Hypertensive disorders of pregnancy and CKD

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OUTLINE

- Definition of hypertensive disorders of pregnancy
- Pre-eclampsia and kidney injury: villain or bystander ?
- Risk factors and co-morbidities
- ***CKD*** as a risk factor for hypertensive disorders of pregnancy
- ***Pre-eclamptic syndromes*** as a risk factor for CKD

- *> 20th week of gestation*
- *new onset Hypertension*

Systolic BP ≥ 140 mmHg

and/or *x2 (>4h)*

Diastolic BP ≥ 90 mmHg

Gestational Hypertension

ACOG Practice Bulletin No. 222

Obstet Gynecol. 2020;135(1):e237

PRE-ECLAMPSIA

- *> 20th week of gestation*
- *new onset Hypertension*

Systolic BP ≥ 140 mmHg

and/or *x2 (>4h)*

Diastolic BP ≥ 90 mmHg

Gestational Hypertension

+

- ***Proteinuria***

10% - 20% without proteinuria !

OR ??...

ACOG Practice Bulletin No. 222

Obstet Gynecol. 2020;135(1):e237

Alternative definition/ 'Atypical' Pre-eclampsia

(no proteinuria / OR ??)

- *(... > 20th week of gestation)*

- ***Newly diagnosed Hypertension***

+

OR ??...

Other maternal end-organ dysfunction

- ***Low platelets*** *(<100.000)*
- ***Impaired Liver function*** *(transaminases > x2)*
- ***Renal insufficiency (Cr >1,1 mg/dl)***
- ***Pulmonary edema***
- ***CNS*** *(visual disturbances/severe headache)*

OR ??...

Uteroplacental dysfunction

ACOG Practice Bulletin No. 222

Obstet Gynecol. 2020;135(1):e237

Hypertensive disorders of pregnancy and CKD:

Villain or bystander ?

Pre eclamptic syndromes and kidney injury mechanisms

1. ***Specific*** *Injury : the* ***pathophysiology of pre eclampsia per se*** ?

or

2. ***Underlying disease ?:*** → ***kidney injury***

   i. ***other****, subclinical, chronic* ***renal disease*** *that flares and accelerates during pregnancy (eg glomerulonephritis) ?*

   ii. ***Common risk factors*** *with* ***other chronic diseases*** *that are* ***associated with renal injury*** *?*

Pre eclamptic syndromes and kidney injury mechanisms

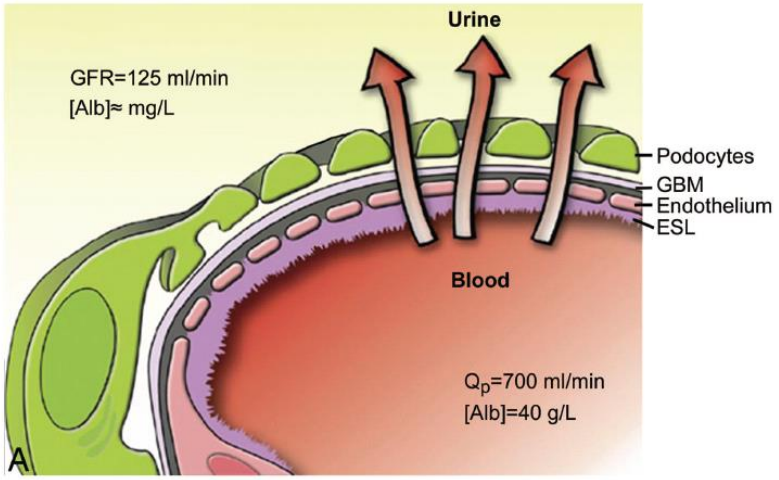
1. ***Specific*** *Injury : the* ***pathophysiology of pre eclampsia per se*** ?

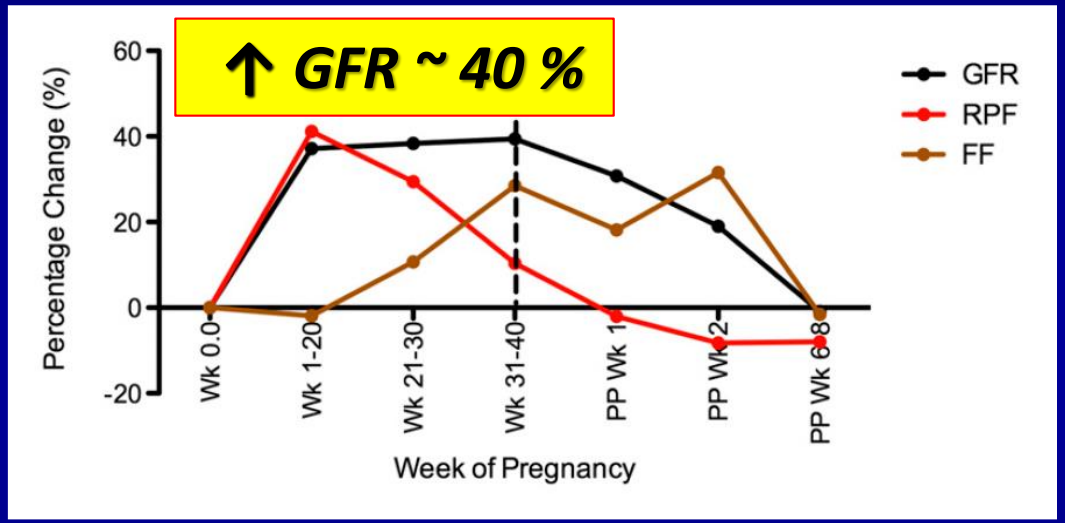
kidney injury

NORMAL ALTERATIONS of kidney function in normal pregnancy

STRESS test !!

Normal Pregnancy : ↑ Qp (GFR)

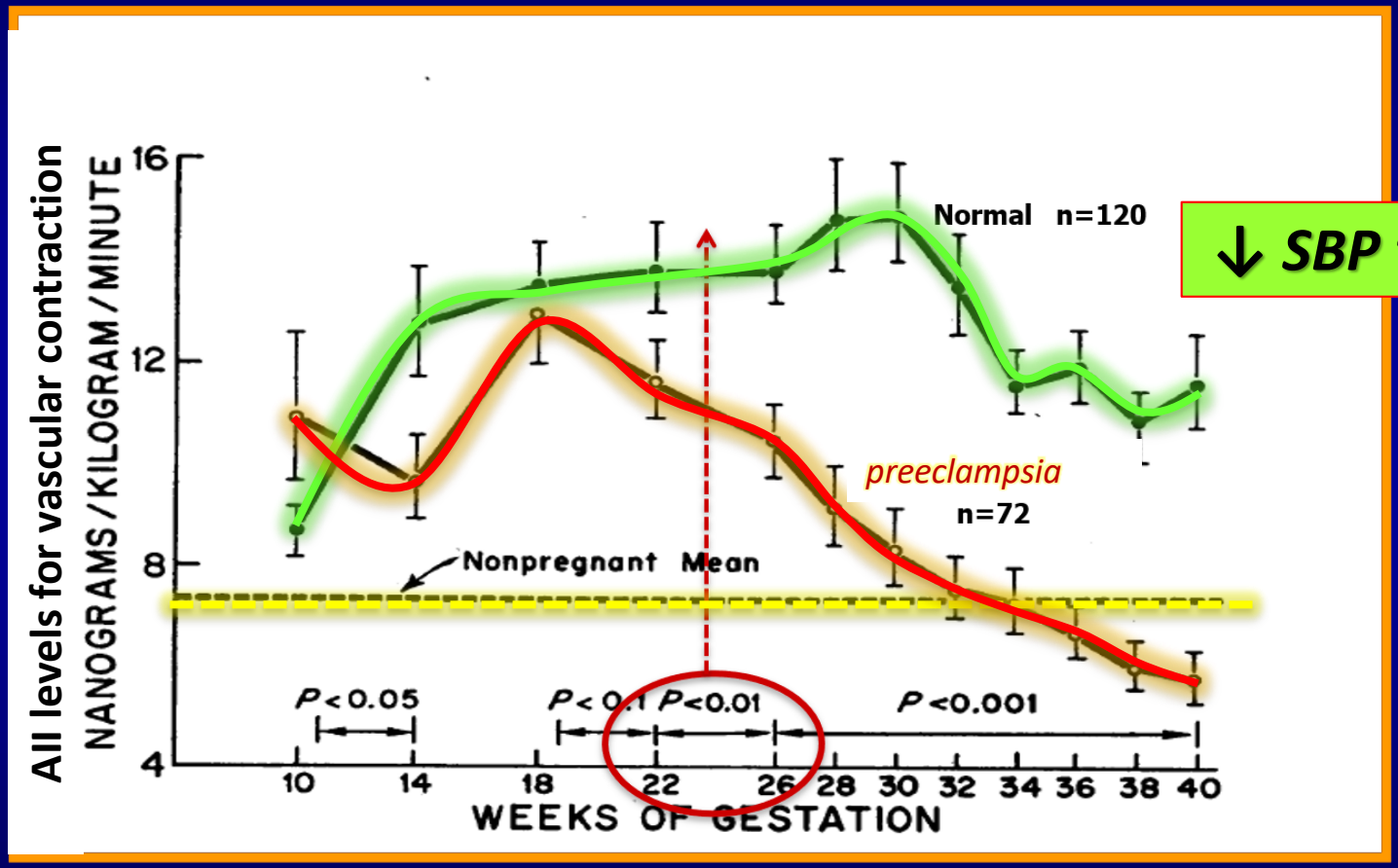




Lindheimer MD and Kanter D
Odutayo A and Hladunevich M

Obstet Gynecol 2010;115:365–75
Clin J Am Soc Nephrol 2012;7: 2073–80

The *normal decrease of BP* in pregnany is associated with a *diminished responsiveness to angiotensin II*



↓ SBP ~ 17 mmHg

Gant NF et al

J Clin Invest 52: 2682, 1973

Pre-eclampsia and glomerular filtration *compared to normal pregnancy*

	GFR (ml/min)	RPF (ml/min)	FF (%)	MAP (mmHg)	U_{Na} (μmol/min)	UAE median (interquartile range) μg/min
Normal LP	158 ± 15	849 ± 50	18.6 ± 1.1	86 ± 3	0.172	6.1 (4.4 to 10.6)
Preeclamptic LP	105 ± 6[c]	781 ± 38[ns]	13.5 ± 1.0[b]	111 ± 1[d]	0.218 ± 0.038[ns]	1817 (1128 to 3455)[d]

Ultrafiltration and decrease of BP in normal pregnancy !!

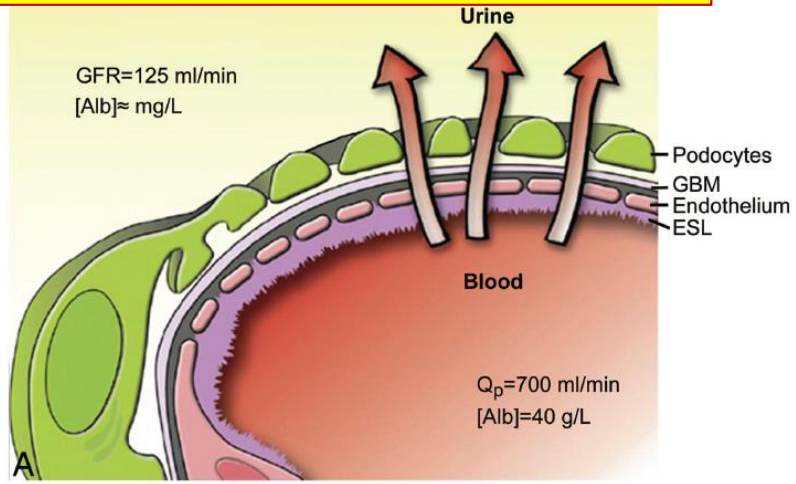
Hypertension and proteinuria in Pre eclampsia !!

Moran P et al

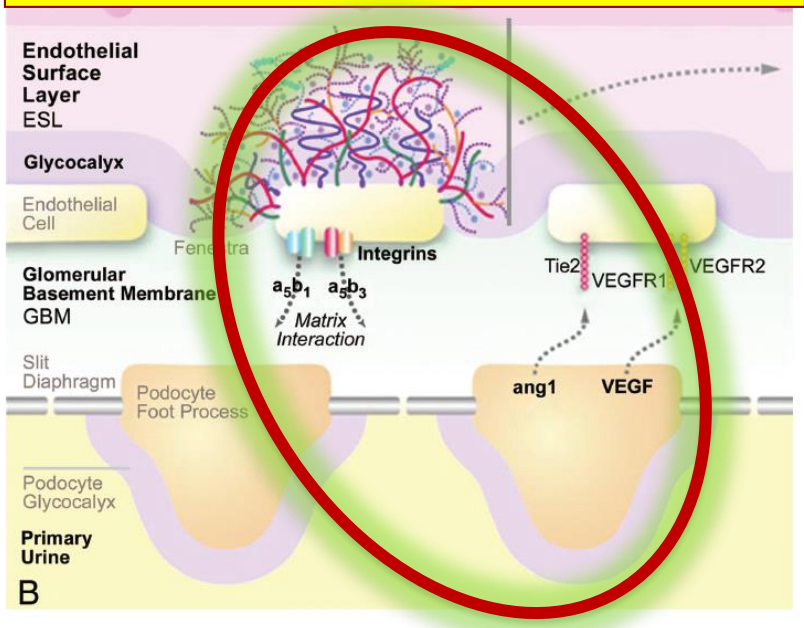
J Am Soc Nephrol 14: 648–652, 2003

Pre-eclampsia and Proteinuria

GFR
Normal Pregnancy > Pre eclampsia



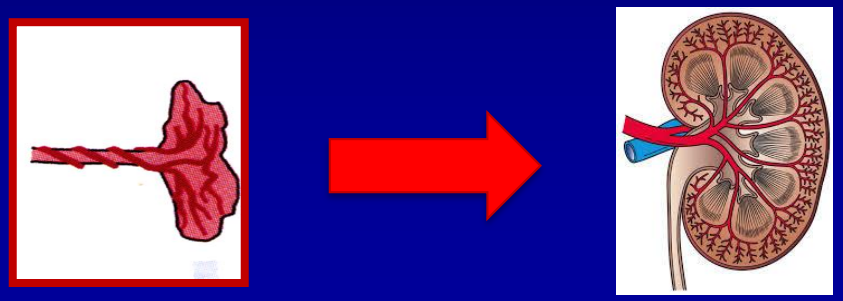
Pre eclampsia: Proteinuria



Lindheimer MD and Kanter D

Obstet Gynecol 2010;115:365–75

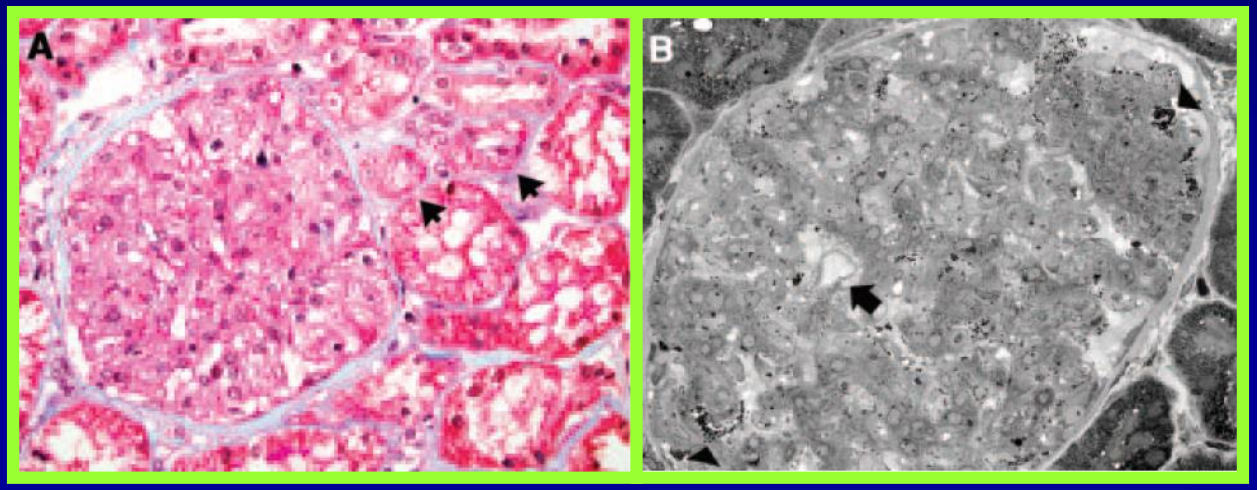
Specific ? pathogenetic mechanisms of kidney injury in pre eclamptic syndromes

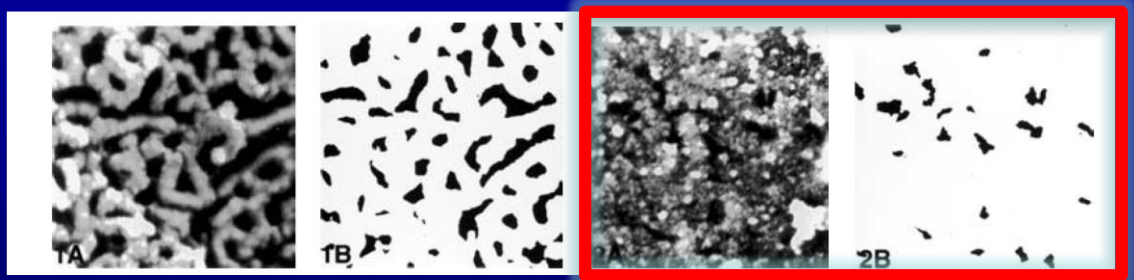


1. *Endothelium* ?
2. *Podocytes*

Specific histologic kidney lesion in pre eclampsia ?

'Glomerular Endotheliosis'





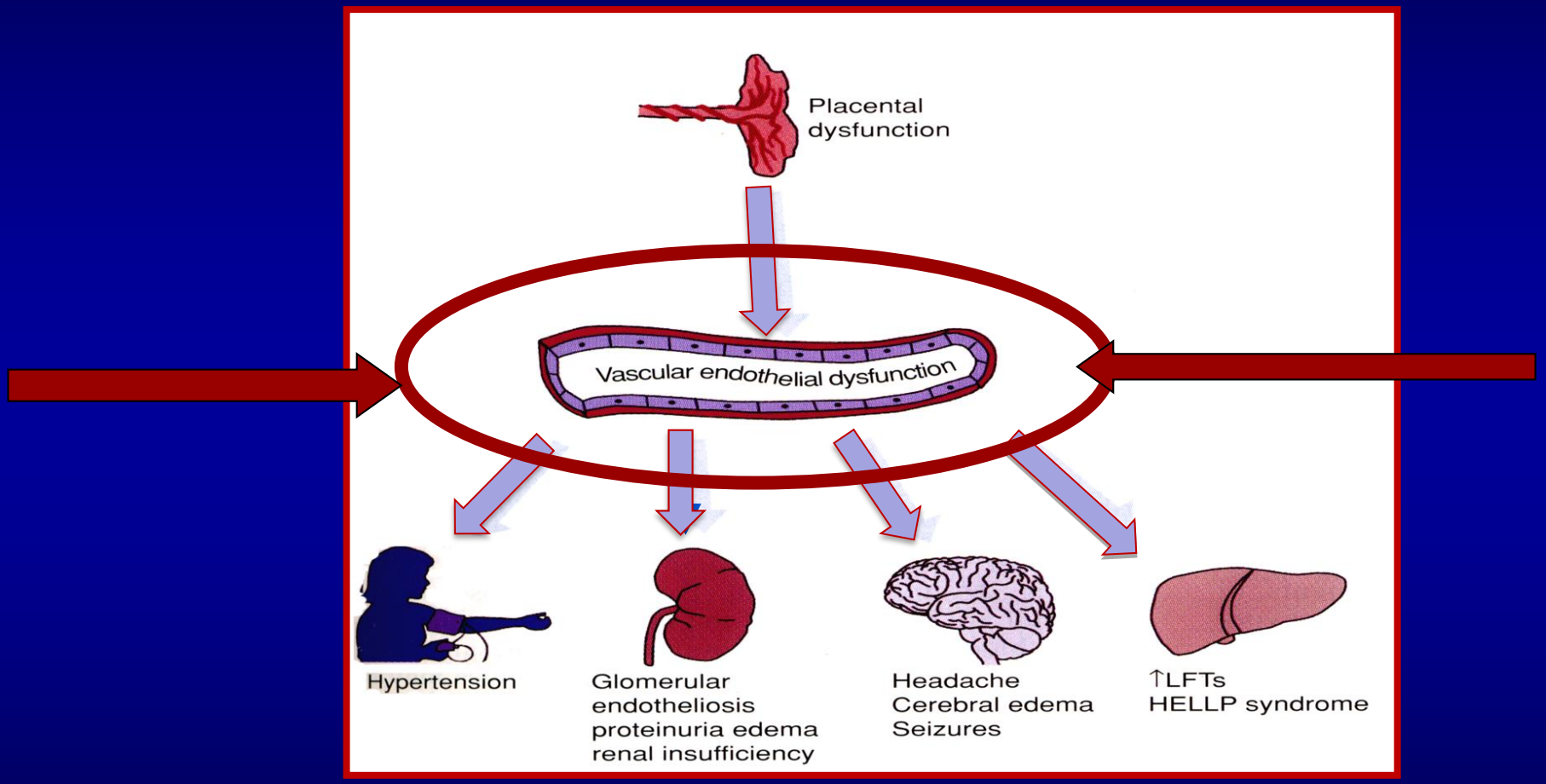
Loss of endothelial fenestrations (EM)

Lafayette R
Stillman IE and Karumanchi A

Kidney Int, 67 (2005), pp. 1194–1203
J Am Soc Nephrol 18: 2281–2284, 2007

Anti angiogenetic factors from the ischemic placenta:

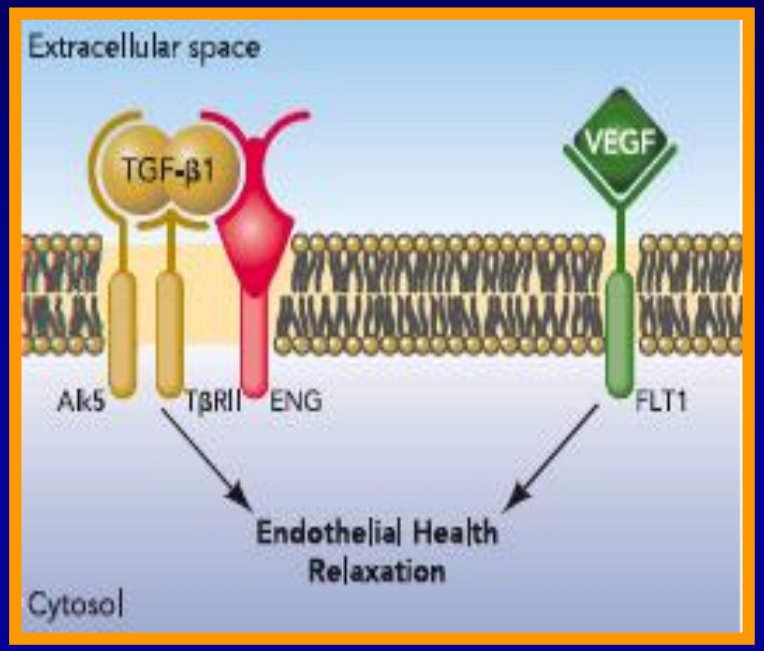
maternal endothelial dysfunction

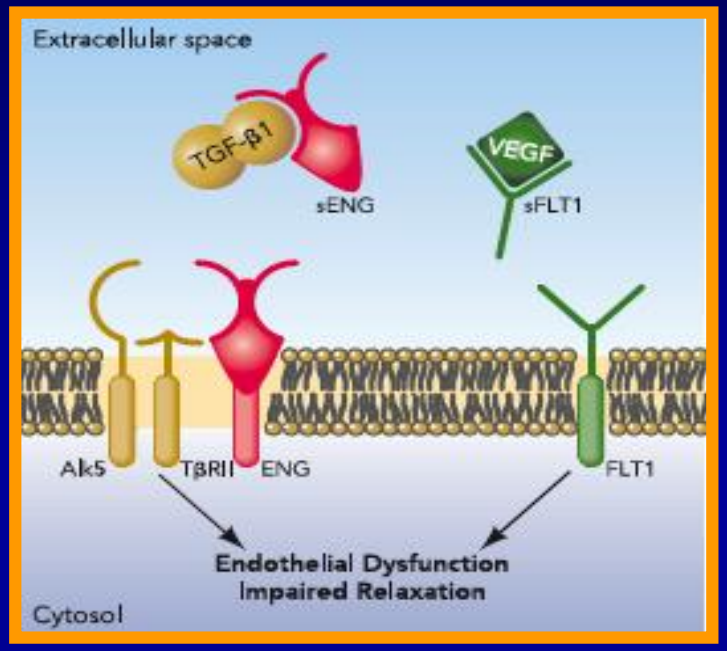


Karumanchi SA et al.

Kidney Int 67: 2101, 2005

Anti angiogenetic factors (soluble receptors) and endothelium *(sFLTs , sENG)*





The soluble forms (sFLT, sENG) **of the receptors** ***that are released from the ischemic placenta,***

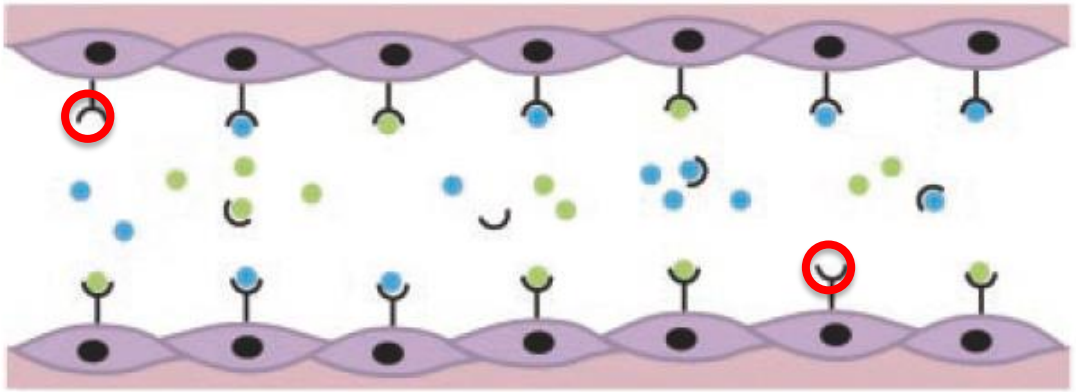
act as antagonists

preventing the adherence of **VEGF, TGFβ1 and PlGF** ***to the endothelial*** **receptors**

Wang A et al. **Physiology 24: 147, 2009**

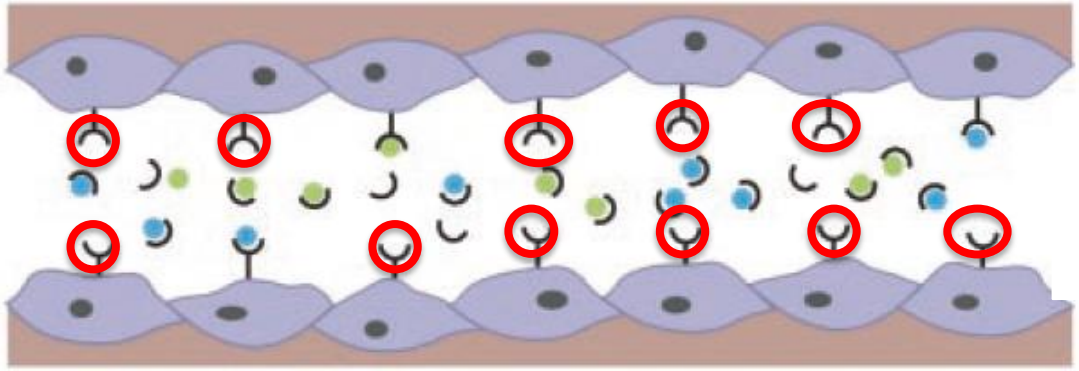
Anti angiogenetic factors (soluble receptors) and endothelium *(sFLTs , sENG)*

NORMAL PREGNANCY



normal
vasodilation

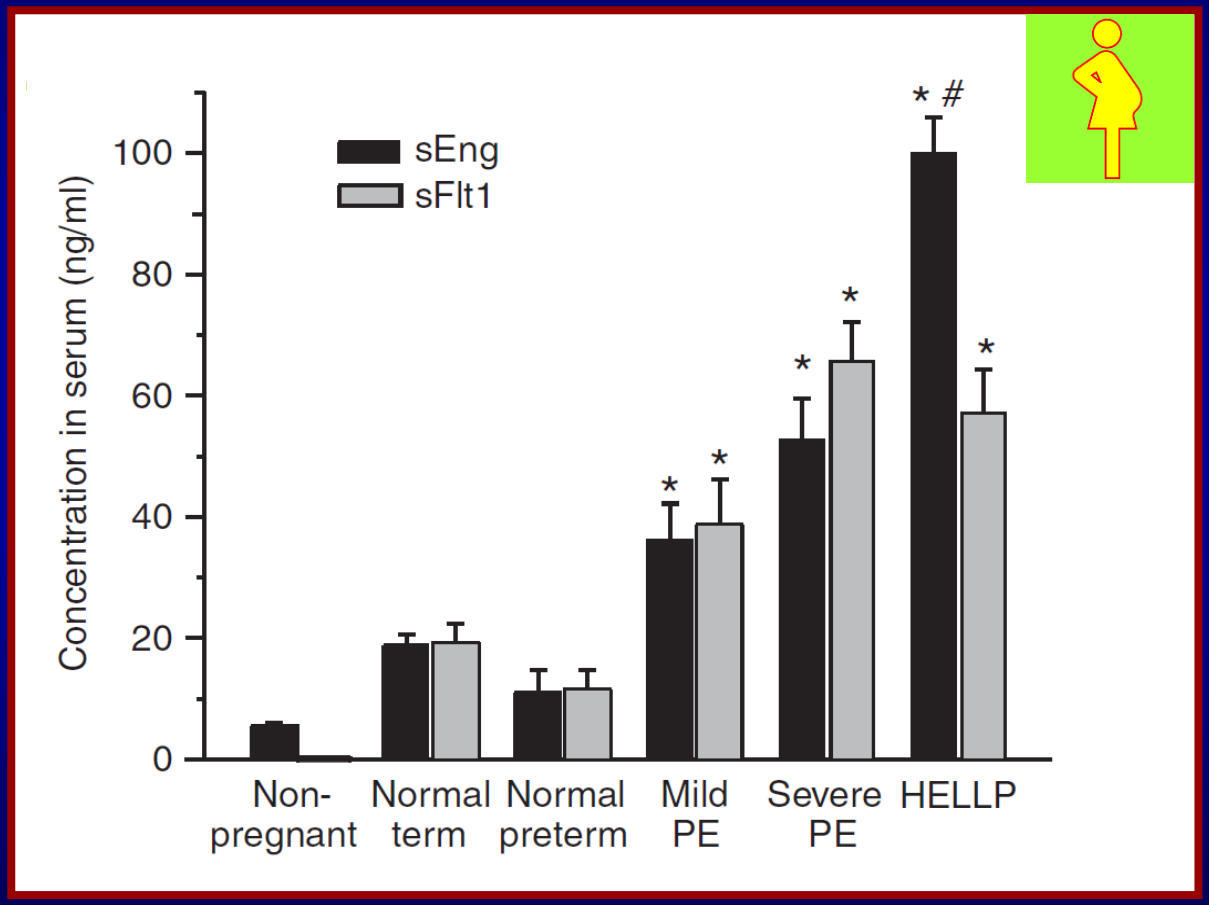
PRE ECLAMPSIA



Davison JM et al.
J Am Soc Nephrol
15: 2440, 2004

Anti-angiogenetic factors *(sFLTs , sENG)* and Preeclamptic syndromes

Levels rise proportionally to the severity of the preeclamptic disorder



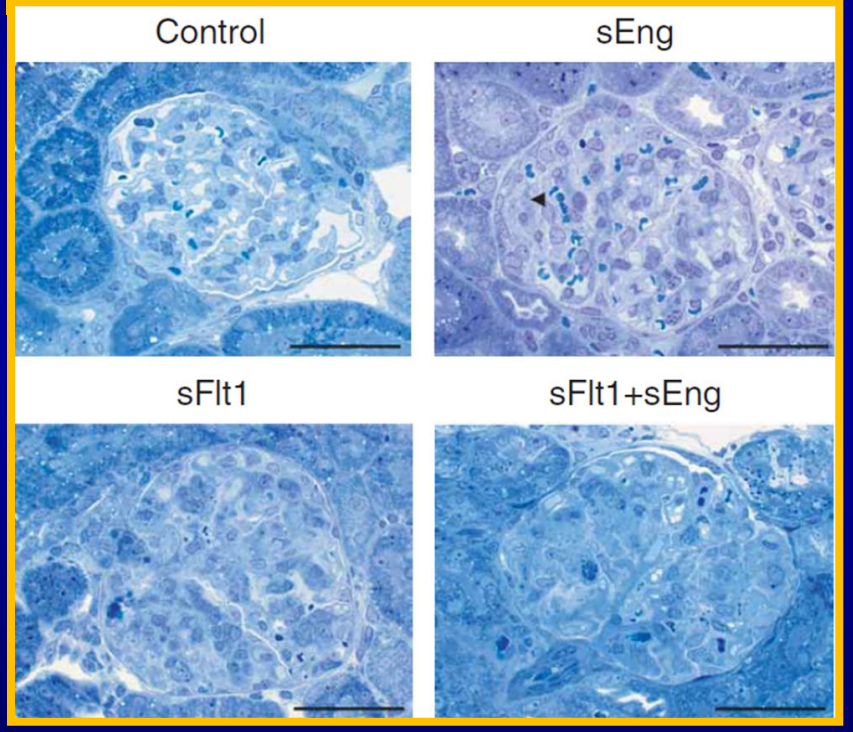
Venkatesha S et al.

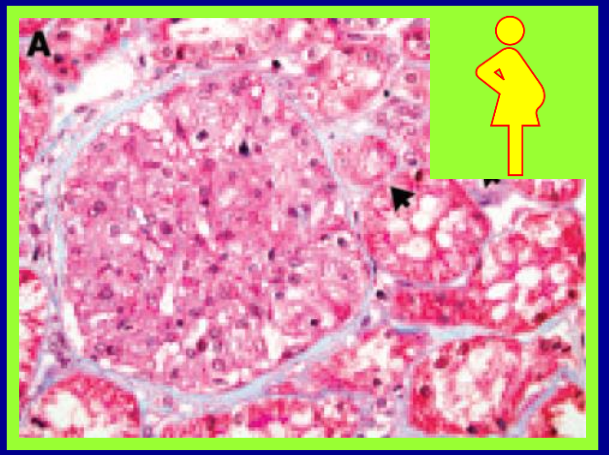
Nature Medicine 12: 642, 2006

Anti-angiogenetic factors (*sFLTs , sENG*) and Preeclamptic syndromes

confirmatory Experimental models !

sFlt-1 and sEng : experimental Glomerular Endotheliosis





Venkatesha S et al.

Nature Medicine 12: 642, 2006

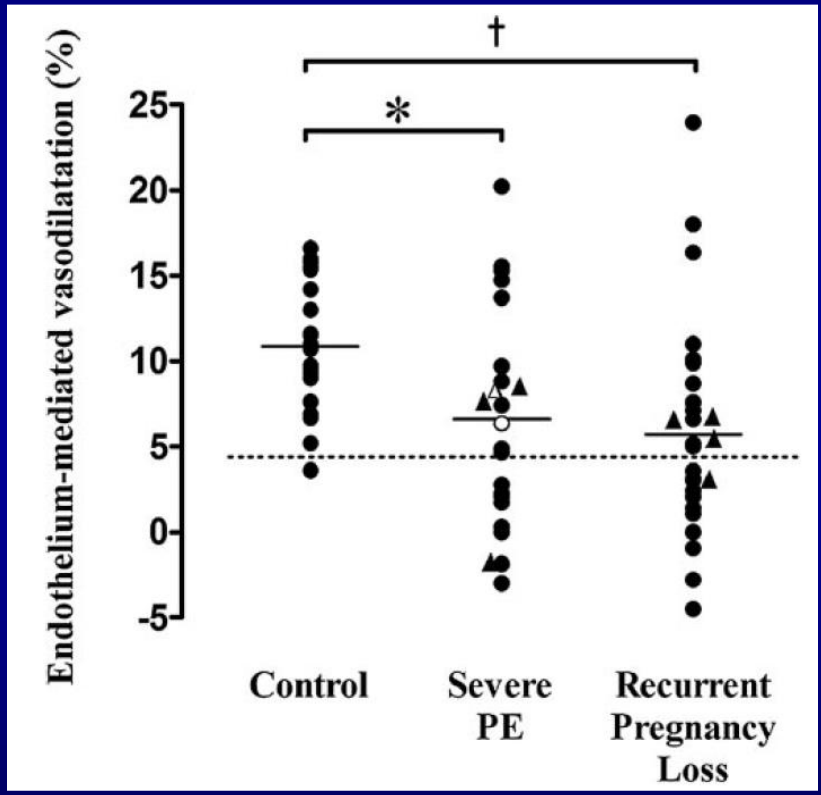
Late endothelial dysfunction post Pre-eclampsia

... even after 1 year !

Endothelial Dysfunction

A Link Among Preeclampsia, Recurrent Pregnancy Loss, and Future Cardiovascular Events?

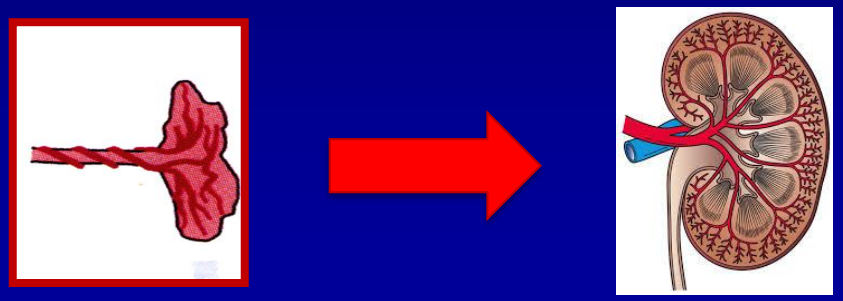
Characteristics	Control (n=22)	Severe Preeclampsia (n=25)*	Recurrent Pregnancy Loss (n=29)
Age, y	32±1.1	31.4±1.2	33.9±0.8
Body mass index, kg/m²	23.6±0.5	24.5±0.9	23.5±0.6
Maternal birth weight, g	3086±78	2941±154	3314±138
Interval from last delivery, months	27±6.9	16±3.5	11±2.2



Germain et al

Hypertension. 2007;49:90-95

Specific ? pathogenetic mechanisms of kidney injury in pre eclamptic syndromes



1. *Endothelium* ✓
2. *Podocutes* ?

Specific histologic kidney injury in pre-eclampsia: *Autopsy*

Histologic Parameter	PE (n=11)	PC (n=25)	HC (n=14)	NPC (n=13)	P Value
Acute tubular necrosis	0 (0)	4 (16)	3 (21)	3 (23)	0.41
Congestion	0 (0)	0 (0)	0 (0)	3 (23)	0.01
Endotheliosis	6 (55)	3 (12)	2 (14)	0 (0)	0.003
<20% of the lumen	1 (17)	3 (100)	1 (50)	NA	
20%–80% of the lumen	3 (50)	0	1 (50)	NA	
>80% of the lumen	2 (33)	0	0	NA	
FSGS	1 (9)	2 (8)	5 (36)	0 (0)	0.03
Global sclerosis>1%	1 (9)	0 (0)	5 (36)	1 (8)	0.04
Glomerulitis	0 (0)	6 (24)	1 (7)	2 (15)	0.23
Hyalinosis	1 (9)	4 (16)	7 (50)	10 (77)	<0.001
Interstitial fibrosis tubular atrophy	0 (0)	0 (0)	2 (14)	0 (0)	0.06
Intima fibrosis	2 (18)	7 (28)	11 (79)	5 (39)	0.01
Ischemia	0 (0)	1 (4)	3 (21)	1 (8)	0.17
Mesangium changes	1 (9)	0 (0)	4 (29)	1 (8)	0.04
Microthrombi	1 (9)	0 (0)	1 (7)	0 (0)	0.20
Edema	1 (9)	0 (0)	0 (0)	1 (8)	0.34
Podocyte changes	2 (18)	0 (0)	0 (0)	0 (0)	0.02
Tram tracking	4 (36)	0 (0)	0 (0)	0 (0)	<0.001

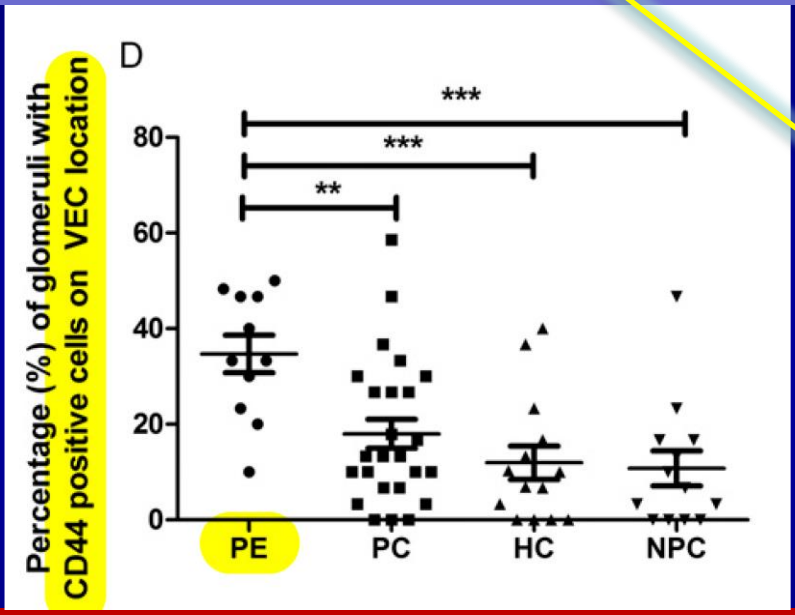
Podocyte changes and Tram tracking are more specific than endotheliosis !

Penning ME et al

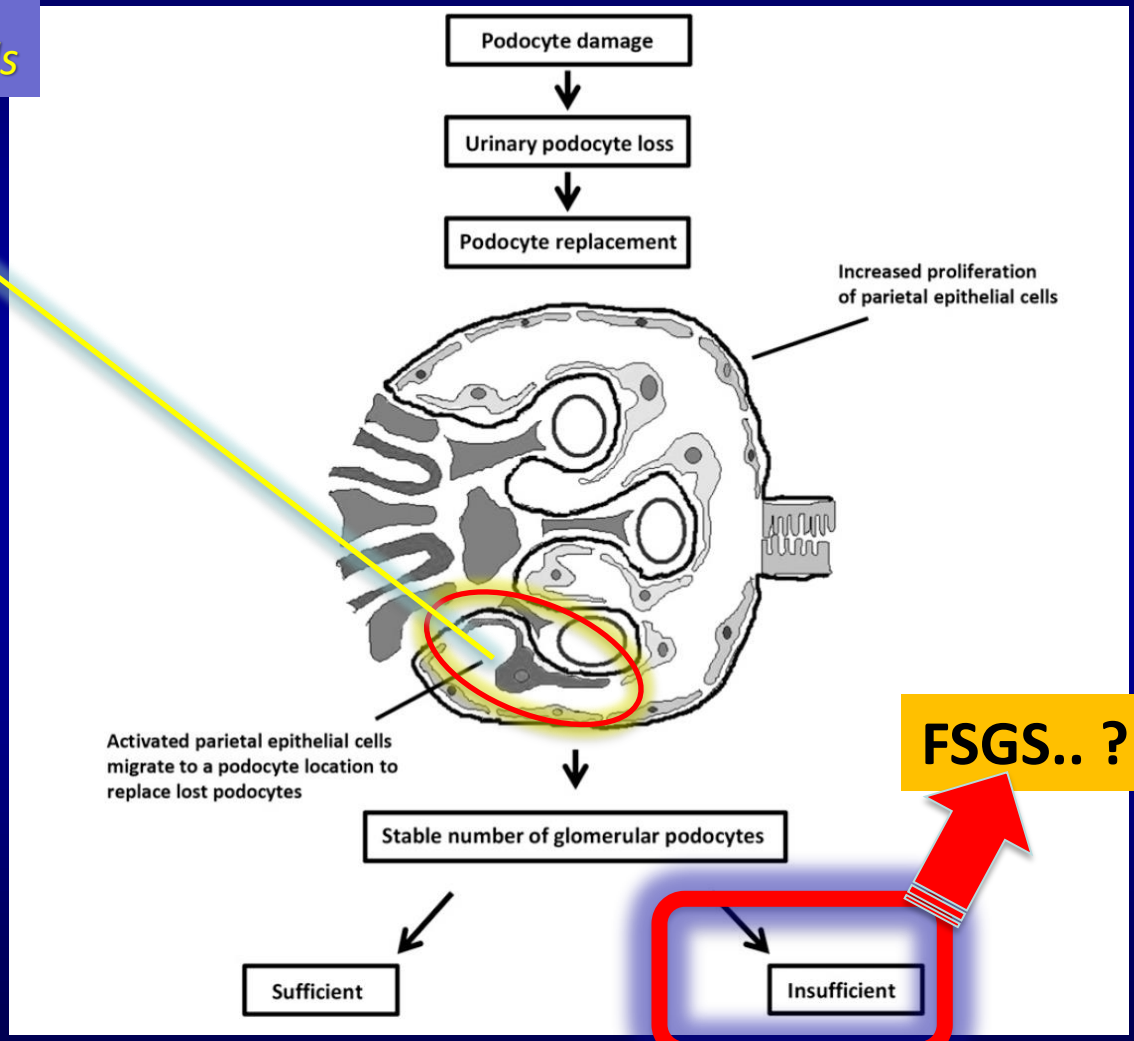
Clin J Am Soc Nephrol 9: 1377–1385, 2014

Histologic findings of *Podocyte injury and loss* in Pre-eclampsia*: Autopsy*

↑ *Replacement of lost original podocytes from migrating / differentiating parietal epithelial cells*



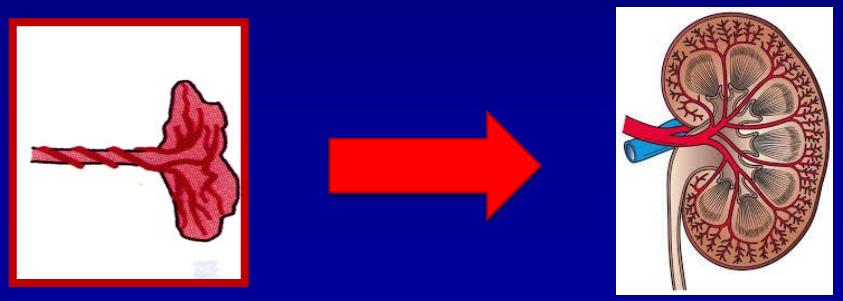
Higher % of glomeruli with CD44 positive cells on vascular endothelial cell location in Pre eclampsia



Penning ME et al

Clin J Am Soc Nephrol 9: 1377–1385, 2014

Specific ? pathogenetic mechanisms of kidney injury in pre eclamptic syndromes



1. *Endothelium* ✓
2. *Podocutes* ✓

Specific histologic kidney lesion in pre eclampsia ?

BIOPSIES ??

Hypertension in Pregnancy: Clinical-Pathological Correlations and Remote Prognosis[1]

KENNETH A. FISHER,[2] ALLEN LUGER,[3] BENJAMIN H. SPARGO AND MARSHALL D. LINDHEIMER

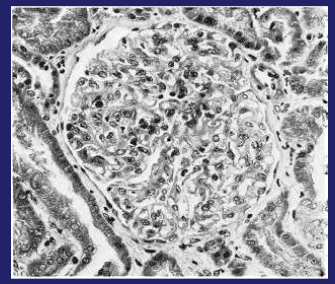
TABLE 1. Renal Pathology in 176 hypertensive pregnant patients

Diagnosis	#	Primigravidas	Multiparas
Preeclampsia*	96	79	17
with nephrosclerosis	13	6	7
with renal disease	3	1	2
with both	2	1	1
Nephrosclerosis	19	3	16
with renal disease	4	2	2
Renal disease	31	12	19
Normal histology	8	0	8
Total	176	104	72

* Only glomerular endotheliosis on biopsy.

Clinical Diagnosis of preeclampsia

Typical/ specific histology glomerular endotheliosis



Primigravidas : ~ 84%

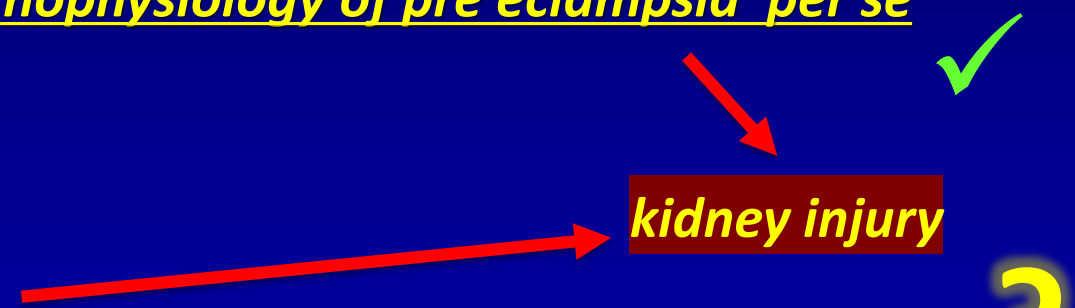
MULTIPARAS : only 38%!!

Fisher KA

MEDICINE 1981;60(4):267-276

Pre eclamptic syndromes and kidney injury mechanisms

1. ***Specific*** *Injury : the* ***pathophysiology of pre eclampsia per se***



2. ***Underlying disease ?:***

    i. ***other****, subclinical, chronic* ***renal disease*** *that flares and accelerates during pregnancy (eg glomerulonephritis) ?*

Histological Differential diagnosis of kidney diseases timely related to pregnancy

RENAL BIOPSIES *during pregnancy or within 1 year postpartum*

A Multicenter Cohort Study of Histologic Findings and Long-Term Outcomes of Kidney Disease in Women Who Have Been Pregnant

Pregnancy-Related Group (n = 173)
- Antenatal biopsies (n=19)
- Post-pregnancy biopsies (n = 154) (women biopsied due to abnormal urinalysis or serum creatinine identified during pregnancy, or within one year postpartum)

VS

Control Group (n = 1226)
- Biopsy performed to investigate abnormal urinalysis or serum creatinine NOT identified during pregnancy or within one year postpartum

Webster et al

CJASN 2016 doi:10.2215/CJN.05610516

Histological Differential diagnosis of kidney diseases timely related to pregnancy

RENAL BIOPSIES *during pregnancy or within 1 year postpartum*

High percentage of *underlying* kidney diseases …*and* … *FSGS*

Variables	Controls	Pregnancy-Related (Antenatal and Postpregnancy)	*P* Value[a]
N	1000	172	
FSGS, *N* (%)	97 (9.7)	56 (32.4)	<0.001
Lupus, *N* (%)	235 (23.5)	24 (13.9)	0.01
IgA, *N* (%)	147 (14.7)	25 (14.5)	0.93
Interstitial nephritis, *N* (%)	62 (6.2)	8 (4.6)	
Membranous, *N* (%)	53 (5.3)	9 (5.2)	
Minimal change, *N* (%)	50 (5.0)	5 (2.9)	
Thin membrane, *N* (%)	30 (3.0)	9 (5.2)	0.14
DM, *N* (%)	35 (3.5)	1 (0.6)	0.04
Crescentic, *N* (%)	14 (1.4)	0 (0.0)	0.12
FSGS (HIV), *N* (%)	6 (0.6)	1 (0.6)	0.97
Other, *N* (%)	271 (27.1)	35 (20.2)	0.06

PE?

80% other, underlying glomerular diseases

Webster et al

CJASN 2016 doi:10.2215/CJN.05610516

Histological Differential diagnosis of kidney diseases timely related to pregnancy

RENAL BIOPSIES *during pregnancy or within 1 year postpartum*

faster GFR loss/ acceleration of underlying kidney disease during pregnancy

clinically presented/diagnosed as preeclampsia !?

Table 4. Follow-up of women of childbearing age—all diagnoses

Variables	Controls	Pregnancy-Related (Antenatal and Postpregnancy)	P Value	Antenatal	Postpregnancy
N =	459	101		14	87
Median follow-up time months (IQR)	44.3 (20.1–77.2)	42.8 (17.4–70.9)	0.48[a]	40.8 (24.2–75.6)	43.3 (17.0–70.8)
Median rate of change in CKD-EPI GFR ml/min per 1.73 m^2 per yr (IQR)	−0.56 (−4.26–3.22)	−2.43 (−8.16–0.18)		−7.36 (−[illegible])	−1.33 (−6.97–0.94)

compared to controls with the same glomerular disease unrelated to pregnancy

During pregnancy compared to those biopsied after pregnancy

Webster et al

CJASN 2016 doi:10.2215/CJN.05610516

Pre eclamptic syndromes and kidney injury mechanisms

1. ***Specific*** *Injury : the* ***pathophysiology of pre eclampsia per se*** ✓

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2. ***Underlying disease ?:*** → ***kidney injury***

   i. ***other****, subclinical,* ***chronic renal disease*** *that flares and accelerates during pregnancy (eg glomerulonephritis) ?* ✓

   ii. ***Common risk factors*** *with* ***other chronic diseases*** *that are* ***associated with renal injury*** *?* ?

Risk factors for development of pre-eclampsia include …

maternal cardiovascular co-morbidities !!

Cardiovascular risk factors

- **BMI > 35 kg/m^2**
- **Diabetes Mellitus** (preceding and/or during gestation)
- **Chronic Hypertension**
- **CKD/ Lower GFR**

Autoimmunity Coagulation disorders

- Antiphospholipid syndrome / other coagulation disorders
- Chronic Autoimmune disease

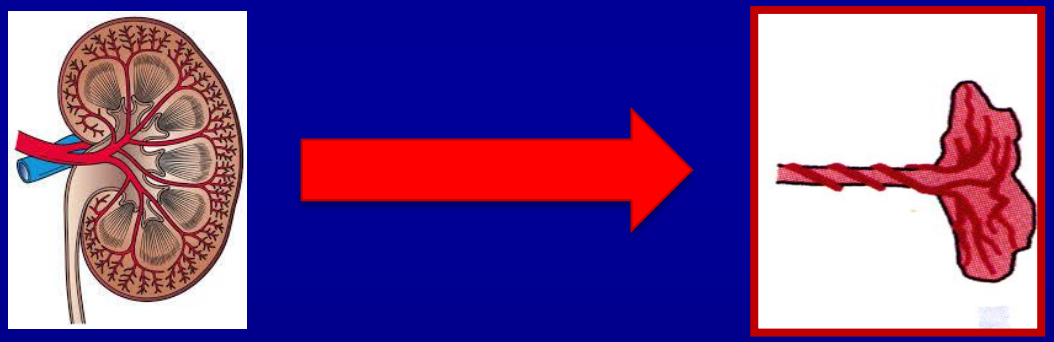
Cardiovascular risk factors and Pre eclampsia

*The incidence of preeclamptic disorders is **3-5 times higher** in women with Hypertension , Diabetes or Renal Disease*

The list of *risk factors that are associated with hypertensive disorders of pregnancy* … is almost identical to the list of ***risk factors for cardiovascular disease and CKD …***

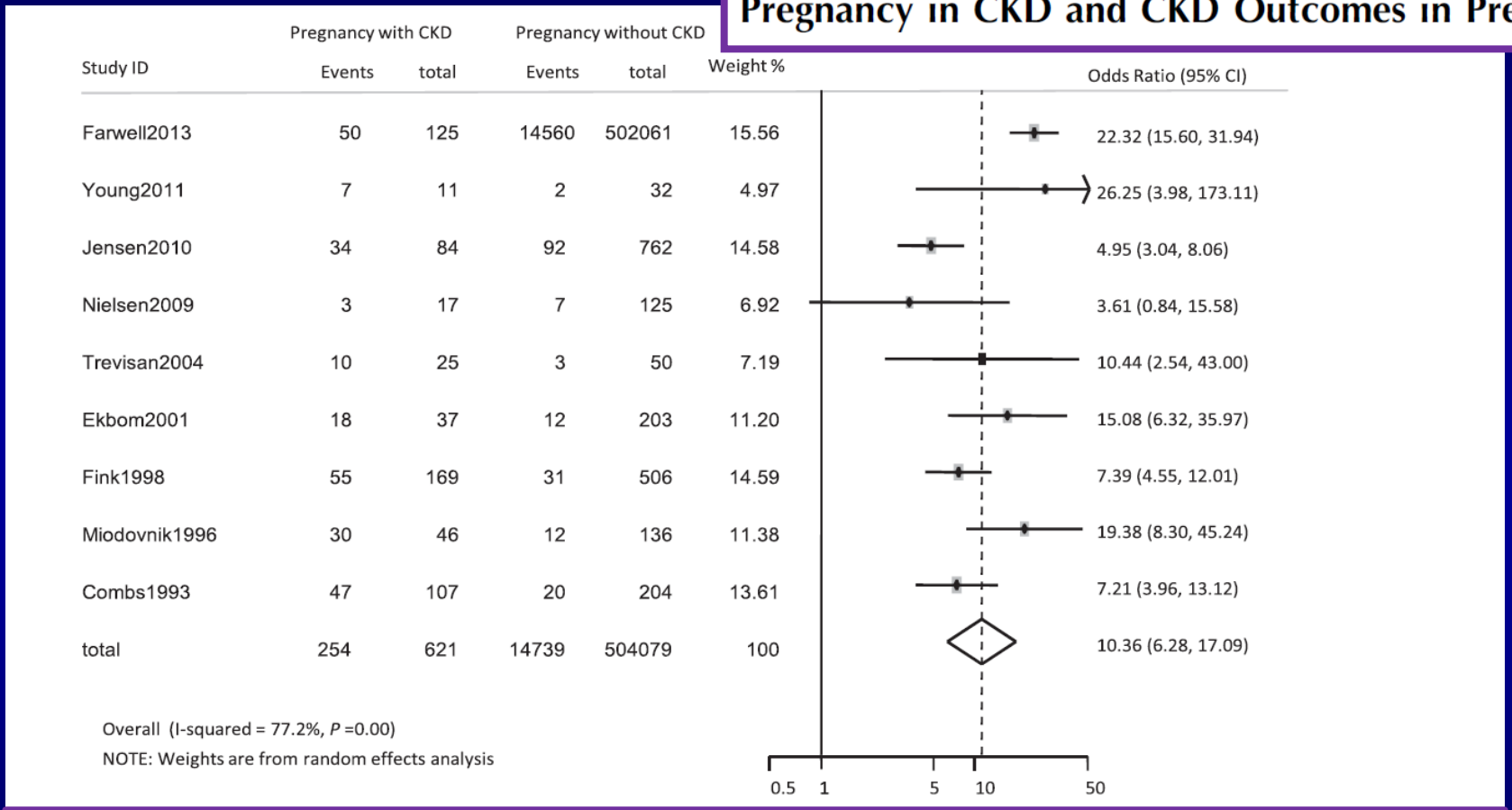
Bystander ? association of hypertensive disorders of pregnancy and CKD ?

CKD as a risk factor for hypertensive disorders of pregnancy



CKD as a risk factor for Pre eclampsia

A Systematic Review and Meta-Analysis of Outcomes of Pregnancy in CKD and CKD Outcomes in Pregnancy



Women with CKD have ~ 10 times higher odds ratio for pre-eclampsia

Zhang J J et al

Clin J Am Soc Nephrol 10: 1964–1978, 2015

CKD as a risk factor for hypertensive disorders of pregnancy

Pre-Pregnancy eGFR and the Risk of Adverse Maternal and Fetal Outcomes: A Population-Based Study

Adverse Outcomes	eGFR ≥90	eGFR 60 to <90	eGFR 45 to <60	eGFR <45
Pregnancies, *N* (%)	522, 752 (92.4)	42, 543 (7.5)	479 (0.08)	133 (0.02)
Gestational hypertension	24,706 (4.7)	2494 (5.9)	50 (10.4)[b]	24 (18.0)[b]
Preeclampsia	31,215 (6.0)	3232 (7.6)	72 (15.0)[b]	33 (24.8)[b]

The risk is higher as the GFR gets lower!!

Tangren J et al

J Am Soc Nephrol. 2023 Apr 1;34(4):656-667

CKD as a risk factor for hypertensive disorders of pregnancy

The risk rises additively and proportionally to the level of proteinuria

eGFR (ml/min/1.73m^2)	Proteinuria category	Additive Interaction[2]	
		Relative excess risk due to interaction[1,3] (Odds Ratio)	95% CI[4]
45 to <60	Moderate	-0.73	-3.41 to 1.95
45 to <60	Severe	10.10	2.20 to 18.00

... And even more so, when GFR <45 ml/min

Tangren J et al

J Am Soc Nephrol. 2023 Apr 1;34(4):656-667

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1. ***Specific*** *Injury : the* ***pathophysiology of pre eclampsia per se*** ✓

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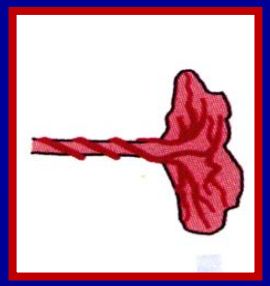
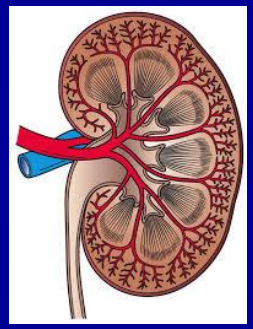
   i. ***other****, subclinical****, chronic renal disease*** *that flares and accelerates during pregnancy (eg glomerulonephritis) ?* ✓

   ii. ***Common risk factors*** *with* ***other chronic diseases*** *that are* ***associated with renal injury*** *?* ✓

Hypertensive disorders of pregnancy as a risk factor for CKD





- *Proteinuria*
- *GFR*
- *ESRD/Dialysis*

Residual morbidity after pre eclampsia ?

Usually quick Remission …

- **vasoconstriction and endothelial dysfunction** within **a few days**
- **hypertension and proteinuria** within **2 to 6 weeks**
- **glomerular endotheliosis** within **8 weeks**

However … LATE residual morbidity!!

Pre eclamptic syndromes as a risk factor for CKD

Proteinuria – *Short term* remission

ORIGINAL ARTICLE

Prevalence of chronic kidney disease after preeclampsia

Veronica Agatha Lopes van Balen[1] · Julia Jeltje Spaan[1] · Tom Cornelis[2] · Marc Erich August Spaanderman[1]

Months postpartum	>3 ACR mg/mmol n/total (%)
4–5	51/150 (25 %)
6–11	33/248 (12 %)
12–17	13/96 (12 %)
18–23	1/58 (2 %)
>24	8/117 (6 %)

Starts to rise again 24 months postpartum …

Lopes van Balen et al

J Nephrol (2017) 30:403–409

Pre eclamptic syndromes as a risk factor for CKD

Higher *late* risk for *microalbuminuria* (30-40% ***after 5 years***)

- **40%** of women **3-5 years** post pre-eclampsia (versus 0% controls)

Bar J et al *Nephrol Dial Tranplant (1999) 14: 1129–1132*

- **META-ANALYSIS *:*** ***7 studies*** *(273 PE vs 333 control)* ***7.1 years follow up***

PE history **31%** **vs** **7%** controls

4 x relative risk

McDonald SD et al *Am J Kidney Dis. 2010 Jun;55(6):1026-39*

Pre eclamptic syndromes as a risk factor for CKD

Late **microalbuminuria – non Specific ?**

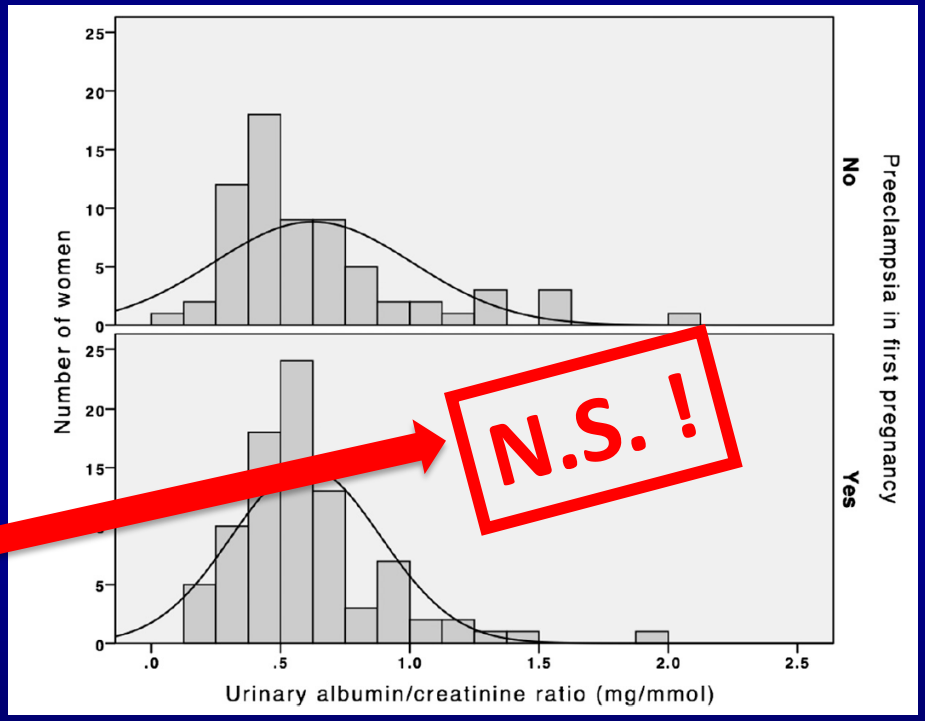
Preeclampsia and Prevalence of Microalbuminuria 10 Years Later

Medical Birth Registry Norway

89 pre eclampsia vs 69 controls

Excluding

DM, Autoimmune disease, Hypertension, Renal disease before gestation and/or history of Pre eclampsia



No difference in incidence of microalbuminuria when excluding co-morbidities!!

Sandvik et al

Clin J Am Soc Nephrol 8: 1126–1134, 2013

Preeclamptic syndromes and long term risk for CKD

Pre-eclampsia and risk of later kidney disease: nationwide cohort study

POPULATION

All women with at least one pregnancy lasting at least 20 weeks between 1978 and 2015.

The cohort consisted of 1 072 330 women followed (average 18.6 years/

230 -300 % higher hazard ratio for CKD (x 2.3-2.9)

Timing of delivery	History of PE	Person years ($\times 10^3$)	Chronic kidney disease	
			No	HR* (95% CI)
Early preterm	Yes	54.0	18	2.90 (1.70 to 4.96)
	No	449.1	53	1 (reference)
Late preterm	Yes	90.7	17	2.24 (1.33 to 3.78)
	No	1027.7	85	1 (reference)
Term	Yes	760.4	104	2.27 (1.85 to 2.78)
	No	17 612.6	1008	1 (reference)
P value for homogeneity				0.69

Kristensen et al

BMJ 2019;365:l1516

Preeclamptic syndromes and long term relative risk of CKD

Proportionally higher according to the severity of the pre eclamptic disorder

Gestational Hypertension	
ESKD	
Crude	4.37 (1.74-10.98)
Adjusted (any)	3.64 (2.34-5.66)
Adjusted for comorbidities	3.64 (2.[illegible])
CKD	
Crude	2.56 (1.09-2.22)
Adjusted (any)	1.49 (1.1[illegible])
Adjusted for comorbidities	NA
Kidney-related hospitalization	
Crude	1.04 (0.92-1.17)
Adjusted (any)	1.84 (0.60[illegible])
Adjusted for comorbidities	NA

Preeclampsia	
ESKD	
Crude	6.16 (4.42-8.57)
Adjusted (any)	4.90 (3.56-6.74)
Adjusted for comorbidities	4.90 (3.56-6.74)
CKD	
Crude	2.27 (1.48-3.49)
Adjusted (any)	2.11 (1.72-2.59)
Adjusted for comorbidities	2.27 (2.02-2.55)
Kidney-related hospitalization	
Crude	1.79 (0.71-4.51)
Adjusted (any)	2.65 (1.03-6.77)
Adjusted for comorbidities	NA

Preeclamptic syndromes and long term risk of CKD

Higher risk for <u>any type</u> of kidney disease (although different)

Hypertensive CKD	
No preeclampsia, no SGA	1.0
Preeclampsia only	3.60 (2.90–4.47)
SGA only	1.54 (1.17–2.02)
Preeclampsia and SGA	5.23 (3.51–7.79)
Diabetic CKD	
No preeclampsia, no SGA	1.0
Preeclampsia only	4.03 (3.42–4.74)
SGA only	1.05 (0.80–1.37)
Preeclampsia and SGA	3.49 (2.36–5.16)
Other/unspecified CKD	
No preeclampsia, no SGA	1.0
Preeclampsia only	1.54 (1.40–1.70)
SGA only	1.24 (1.13–1.37)
Preeclampsia and SGA	1.46 (1.15–1.84)

Tubulointerstitial CKD	
No preeclampsia, no SGA	1.0
Preeclampsia only	1.47 (1.25–1.73)
SGA only	1.30 (1.11–1.51)
Preeclampsia and SGA	1.41 (0.97–2.07)
Glomerular/proteinuric CKD	
No preeclampsia, no SGA	1.0
Preeclampsia only	2.11 (1.90–2.33)
SGA only	1.46 (1.32–1.62)
Preeclampsia and SGA	2.16 (1.71–2.71)

Hypertensive disorders of pregnancy and the risk of chronic kidney disease: A Swedish registry-based cohort study

1.924.409 women
3.726.554 births

Barrett et al

PLoS Med 2020; 17(8): e1003255

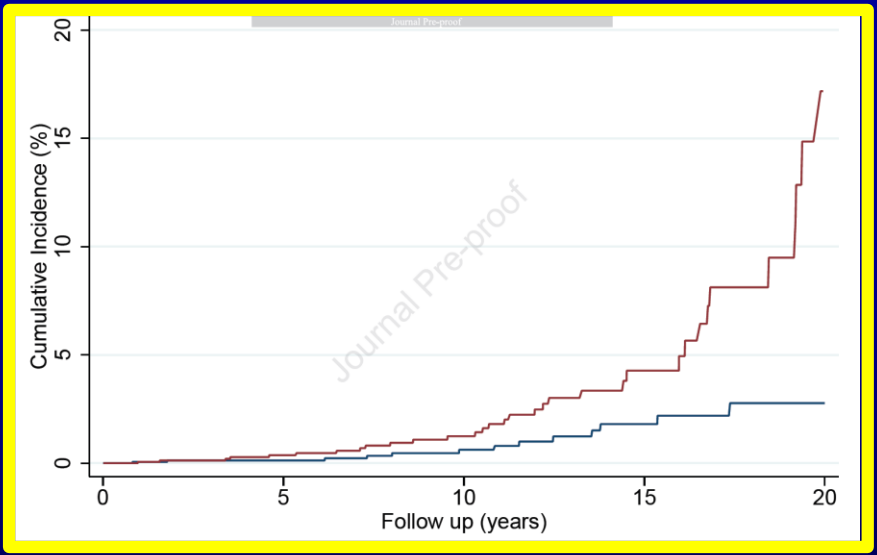
Preeclamptic syndromes and long term risk for CKD

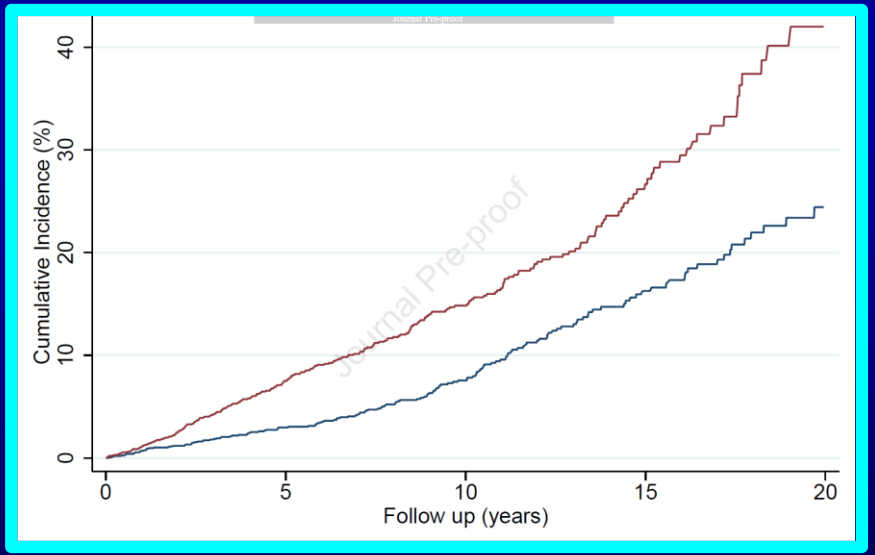
(GFR<60 ml/min or Albuminuria)

Matched cohorts
N= 2276 /group
follow up ~ 8years

Table 3. Hazard Ratios (95% Confidence Intervals) For Adverse Outcomes For Preeclampsia Cases In Matched Cohort.

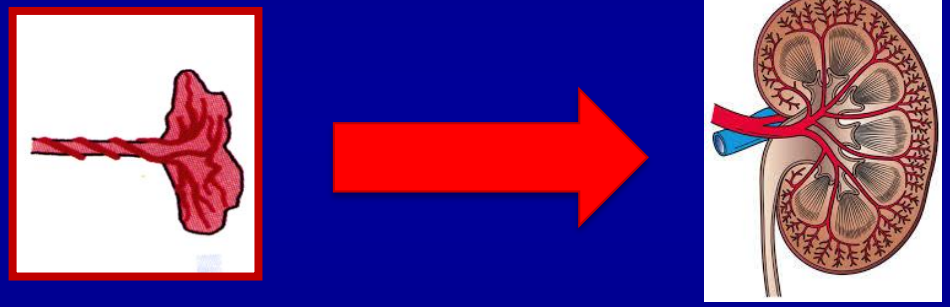
Outcome	Hazard Ratio (95% CI)	p-value
Incident Hypertension	1.77 (1.45 - 2.16)	< 0.001
Incident eGFR< 60ml/min/1.73m²	3.23 (1.64 - 6.36)	< 0.001
Incident Albuminuria	3.60 (2.38 - 5.44)	< 0.001
Preeclampsia in Subsequent Pregnancy*	24.56 (12.47-48.36)	< 0.001





Am J Kidney Dis. 2023 Jul 27:S0272-6386(23)00732-1

Hypertensive disorders of pregnancy as a risk factor for *ESRD*



- *Proteinuria*
- *GFR*
- *ESRD/Dialysis*

Preeclamptic syndromes and long term *relative* risk for *ESRD*

Relative risk x 3-5, rises according to the number of preceding pregnancies

Table 2. Preeclampsia and the Risk of End-Stage Renal Disease (ESRD) after a First, Second, or Third Pregnancy.*

~550.000 women

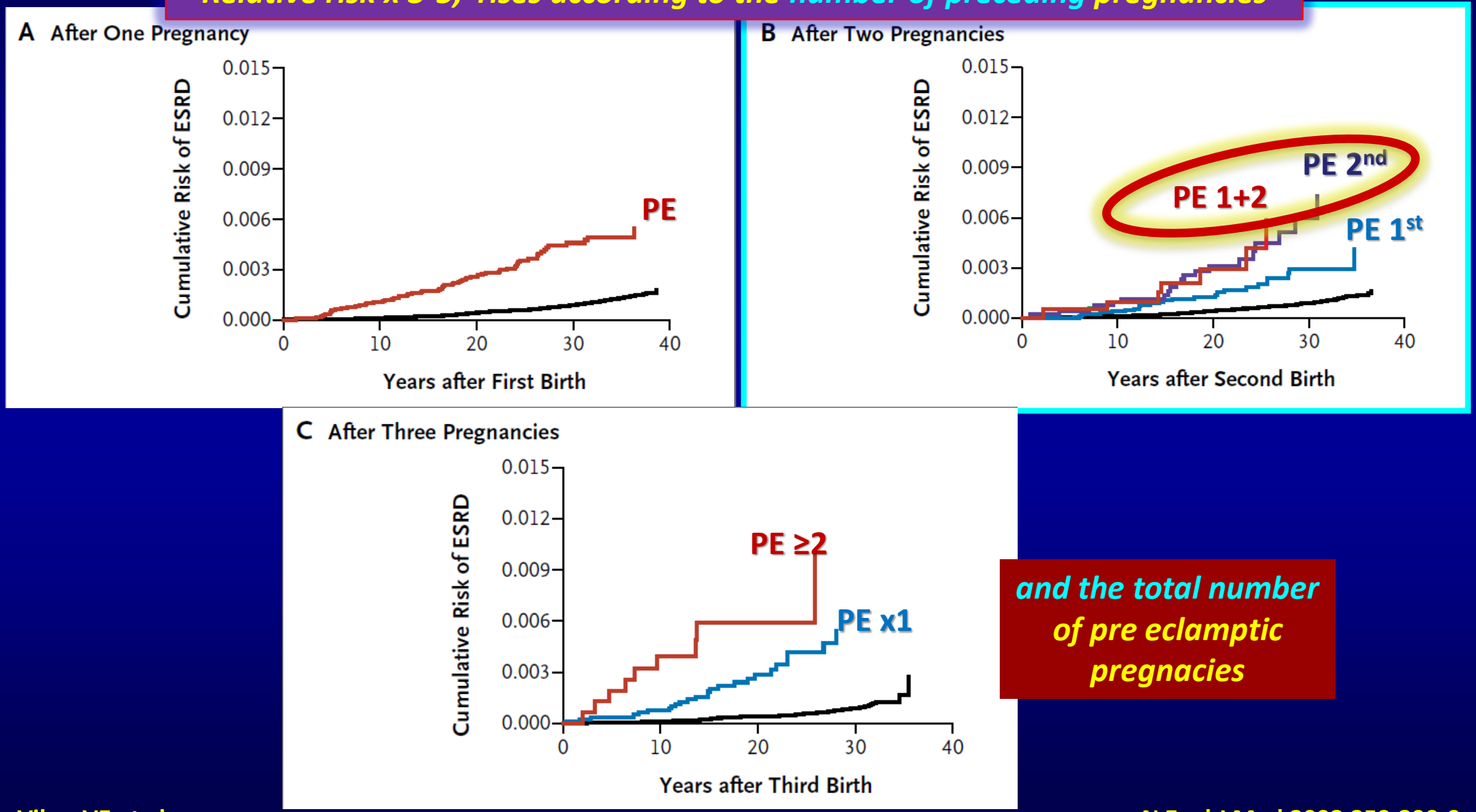
Variable	Total No. of Women	No. with ESRD	No. with Data Censored at Time of Death	No./100,000 Person-Yr (95% CI)†	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)	
						Model 1‡	Model 2§
After 1 pregnancy (all women)							
No preeclampsia	549,515	410	12,848	3.3 (2.9–3.6)	1.0	1.0	1.0
Preeclampsia	20,918	67	495	14.5 (11.2–18.1)	4.7 (3.6–6.1)	4.3 (3.3–5.6)	3.2 (2.2–4.5)
After 2 pregnancies (women with ≥2 pregnancies)							
No preeclampsia	456,884	266	9,033	2.8 (2.5–3.1)	1.0	1.0	1.0
Preeclampsia in first pregnancy only	14,588	25	255	8.6 (5.6–12.3)	3.2 (2.2–4.9)	3.1 (2.0–4.7)	2.3 (1.3–4.1)
Preeclampsia in second pregnancy only	6,120	20	124	16.8 (10.3–25.0)	6.7 (4.3–10.6)	5.3 (3.3–8.5)	4.7 (2.5–9.0)
Preeclampsia in both pregnancies	2,411	7	39	15.4 (6.1–29.0)	6.4 (3.0–13.5)	4.7 (2.1–10.7)	2.6 (0.6–10.6)
After 3 pregnancies (women with ≥3 pregnancies)							
No preeclampsia	198,192	84	3,315	2.4 (1.9–2.9)	1.0	1.0	1.0
Preeclampsia in 1 pregnancy only	10,727	26	159	14.4 (9.4–20.5)	6.3 (4.1–9.9)	5.8 (3.7–9.1)	5.3 (3.0–9.6)
Preeclampsia in first pregnancy only	5,930	6	80	6.0 (2.1–11.7)	2.6 (1.1–5.9)		
Preeclampsia in second pregnancy only	1,875	5	28	16.2 (5.1–33.4)	7.3 (3.0–18.1)		
Preeclampsia in third pregnancy only	2,922	15	51	30.6 (17.1–48.1)	14.3 (8.2–24.7)		
Preeclampsia in ≥2 pregnancies	1,741	9	27	32.9 (14.9–57.9)	15.5 (7.8–30.8)	10.9 (5.0–23.8)	3.0 (0.4–21.9)

Vikse VE et al

N Engl J Med 2008;359:800-9

Preeclamptic syndromes and long term *relative* risk for ESRD

Relative risk x 3-5, rises according to the number of preceding pregnancies



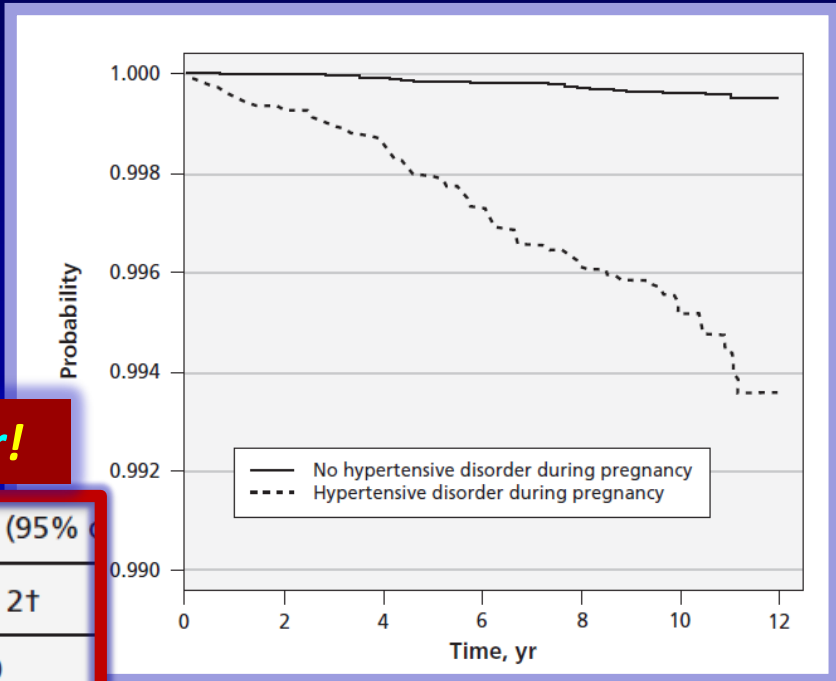
and the total number of pre eclamptic pregnacies

Vikse VE et al

N Engl J Med 2008;359:800-9

Hypertensive disorders of pregnancy as a risk factor for ESRD

from 1998 to 2009 to identify 26 651 women aged 19–40 years old who experienced hypertensive disorders during pregnancy; these women had no history of hypertension, diabetes, kidney disease or lupus. We also randomly selected 213 397 women without hypertensive disorders during pregnancy as a comparison cohort; the frequency was



Proportional to the severity of the pre-eclamptic disorder!

Variable, *n* of women	End-stage renal disease	Incidence rate per 10 000 person-years	Hazard ratio (95%	
			Model 1*	Model 2†
No hypertensive disorders in pregnancy, *n* = 213 397	45	0.34	1.00	1.00
Hypertensive disorders in pregnancy, *n* = 26 651	79	4.72	14.1 (9.76–10.3)	12.4 (8.54–18.0)
Gestational hypertension, *n* = 8 653	18	3.40	10.2 (5.89–17.6)	9.03 (5.20–15.7)
Preeclampsia/eclampsia, *n* = 17 998	61	5.33	15.9 (10.8–23.3)	14. 0 (9.43–20.7)
p for trend		< 0.001¶	< 0.001**	< 0.001**

Wang et al

CMAJ 2013; 185(3): 207-213

Hypertensive disorders of pregnancy as a risk factor for ESRD

Large proportion of the risk (~ 80%) is explained by adjustment for cardiovascular co-morbidities !!

Hypertension /DM

Variable, *n* of women	End-stage renal disease	Incidence rate per 10 000 person-years	Hazard ratio (95% confidence interval)		
			Model 1*	Model 2†	Model 3‡
No hypertensive disorders in pregnancy, *n* = 213 397	45	0.34	1.00	1.00	1.00
Hypertensive disorders in pregnancy, *n* = 26 651	79	4.72	14.1 (9.76–10.3)	12.4 (8.54–18.0)	2.72 (1.76–4.22)
Gestational hypertension, *n* = 8 653	18	3.40	10.2 (5.89–17.6)	9.03 (5.20–15.7)	1.81 (0.99–3.30)
Preeclampsia/eclampsia, *n* = 17 998	61	5.33	15.9 (10.8–23.3)	14. 0 (9.43–20.7)	3.19 (2.02–5.02)
p for trend		< 0.001¶	< 0.001**	< 0.001**	< 0.001**

Wang et al

CMAJ 2013; 185(3): 207-213

Preeclamptic syndromes and long term *relative* risk for ESRD

JAMA Network Open

Original Investigation | Obstetrics and Gynecology

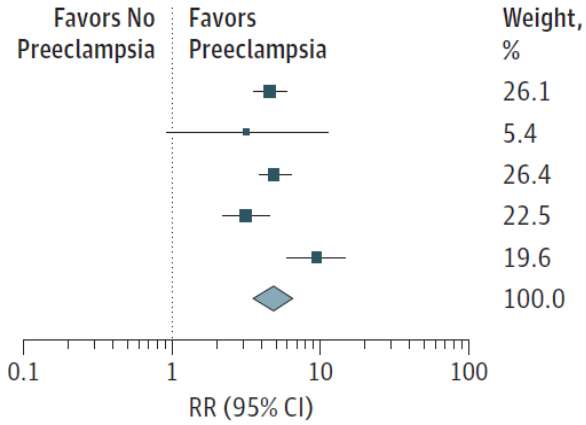
Adverse Pregnancy Outcomes and Long-term Maternal Kidney Disease
A Systematic Review and Meta-analysis

Peter M. Barrett, MB, MSc, MFPHMI; Fergus P. McCarthy, MB, PhD; Karolina Kublickiene, MB, PhD; Sarah Cormican, MB, MRCPI; Conor Judge, MB, MRCPI; Marie Evans, MB, PhD; Marius Kublickas, MB, PhD; Ivan J. Perry, MB, PhD; Peter Stenvinkel, MB, PhD; Ali S. Khashan, MSc, PhD

Figure 2. Forest Plot for Studies of the Association of Preeclampsia and End-Stage Kidney Disease

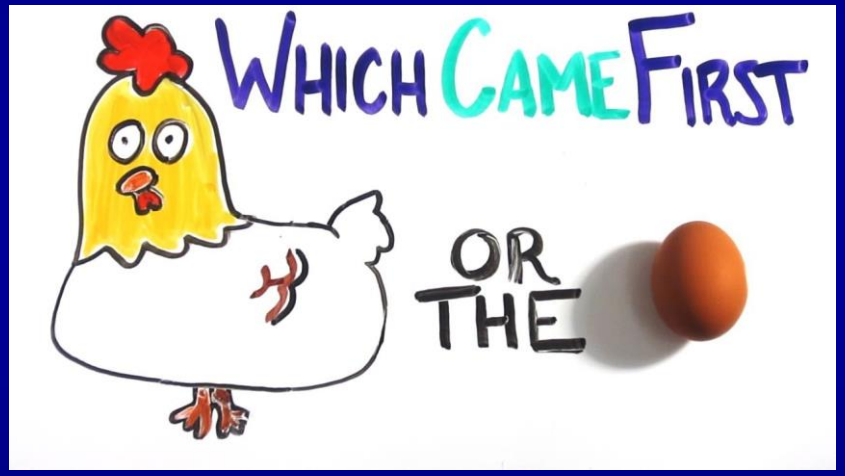
B Adjusted risk ratios

Source	Log (Risk Ratio)	SE	Risk Ratio (IV, Random, 95% CI)	Weight, %
Dai et al,[28] 2018	1.5403	0.1277	4.67 (3.63-5.99)	26.1
Kattah et al,[27] 2017	1.1787	0.6389	3.25 (0.93-11.37)	5.4
Khashan et al,[35] 2019	1.6014	0.124	4.96 (3.89-6.32)	26.4
Vikse et al,[8] 2008	1.1569	0.1811	3.18 (2.23-4.54)	22.5
Wu et al,[37] 2014	2.2471	0.2241	9.46 (6.10-14.68)	19.6
Total			4.90 (3.56-6.74)	100.0
Heterogeneity: $\tau^2 = 0.09$; $\chi^2_4 = 14.83$; $P < .005$; $I^2 = 73\%$				
Test for overall effect: $z = 9.76$; $P < .001$				



Chronic Kidney Disease

Hypertensive Disorders of Pregnancy



Cardiovascular morbidity