?



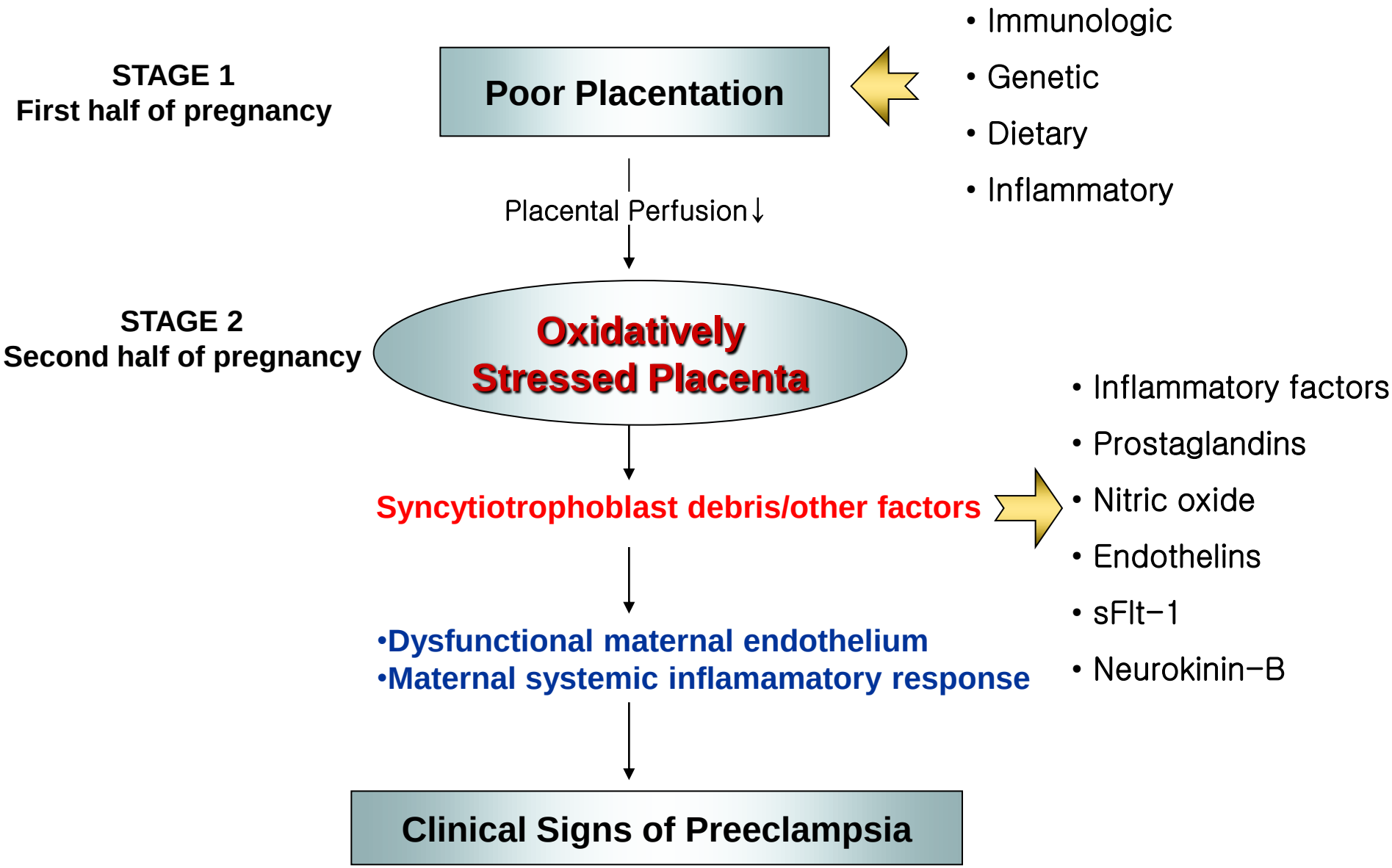




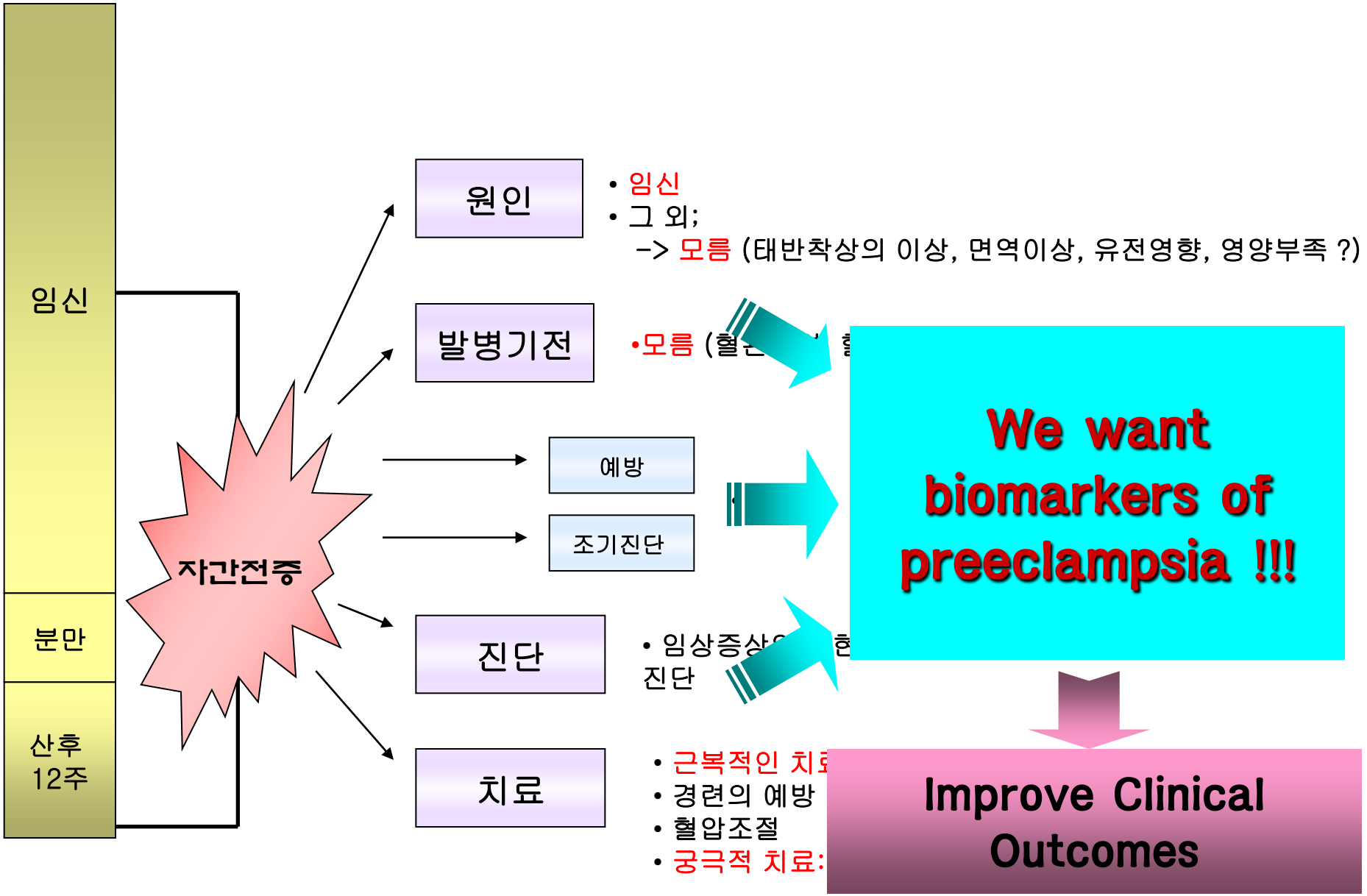
Placenta ;
essential source of preeclampsia



Theories about the pathophysiology or causes of PE



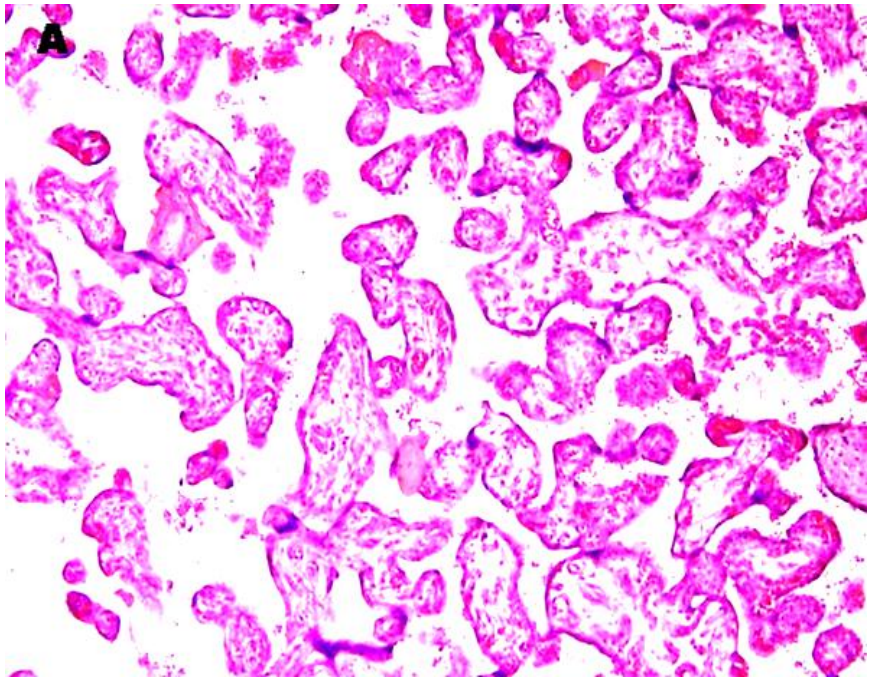
The actual states of Clinical Preeclampsia



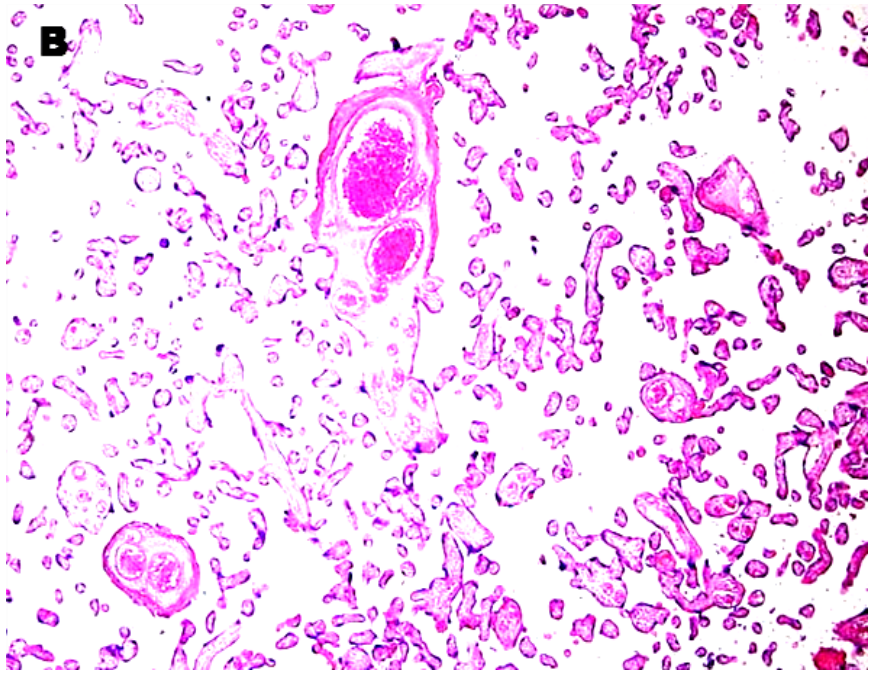
Studies for further understanding of Preeclampsia !!

Morphology of Preeclamptic placentas

LM (H&E stain, x100)



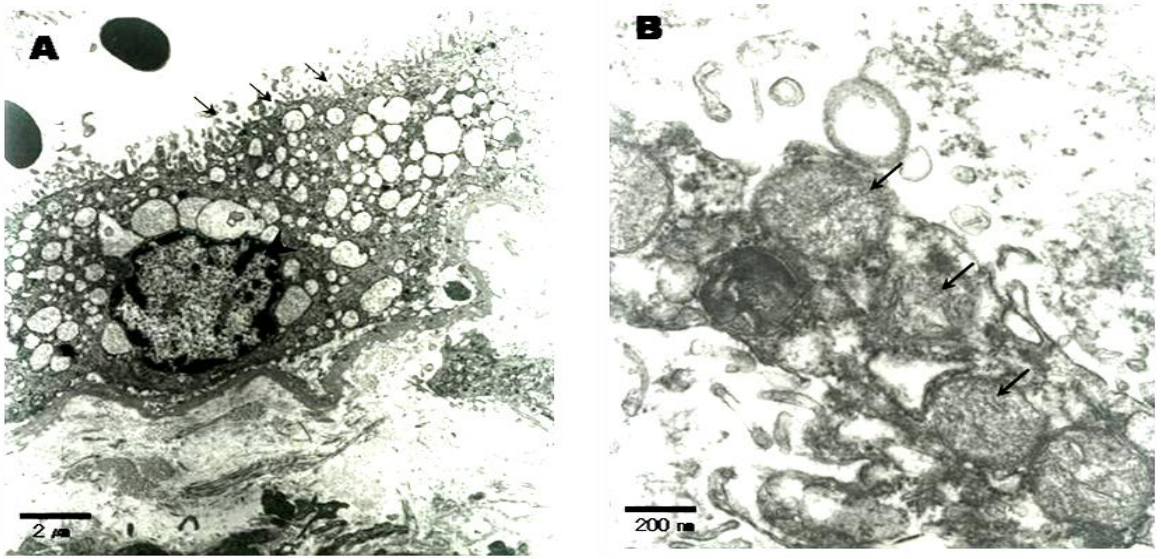
Normal



Preeclampsia

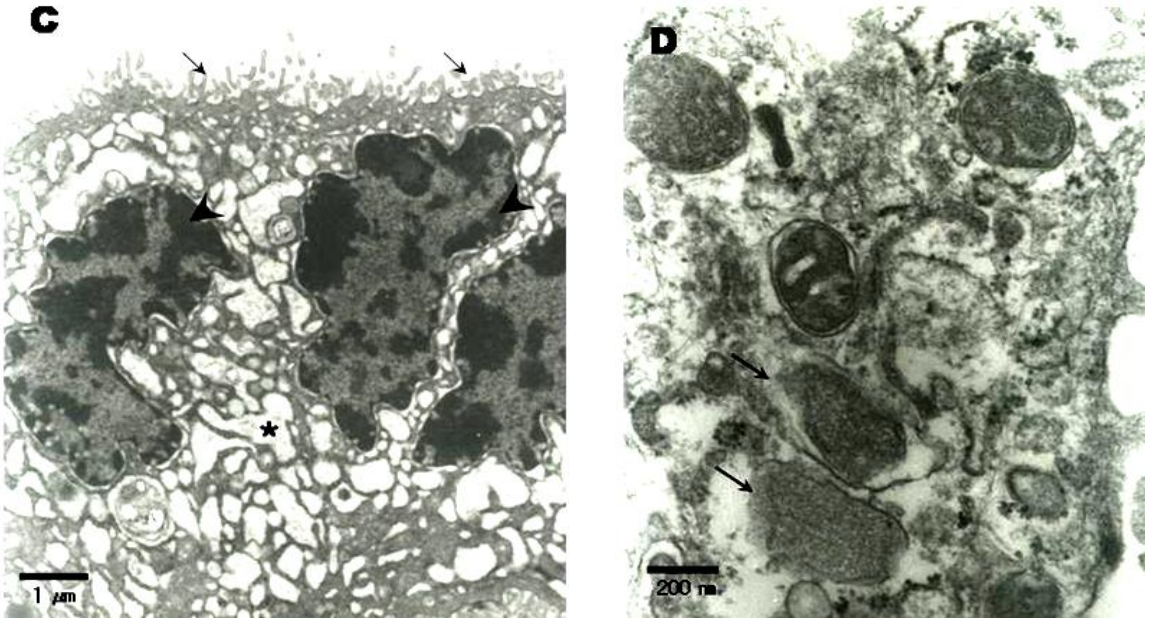
Morphology of Preeclamptic placentas

EM



A,B;

Normal



C,D;

Preeclampsia

Maternal serum markers

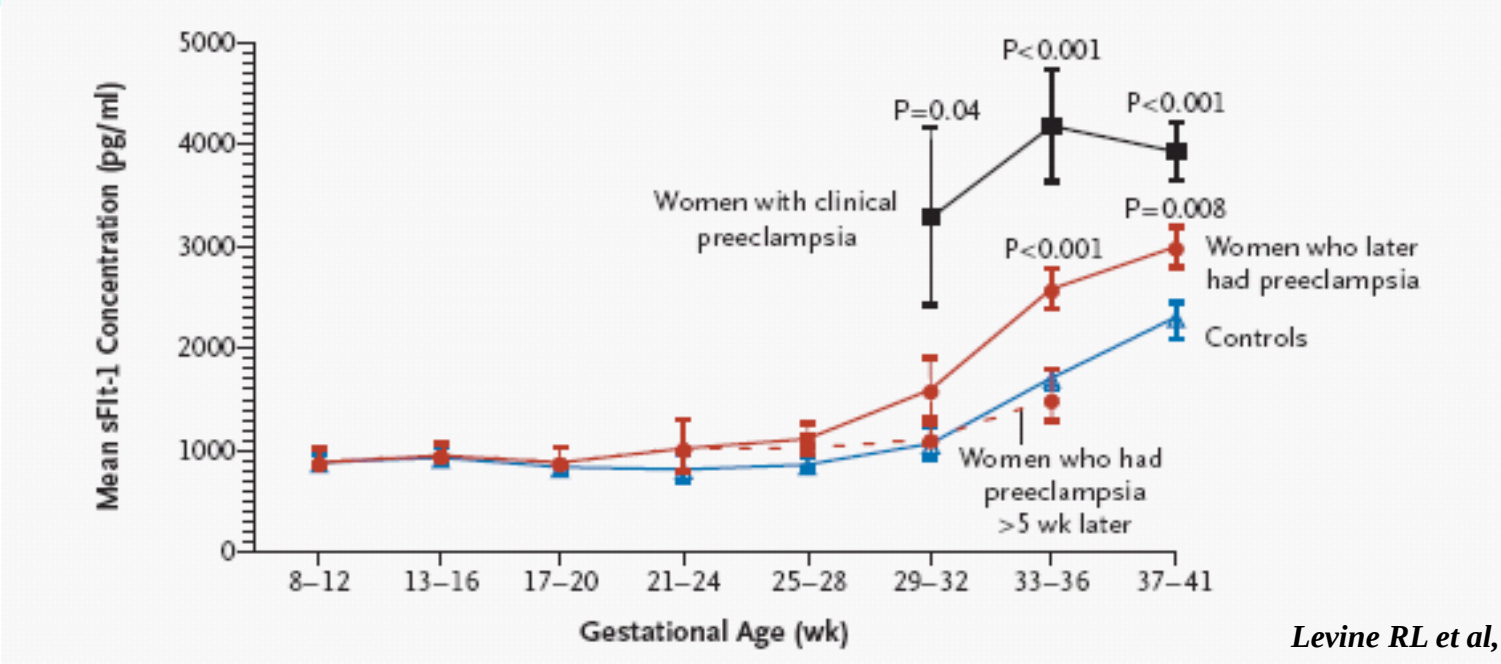
- *Inhibin A/ Activin A*
- *Fibronectin*
- *Corticotrophin-releasing hormone (CRH)*
- *Homocysteine*
- *Neurokinin B (NKB)*
- *Placental growth factor*
- *Soluble Flt-1*
- *Soluble Endoglin*

Maternal serum markers

Soluble Fms-like tyrosine kinase (sFlt-1)

- Splice variant of Vascular Endothelial Growth Factor receptor-1 (VEGFR-1)
- Bind VEGF and inhibits biologic activities of VEGF
- Anti-angiogenesis

✓ The sFlt-1 level is increased beginning approximately five weeks before the onset of preeclampsia



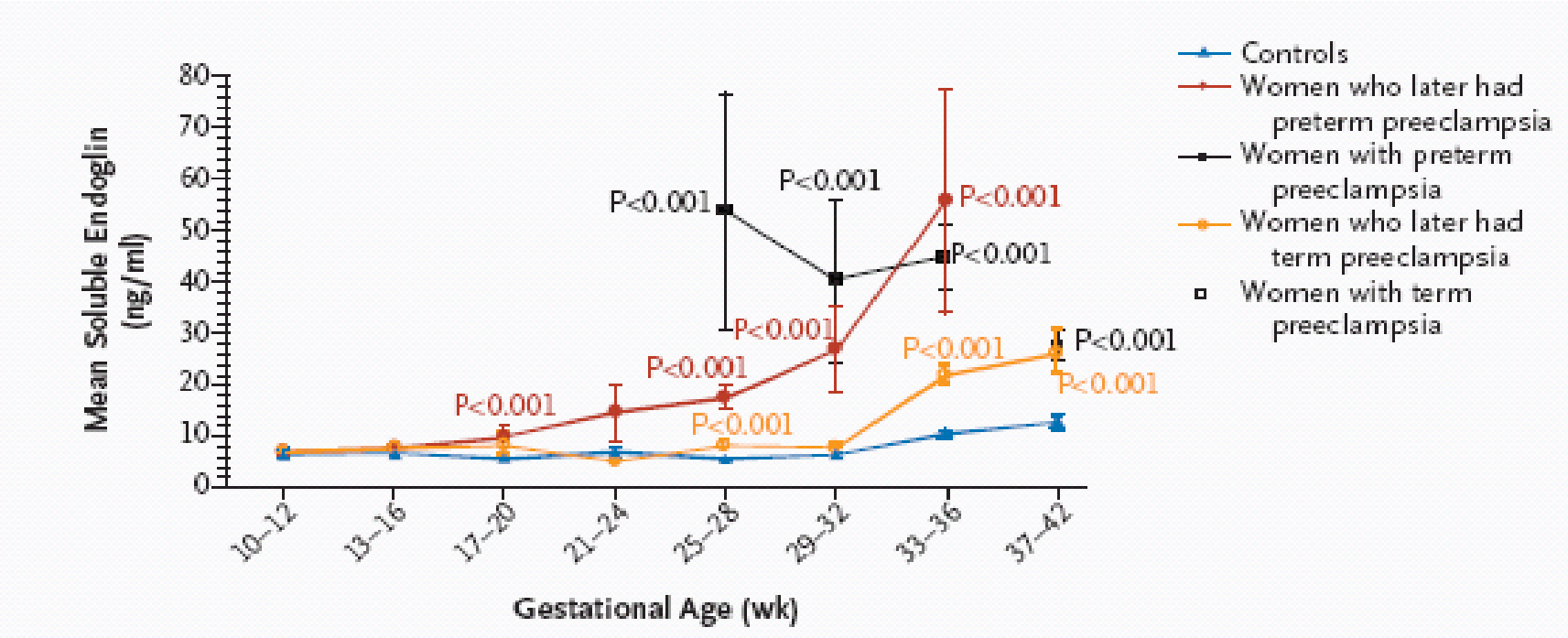
Levine RL et al, NEJM, 2004

Maternal serum markers

Soluble Endoglin

- **Coreceptor for Transforming Growth Factor-β1 and β3 (TGF-β1, β3)**
- **Inhibit TGF-β1 signaling in vasculature.**
- **Anti-angiogenesis**

✓ **Circulting soluble endoglin levels increased markedly before the onset of preeclampsia**

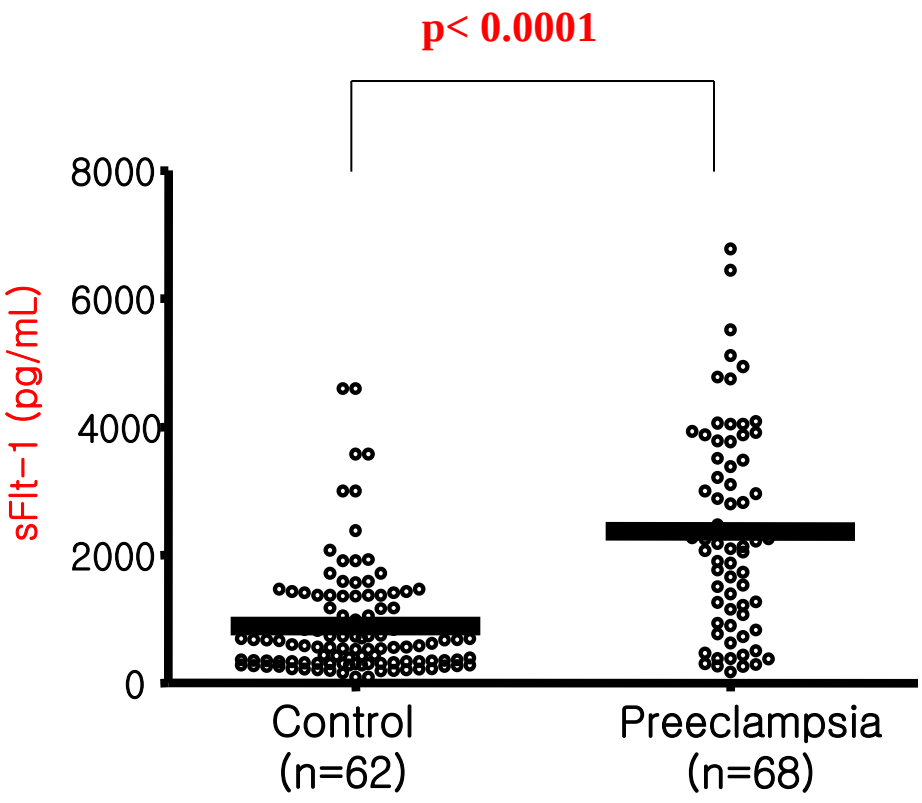


Richard, NEJM, 2006

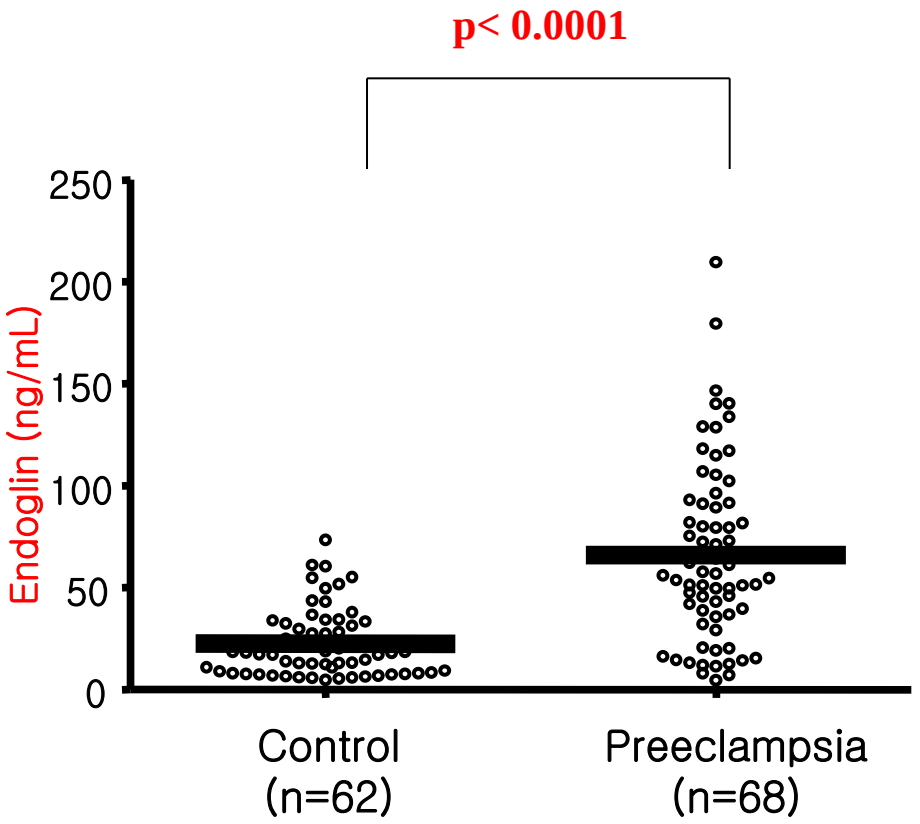
Maternal serum markers

Maternal levels of sFlt-1 / Endoglin between Control and Preeclampsia

sFlt-1



Soluble endoglin

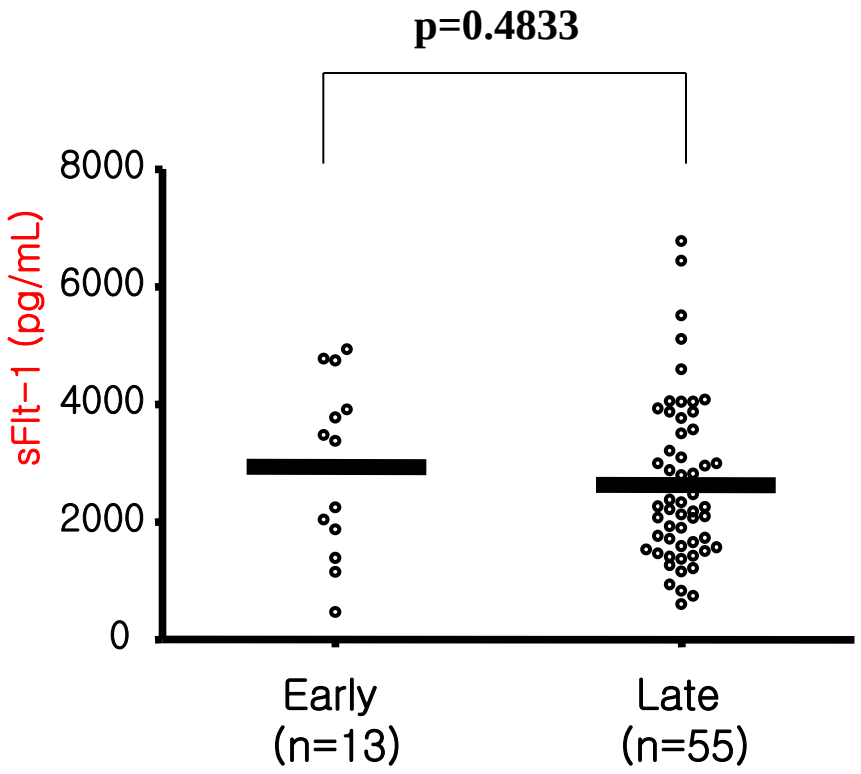


YN Kim, Prenat Diag, 2009

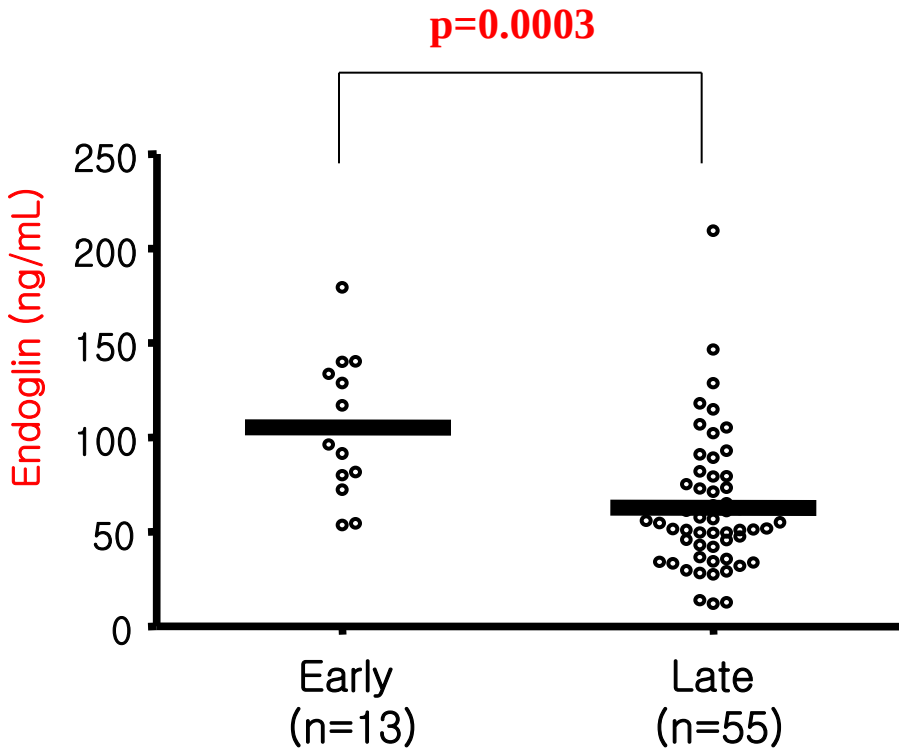
Maternal serum markers

sFlt-1 / Endoglin levels Between Early- and Late-onset preeclampsia

sFlt-1



Soluble endoglin



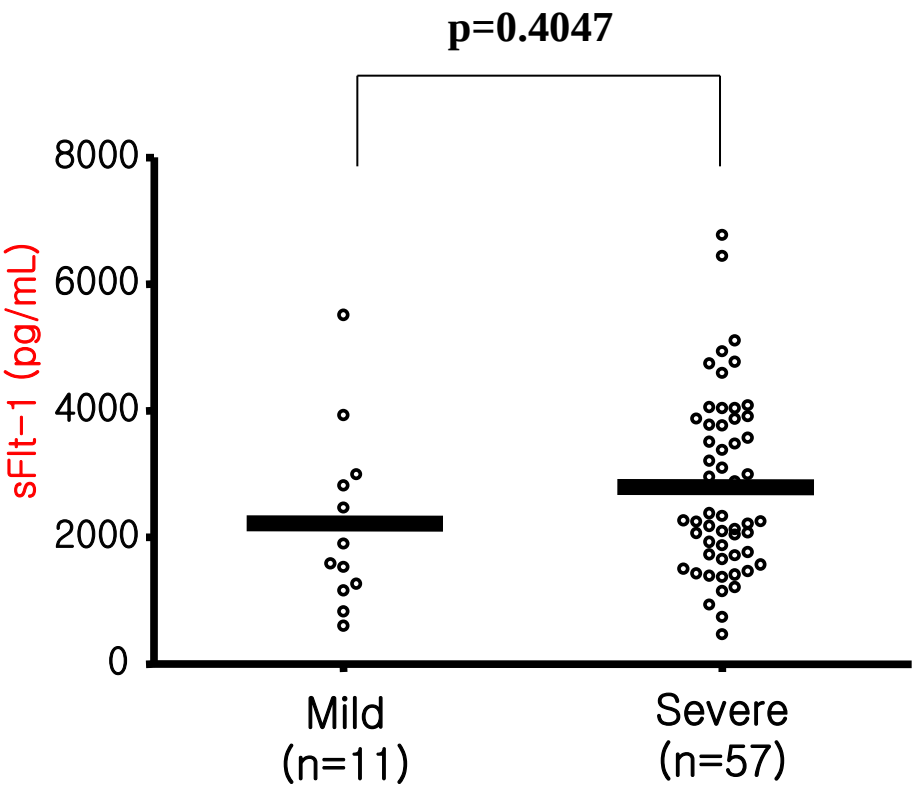
*** Early-onset; Clinical manifestation occur before 32 weeks of gestation**

YN Kim, Prenat Diag, 2009

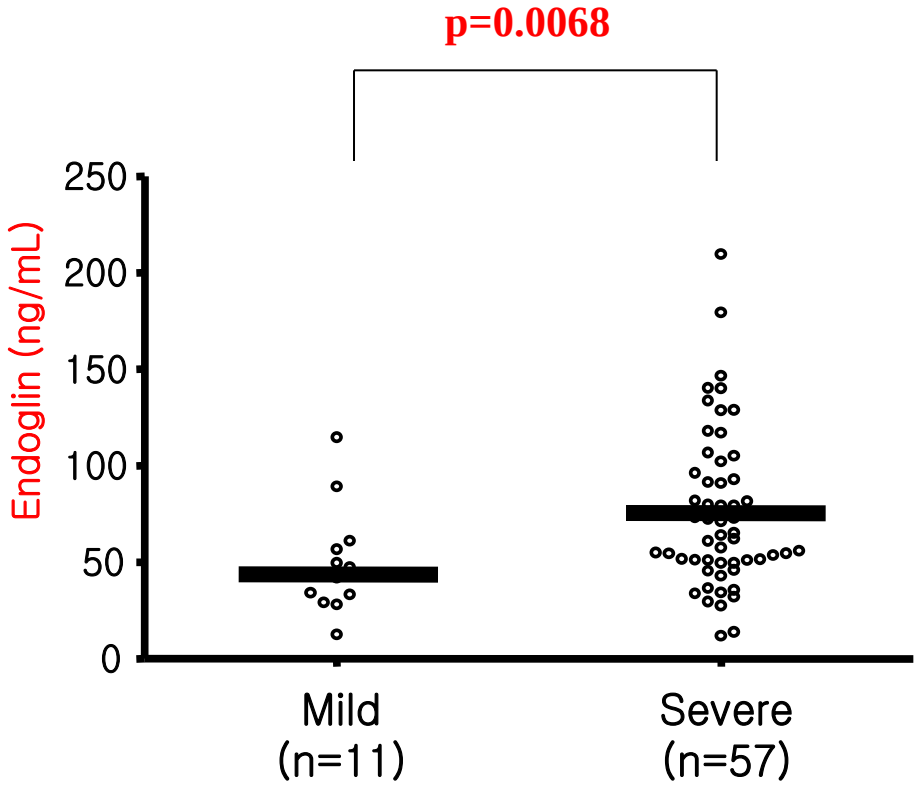
Maternal serum markers

Comparison of sFlt-1 / Endoglin between Mild and Severe Preeclampsia

sFlt-1



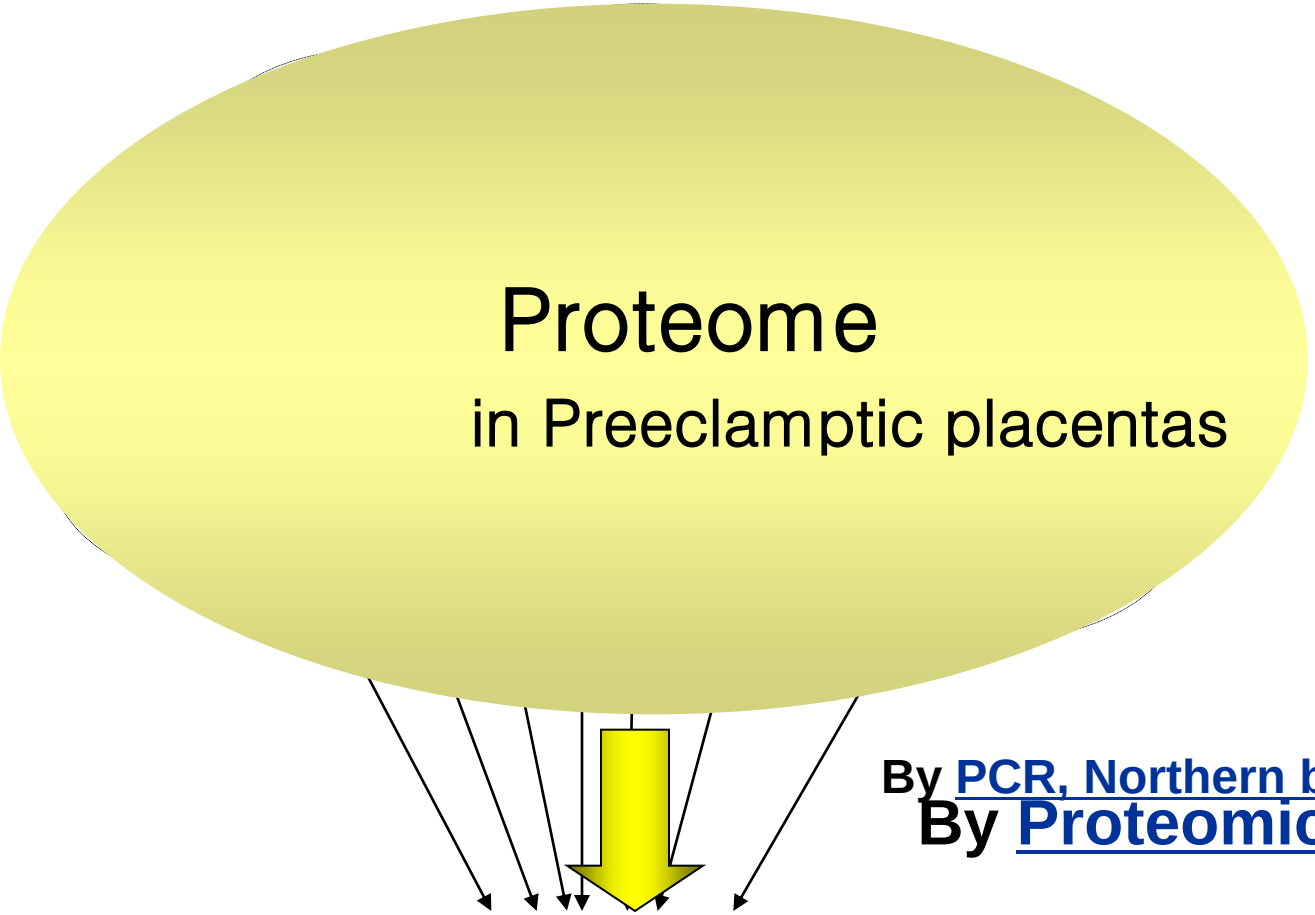
Soluble endoglin



*** Severe Criteria ; Adopted by Working group of the NHBPEP (2000)**

YN Kim, Prenat Diag, 2009

Proteomic approach to Preeclampsia



By PCR, Northern blot, Western blot, ELISA

By Proteomics

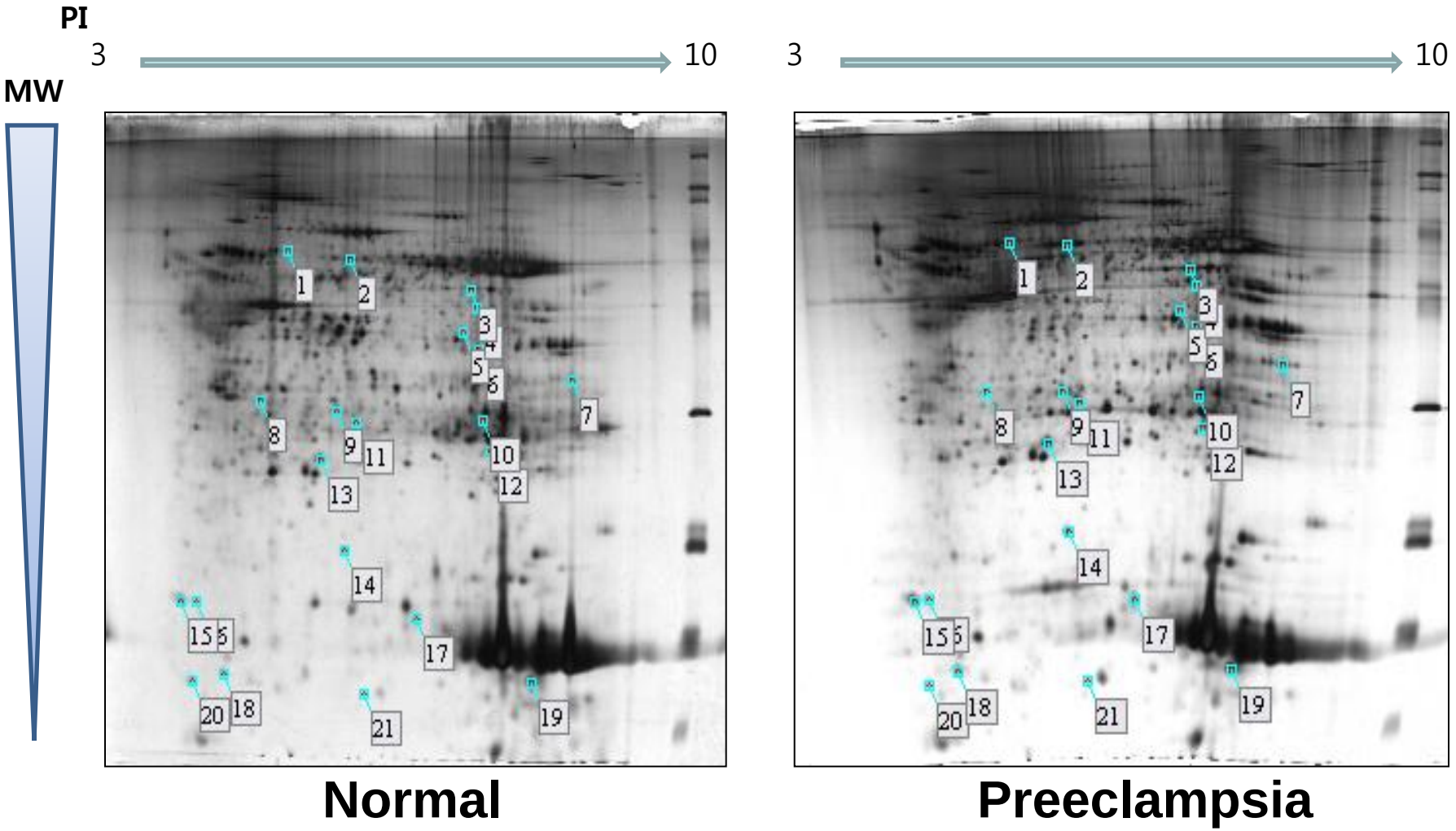
Pathophysiologic factor ?

or

Cause ?

Comparative proteomics of placental proteins

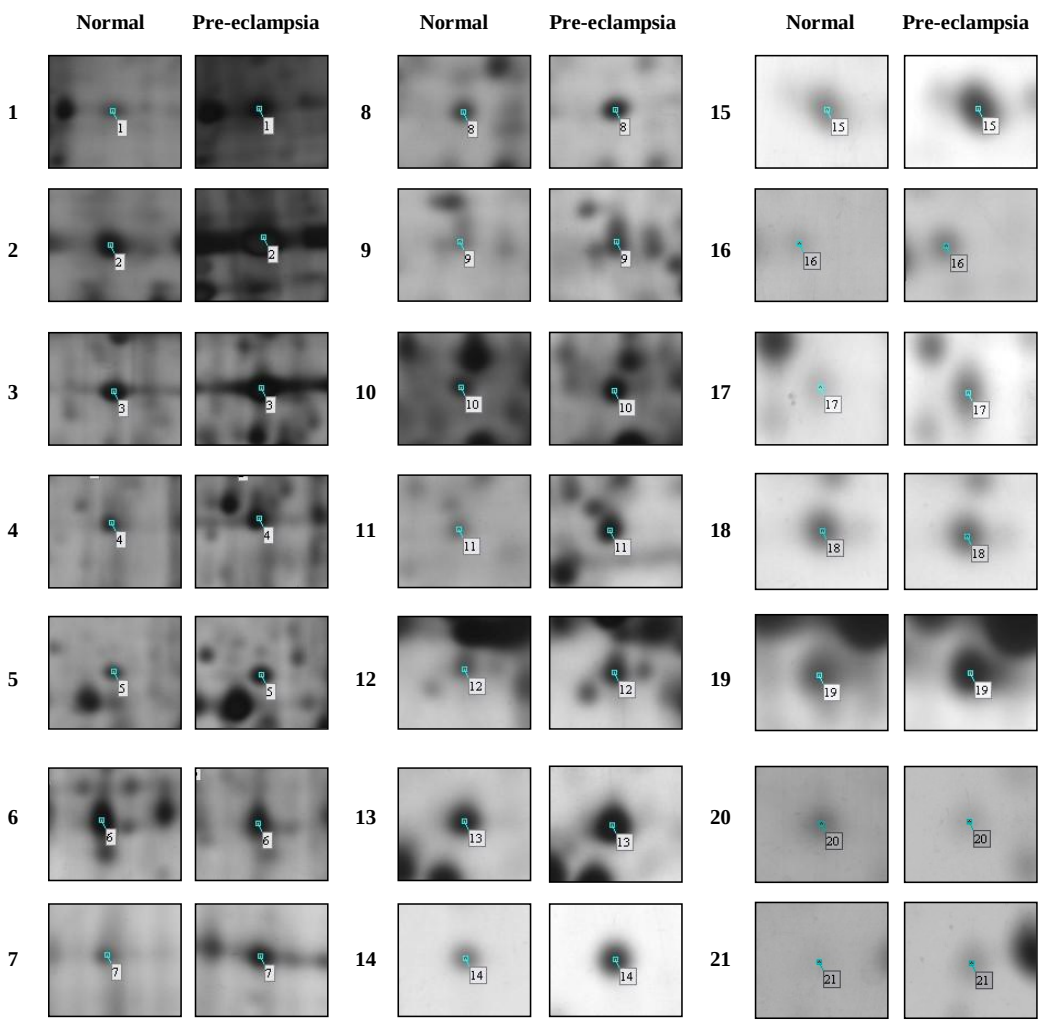
- 2DE gel image



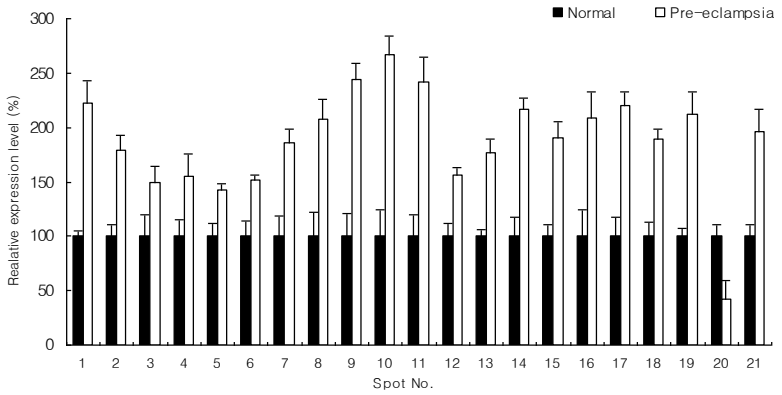
YN Kim, Proteomics, 2007

Proteomics of Preeclampsia

A



B



< Differentially expressed proteins between normal and preeclamptic placenta >

YN Kim, Proteomics, 2007

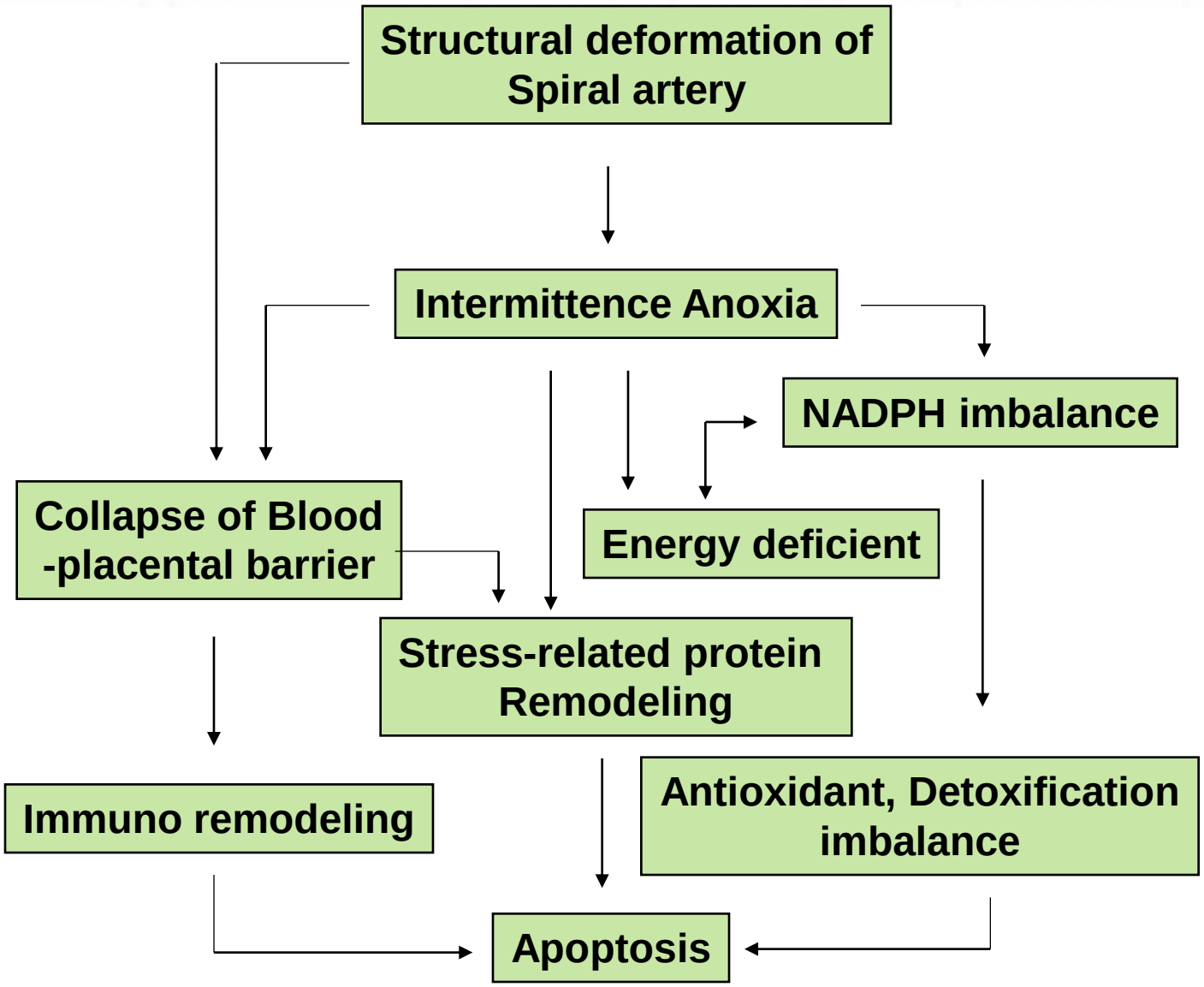
Protein Identification of Differentially Expressed proteins

Spot #	NCBI acc#	protein identification	MS score	Mr	pI	#pep	seq. (%)
1	49522865	chaperonin	83	61016	5.7	15	32
2	1208427	ER-60protease	184	56761	5.98	27	49
3	1167843	alpha-enolase	114	47139	7.01	19	55
4	28178825	Isocitrate dehydrogenase 1	120	46630	6.53	19	46
5	1633300	Aldehyde reductase	81	36419	6.34	13	47
6	493797	Chain B, Fidarestat Bound to human Aldose reductase	120	35699	6.56	17	66
7	14250132	Voltage-dependant anion channel 1	100	30754	8.62	13	63
8	4588526	Nuclear chloride channel	121	26907	5.02	15	65
9	5822091	Chain H, Cathepsin D	86	26229	5.31	15	53
10	56081766	Phosphoglycerate mutase 1	148	28786	6.67	19	74
11	5803013	Endoplasmic reticulum protein	81	28975	6.77	13	43
12	50881968	PSMA2 protein	57	24854	7.08	9	47
13	2204207	Glutathione S-transferase	81	23367	5.43	13	57
14	8249777	Ig heavy chain v region	43	12561	5.47	5	65
15	16924329	Smooth muscle myosin alkali light chain	79	16919	4.56	10	62
17	4557581	Fatty acid binding protein	88	15155	6.6	16	77

Categorization of identified proteins

Category	Protein	Relative change (%)
Structural		
	Smooth muscle myosin alkali light chain	191
Antioxidant and detoxicant		
	Glutathione S-transferase	177
	Isocitrate dehydrogenase	155
Stress-related protein remodeling		
	Chaperonin (heat shock protein 60)	223
Apoptosis		
	Voltage-dependent anion channel	185
	Nuclear chloride channel	208
	Chain H, Cathepsin D at pH 7.5	245
Reduced $NADP^+$-regeneration		
	Aldehyde reductase	142
	Chain B, Fidarestat bound to human aldose reductase	151
Glycolysis		
	Phosphoglycerate mutase	267
	Alpha enolase	149
Immunoremodeling		
	ER-60 protease	179
Others		

Hypothesis of pathophysiology of preeclampsia



YN Kim, Proteomics, 2007

Genome profiling using high density oligo-nucleotide microarray

Microarray analyses with 55,000 human gene targets

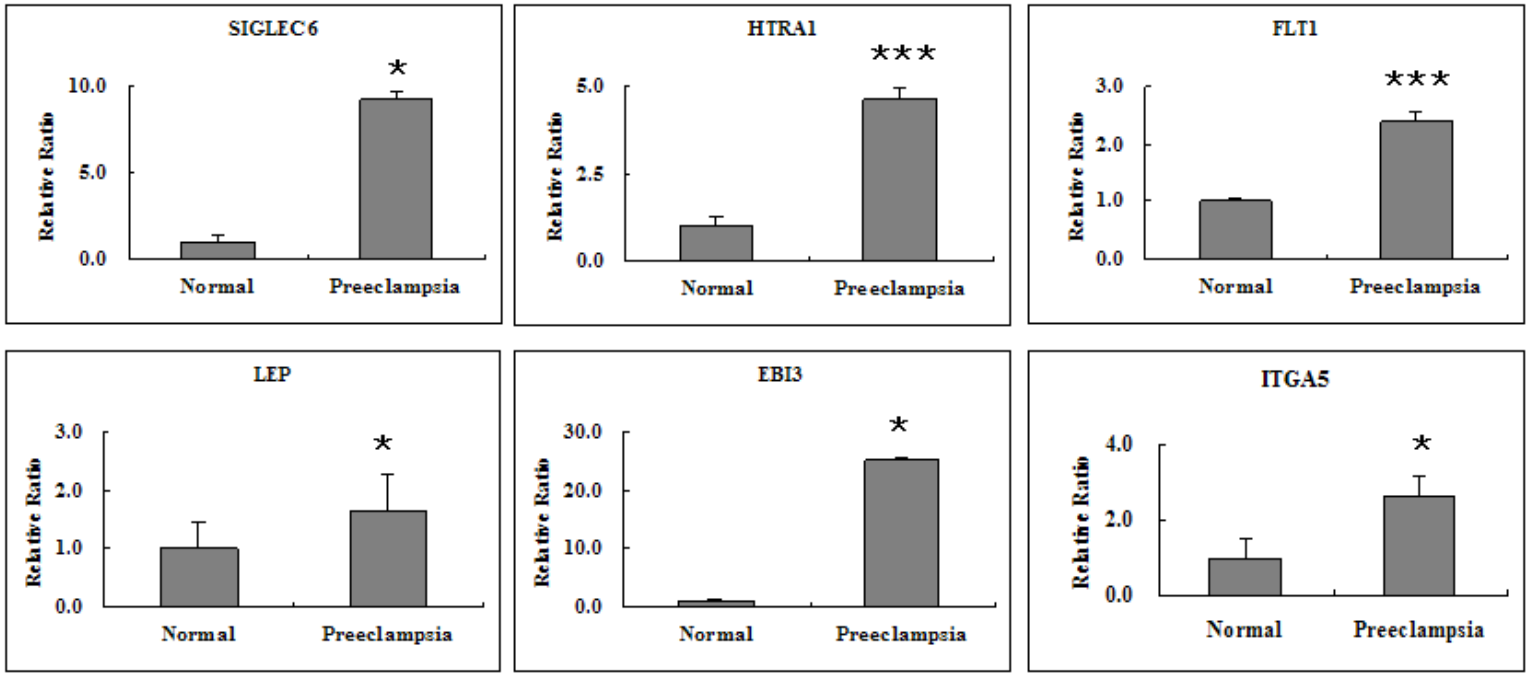
Selected differentially expressed genes in preeclamptic placenta

Function	Systematic name	Fold change	Gene symbol	Function	Systematic name	Fold change	Gene symbol
cell proliferation and differentiation	GE58298	2.053	SUV39H1	transcription and translation regulation	GE58207	2.637	ENG
	GE79387	3.961	HTRA1		GE61139	2.027	FHL2
	GE83202	2.171	TRIM27		GE87986	2.285	DDX54
	GE81269	2.08	UMOD		GE86465	2.116	TGFB1I1
	GE59757	2.092	FLT1		GE81172	2.113	PITX1
	GE57275	2.692	DGKD		GE79242	2.306	FABP4
immune regulation	GE81553	2.033	EB13	others	GE81173	2.459	PKM2
	GE80988	2.714	ANXA11		GE83622	11.52	PIGS
lipid biosynthesis and transport	GE57393	2.789	LPIN2		GE60423	3.022	PPP1R7
	GE60473	4.341	SLCO2A1		GE53189	2.029	AUTS2
	GE57831	2.051	CYP11A1		GE54586	2.368	SMTN
protein biosynthesis and transport	GE79201	2.42	MARS		GE61751	2.485	HCCS
	GE82893	2.554	IPO4		GE59110	2.392	CPSF1
signal transduction	GE57358	2.974	SIGLEC6		GE58106	2.025	CA4
	GE81036	2.05	PRMT2		GE80892	2.291	EPB42
	GE87262	7.973	LEP		GE61924	2.27	PPAN
	GE59678	2.616	ITGA5		GE81505	0.383	SEPP1
	GE80129	2.313	GPR30				
	GE59865	2.199	TIE1				

Unpublished

Genome profiling using microarray

qRT-PCR confirmation of differentially expressed genes



Unpublished

Conclusion

- **Preeclampsia is a potential cardiovascular disorder in pregnancy**

- **It needs more studies for etiologies and pathophysiologies to understand preeclampsia**

- **Proteomic & Genomic analysis**
  - will give a chance to clarify pathophysiologic mechanisms of preeclampsia

  – will give a change to identify diagnostic or prognostic markers for preeclampsia.

경청해 주셔서 감사합니다.