Division of Women's Health
Women's Health Academic Centre

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An Academic Health Sciences Centre for London

Pioneering better health for all

AKI in Pregnancy

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Charter for women in science
Recognising commitment to advancing women's careers in STEMM academia

KING'S College LONDON

Guy's and St Thomas' NHS Foundation Trust

King's College Hospital NHS Foundation Trust

South London and Maudsley NHS Foundation Trust

Physiology changes in pregnancy

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↑ proteinuria

No increase in glomerular capillary pressure and no long-term adverse effects on glomerular morphology

Normal ranges in pregnancy

Creatinine < 75μmol/l [0.9 mg/dl]

1st trim	**52-68 μmol/l**
2nd trim	**44-64 μmol/l**
3rd trim	**55-73 μmol/l**
Urea	**< 4.5 mmol/l**
Proteinuria	**< 0.3 g/24 hrs or PCR <30 mg/mmol**

- **eGFR not validated in pregnancy**
- **AKIN classification is not validated in pregnancy**
- **Creatinine rise >90μmol/l indicative of renal impairment in pregnancy**

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- NSAIDs
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- Acute fatty liver of pregnancy (AFLP)
- New presentation of glomerulonephritis
- Undiagnosed / unrecognized CKD

case mix programme

Female admissions (aged 16-50 years) to adult, general critical care units in England, Wales and Northern Ireland reported as 'currently pregnant' or 'recently pregnant'

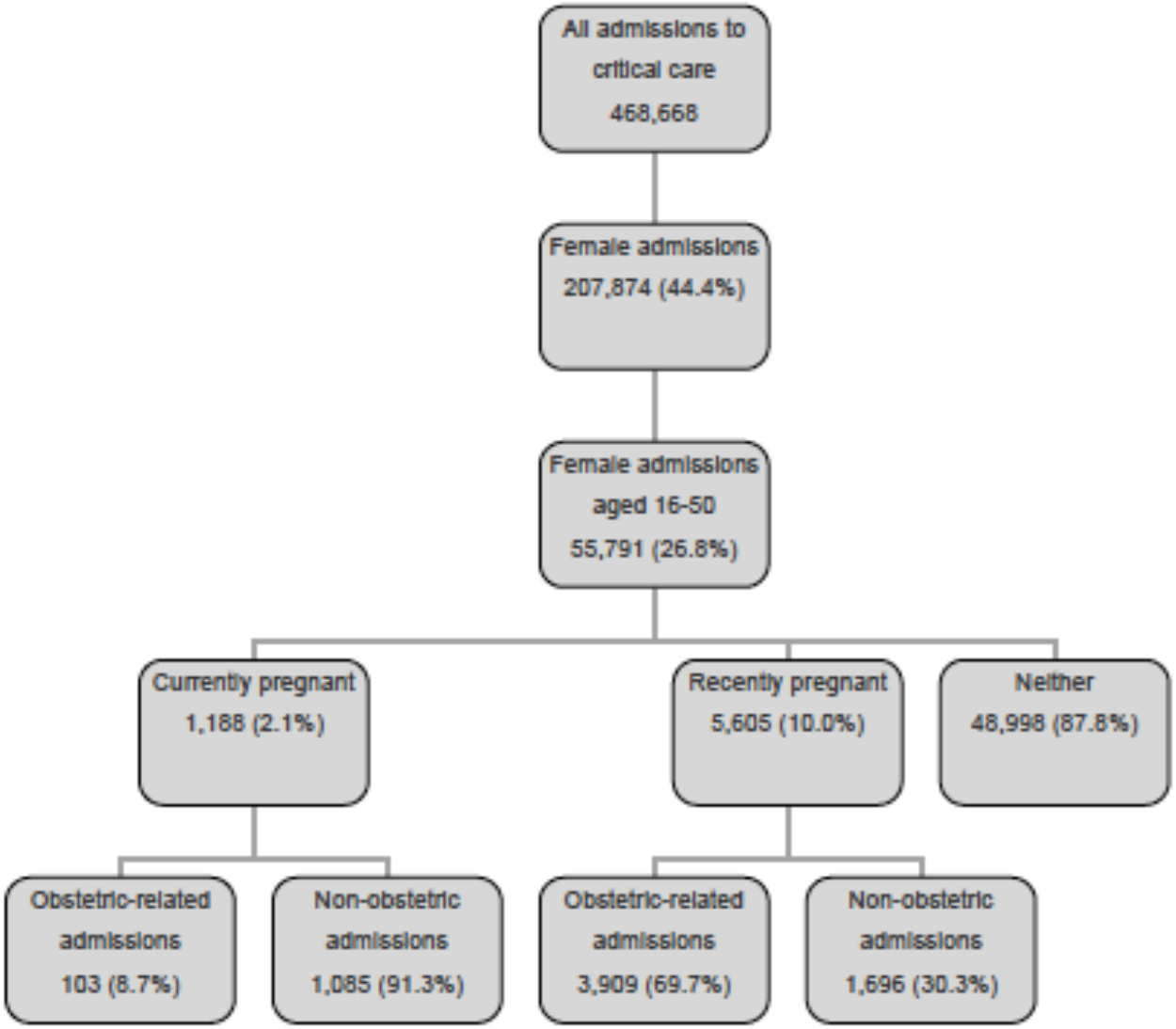
Report from the Intensive Care National Audit & Research Centre

1 January 2009 to 31 December 2012

ICNARC 2009-2012

- 1188 currently pregnant
- 5605 recently pregnant (within 42 days)
- 12.1% of total female admission aged 16-50 years
- Mean age 30
- Maternity admissions 290/100,000 maternities
- Maternal death rate 14/100,000 in 2011 CMACE report

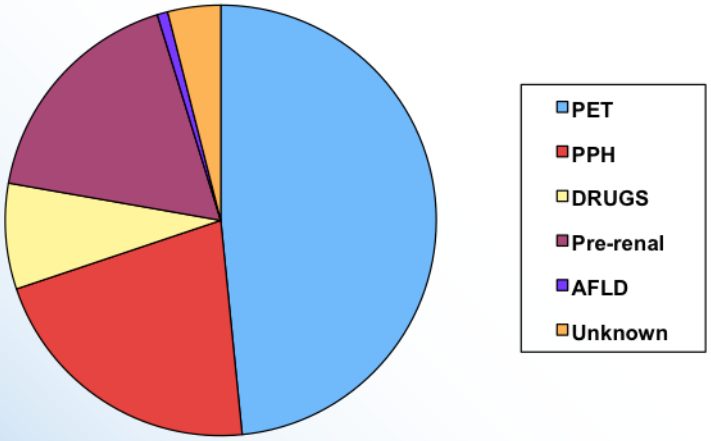
Figure 5. Flow diagram of female admissions to critical care aged 16-50 years reported as 'currently pregnant', 'recently pregnant' or neither on admission to the critical care unit



	Pregnant	Post partum
Obstetric	**9%**	**70%**
PPH		36%
Pre-eclampsia	2%	4%
HELLP	0.7%	2.5%
Non obstetric	**91%**	**30%**
Pneumonia	23%	4.3%
Pulmonary oedema	1.9%	1.6%
Pelvic infection		1.9%
AKI	**0.3%**	**0.8%**
Asthma	8%	0.6%
Cardiovascular	8%	5.6%
GI	10%	4.5%
Neuro	9%	3.5%
Endo	12%	1.6%

AKI causes in pregnancy: St Thomas Hospital, 2011

Causes of AKI	
Pre-eclampsia	61 cases
Post partum haemorrhage	27 cases
Drugs NSAIDS / ACE inhibitors	10 cases
Pre-renal	22 cases
AFLP	1 case
Unknown	5 cases



Trimester of AKI presentation 3rd trimester Postpartum	 60% 40%
AKI recognised & documented in medical notes	45%
Review of drug chart on recognition of AKI	17%
Peak creatinine (umol/L)	111.9 (90-263)
Peak Potassium (mmol/L)	4.87 (4-7)
Complete Recovery of AKI	60%
Partial Recovery of AKI	24%
Unknown-no documentation of AKI	16%

Pathophysiology

Pre-eclampsia **ELLP** **HELLP** **AFLP**

Pre-eclampsia **HELLP** **HUS**

TTP

Pathophysiology

Pre-eclampsia **ELLP** **HELLP** **AFLP**

Pre-eclampsia **HELLP** **HUS**

TTP

Pathophysiology

Pre-eclampsia **ELLP** **HELLP** **AFLP**

Pre-eclampsia **HELLP** **HUS**

TTP

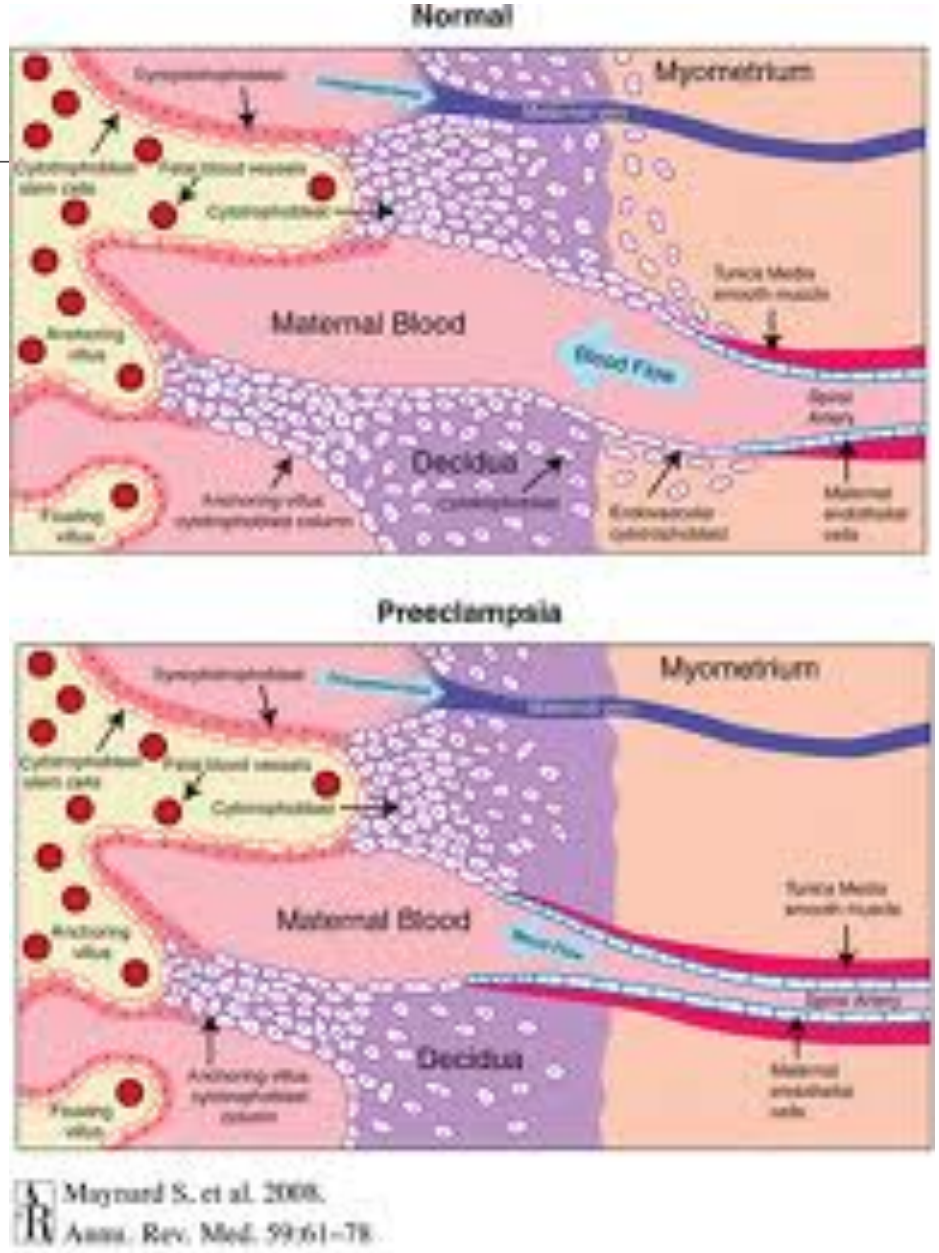
Pathophysiology of Pre-eclampsia

Normal Placentation

Weeks 8-18
Cytotrophoblast invasion
Spiral artery remodelling
Low pressure / High capacitance

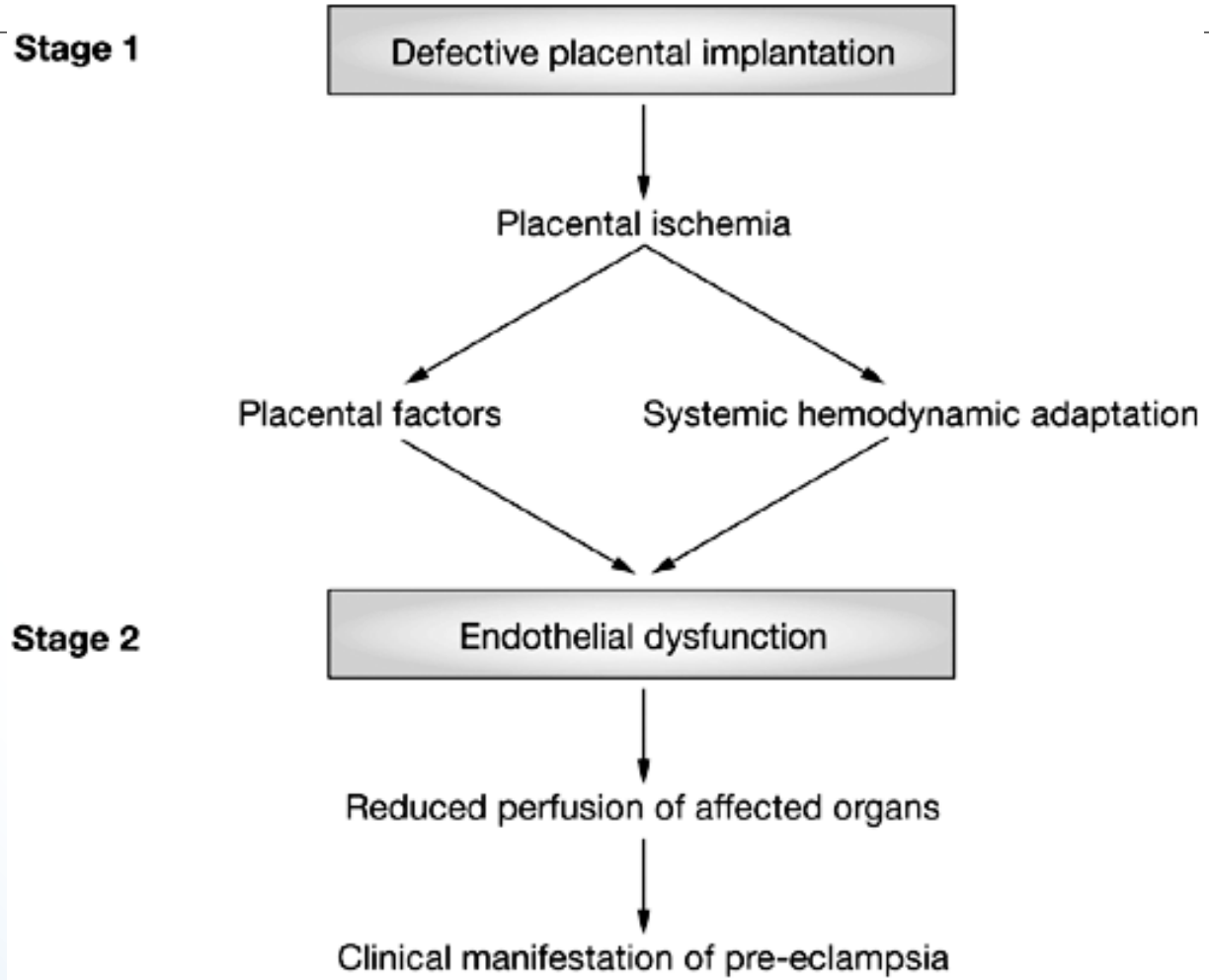
Defective Placentation

Inadequate spiral artery remodelling
Less dilated
More vascular smooth muscle
Acute atherosis: Endothelial accumulation fat-filled macrophages
Thrombosis



Maynard S. et al. 2008. Annu. Rev. Med. 59:61–78

Figure 2 Pathophysiology of pre-eclampsia: the facts

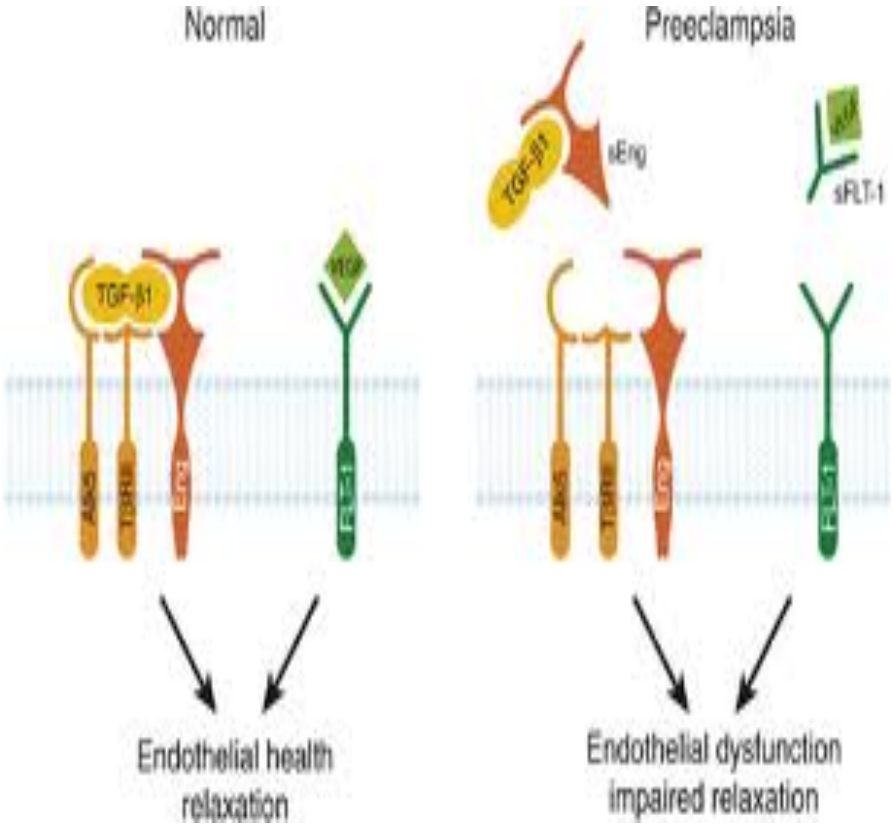


Noris M et al. (2005) Mechanisms of Disease: pre-eclampsia
Nat Clin Pract Neprol **1:** 98–114 doi:10.1038/ncpneph0035

nature CLINICAL PRACTICE NEPHROLOGY

Placental anti-angiogenic factors

- soluble fms-related tyrosine kinase 1 (sFLT-1)
- soluble endoglin,
- upregulated in preeclampsia
- released into the maternal circulation
- their actions disrupt maternal endothelium



Wang, Rana, Karumanchi Physiology 2009; 24:147.

Placental anti-angiogenic factors

During **normal** pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and transforming growth factor (TGF-β1) signalling in the vasculature.

In **preeclampsia**, excess placental secretion of **sFLT-1 and sEng** inhibits VEGF and TGF- β1 signalling, respectively, in the vasculature.

Predictive / Diagnostic tests:

↑sFLT – 1

↓PIGF – placental growth factor

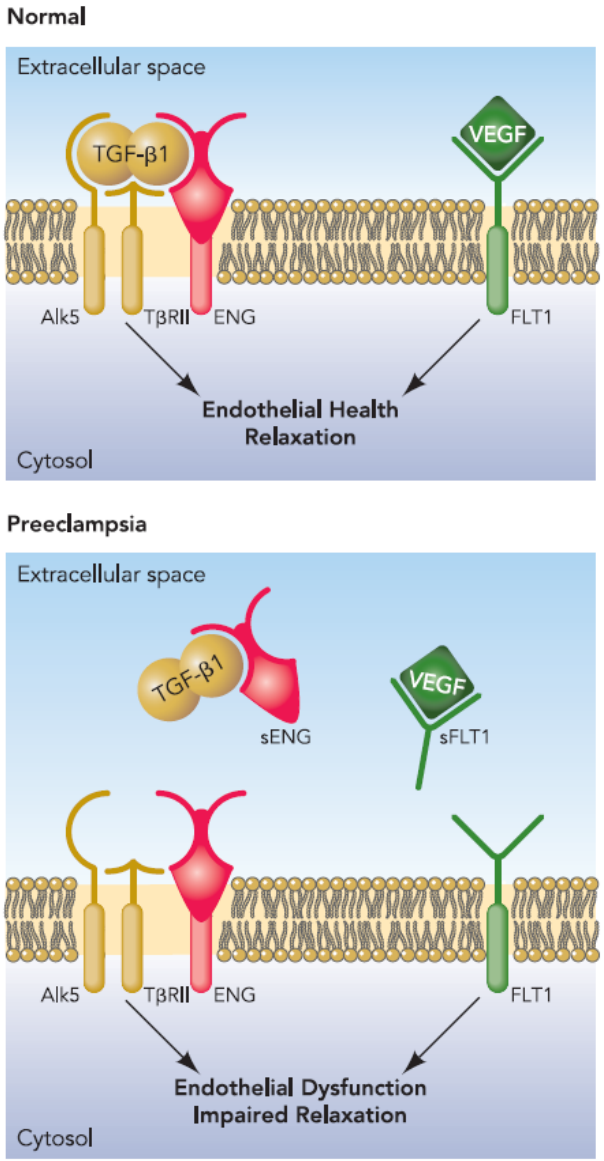
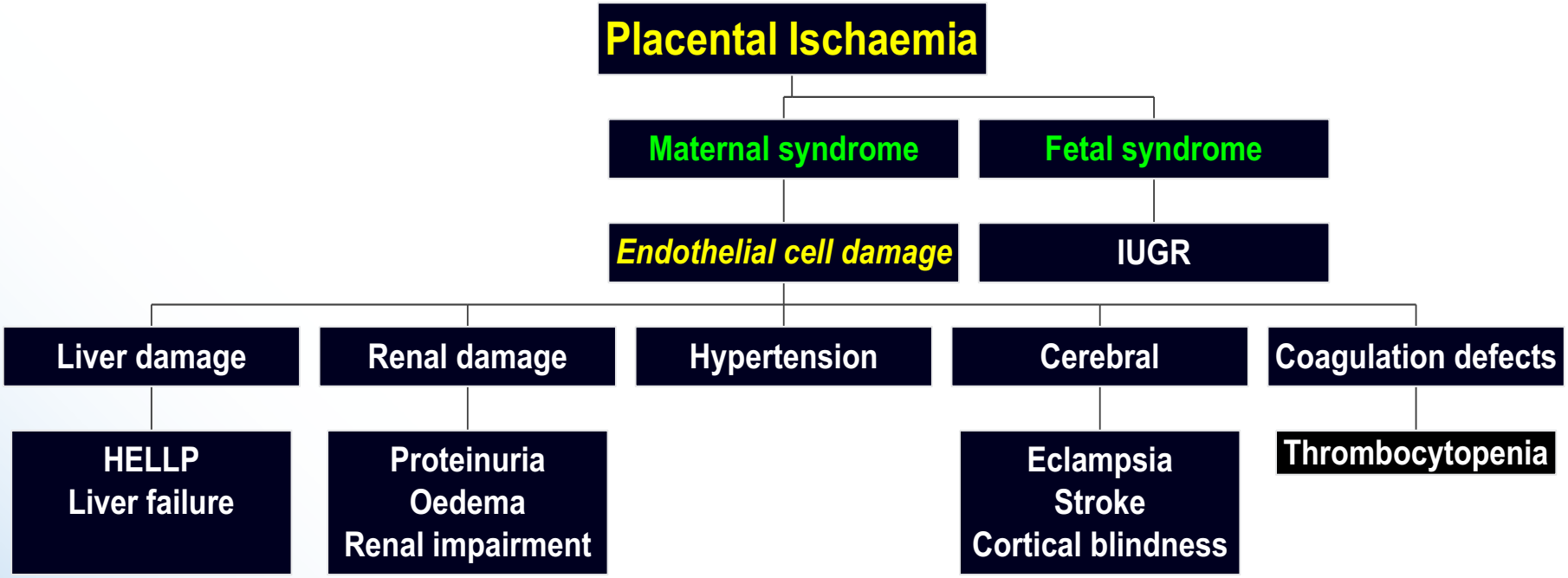
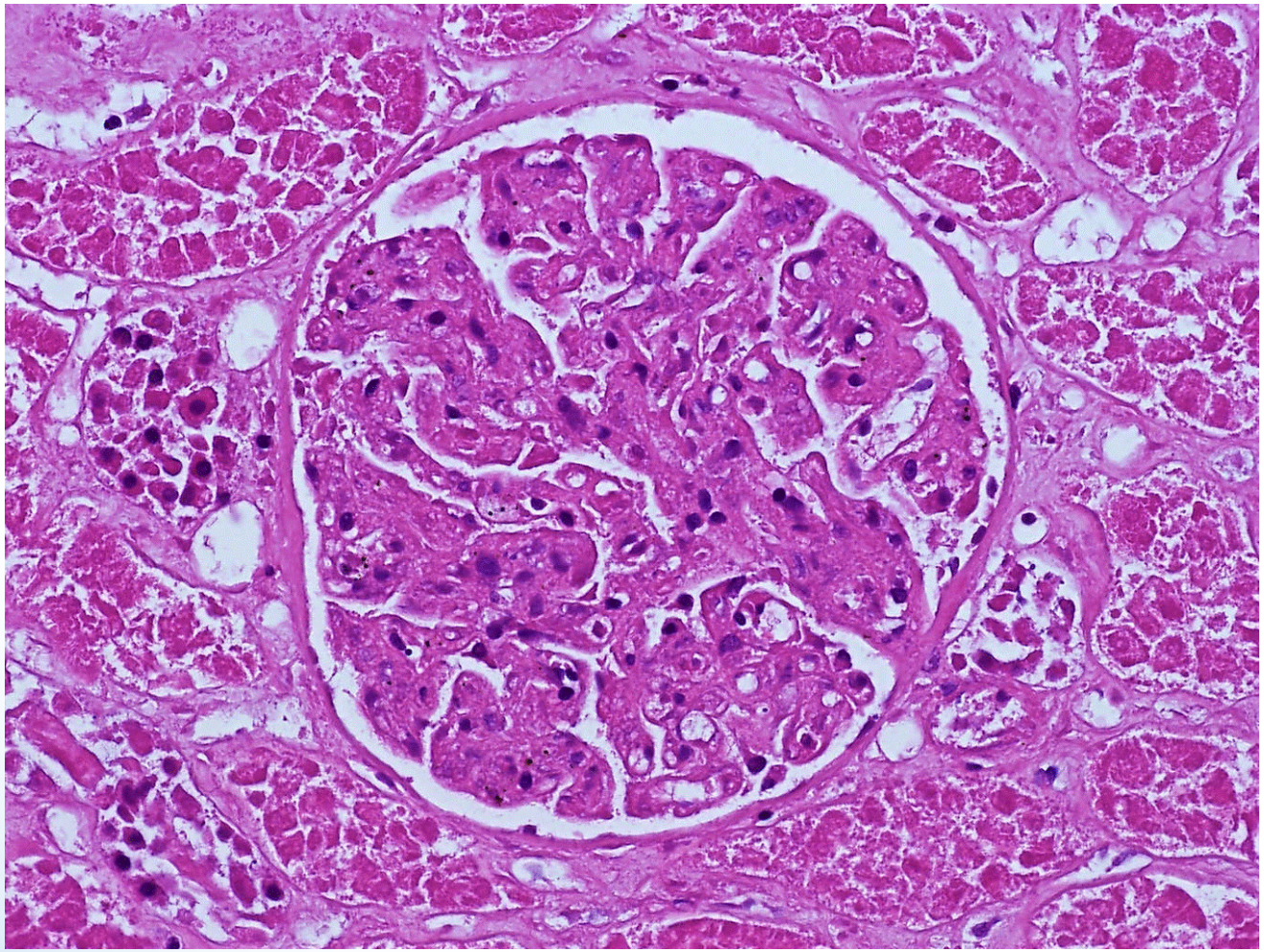


FIGURE 3. sFlt1 and sEng cause endothelial dysfunction by antagonizing VEGF and TGF-β signaling

Pathophysiology of Pre-eclampsia



Glomerular endotheliosis



Pre-eclampsia - potential crises

Cerebral haemorrhage

Eclampsia

DIC

HELLP

AKI

Hepatic failure / liver rupture

Pulmonary oedema

Cortical blindness

Placental abruption

Intra-uterine death

Yorkshire Critical Care Group

n = 210,631; 16 units; 1999 - 2003.

1087 severe pre-eclampsia or eclampsia (5.2/1000)

151 serious complications

82 (39/10,000) having eclamptic seizures and
49 (23/10,000) requiring ICU admission.

82 eclampsia

45 occurred antenatally (55%)

- 18 before admission to the maternity unit

11 in labour (13%)
26 following delivery (32%).

25 pulmonary oedema (2.3% of cases)

6 renal dialysis (0.55% of cases).

BJOG. 2005; 112:875-80

Renal failure complicating Pre-eclampsia

Cohort study;1995-1998

Groote Schuur, Cape Town; 28,000 deliveries/yr

588 admitted to obstetric HDU

89 severe pre-eclampsia + AKI (Cr>100+ oliguria)

1:1500; 73 cases reviewed

Median max Cr = 341 umol/l

Drakeley et al. AJOG 2002; 186: 253.

AKI in Pre-eclampsia

57% multips, 43% primips

Mean gestation at delivery = 32 weeks

16% Hx chronic renal disease / hypertension

48% HELLP

30% abruption

16% eclampsia

Perinatal mortality = 45%; maternal mortality = 0%

10% required short term dialysis

None required long term dialysis / transplant

Drakeley et al. AJOG 2002; 186: 253.

Fluid management in Pre-eclampsia

- **Post delivery oliguria is obligatory**
- **Anuria is a blocked catheter or obstructed / cut ureters until proved otherwise**
- **AKI does not kill but pulmonary oedema and ARDS does**
  - 2.3% pulmonary oedema vs. 0.55% dialysis (*Tuffnell et al. BJOG 2005*)
- **Fluid restriction is appropriate and necessary in the Mx of Pre-eclampsia**
  - 85 mls / hour in the absence of haemorrhage
- **Avoid NSAIDs**

BMJ 2014;349:g4731 doi: 10.1136/bmj.g4731 (Published 30 July 2014)

RESEARCH

Hypertensive disorders of pregnancy and the recent increase in obstetric acute renal failure in Canada: population based retrospective cohort study


OPEN ACCESS

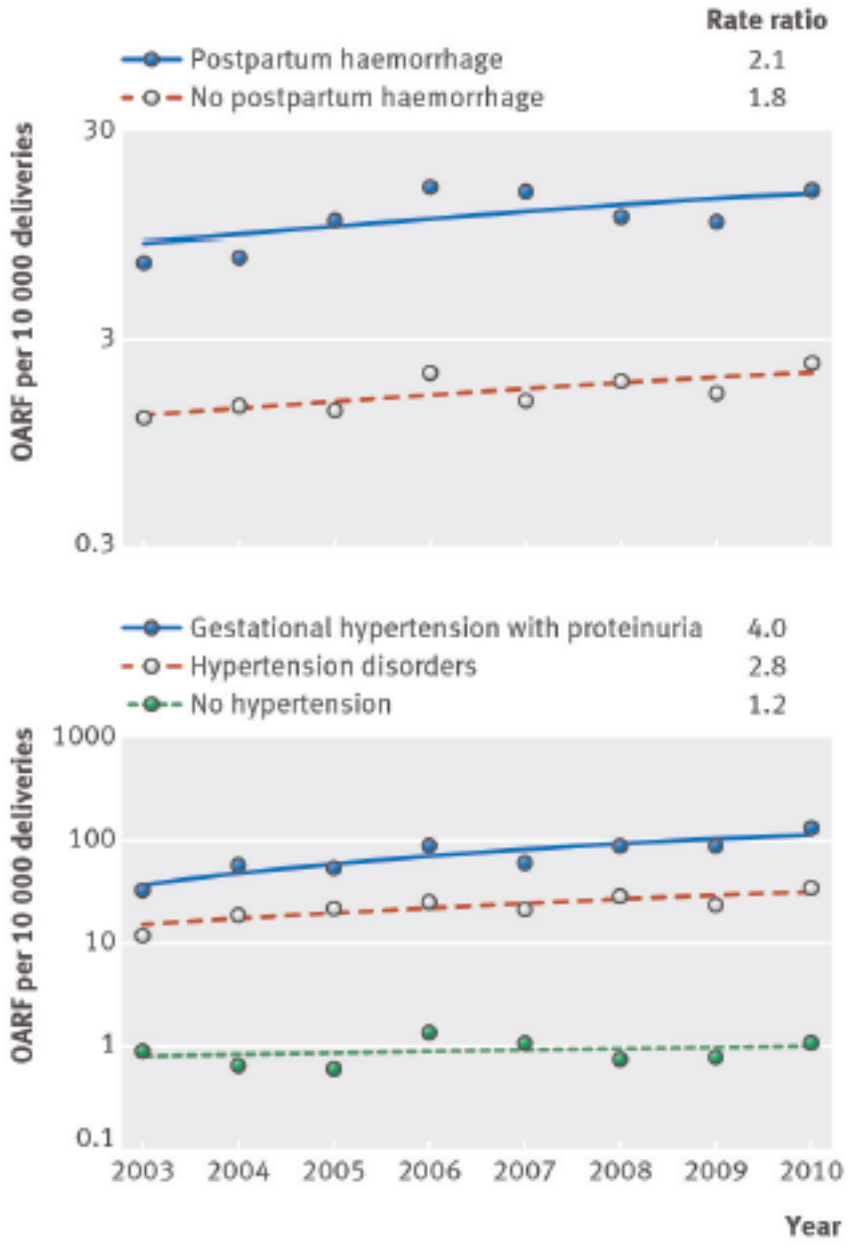
Azar Mehrabadi *PhD candidate*[1 2], Shiliang Liu *senior research scientist*[3], Sharon Bartholomew *senior epidemiologist*[3], Jennifer A Hutcheon *assistant professor*[1 2], Laura A Magee *clinical professor*[1 2 4], Michael S Kramer *professor*[5], Robert M Liston *professor emeritus*[1], K S Joseph *professor*[1 2], for the Canadian Perinatal Surveillance System (Public Health Agency of Canada)

Table 1| **Temporal trends in obstetric acute renal failure and in postpartum haemorrhage, hypertensive disorders of pregnancy, and other risk factors for obstetric acute renal failure, Canada (excluding Quebec), 2003-10 (n=2 193 425)**

Outcome/risk factor	No of cases 2003-10	Years				P for trend*
		2003-04	2005-06	2007-08	2009-10	
Acute renal failure per 10 000 deliveries	502	1.66	2.35	2.40	2.68	<0.001

	2003-4	2009-10	aOR
Hypertensive disorders	15.6	28.8	1.95 (1.4-2.8)
Pre-eclampsia	45.5	109.6	2.7 (1.7-4.3)
No hypertension	0.77	0.93	1.1 (0.7-1.7)

The temporal increase in acute renal failure was restricted to deliveries (6%) with **hypertensive disorders** (adjusted **increase 95%**, 95% CI 38% to 176%)
And especially
gestational hypertension with significant proteinuria (!%) (**PRE-ECLAMPSIA**) (adjusted **increase 171%**, 71% to 329%).
No significant increase occurred among women without hypertensive disorders (adjusted increase 12%, −28 to 72%).



Rates of obstetric acute renal failure (OARF) Canada (excluding Quebec), 2003-10.

Rate ratios express changes between 2003 and 2010

Temporal patterns in OARF were different among women with and without hypertension (but not among women with and without PPH)

HELLP Syndrome

(Haemolysis, Elevated Liver enzymes, Low Platelets)

Incidence

4-20% of PET

21% of early-onset <30 /40

Murphy & Stirrat. Hypertension in pregnancy 2000; 19: 221-231

10-30% arise post partum

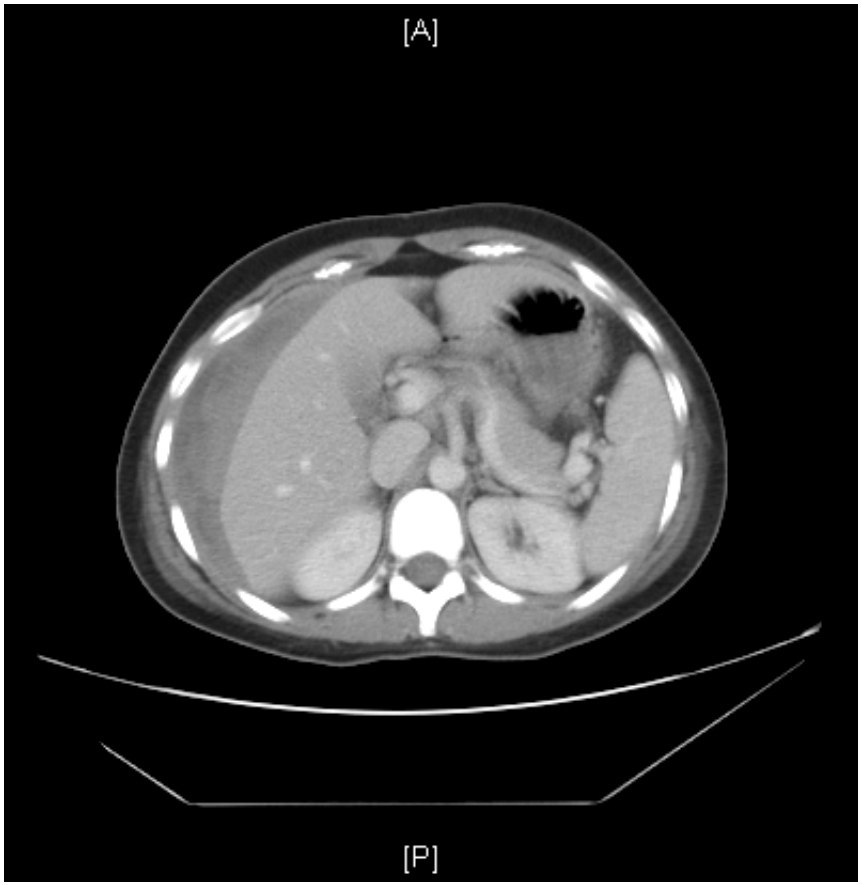
HELLP syndrome - CRISES

Acute kidney injury – 7%

Abruption – 16%

Liver haematoma

Liver rupture



A prospective national study of acute fatty liver of pregnancy in the UK

M Knight,[1] C Nelson-Piercy,[2] J J Kurinczuk,[1] P Spark,[1] P Brocklehurst,[1] on behalf of UK Obstetric Surveillance System (UKOSS)

Gut 2008; 57:951-6

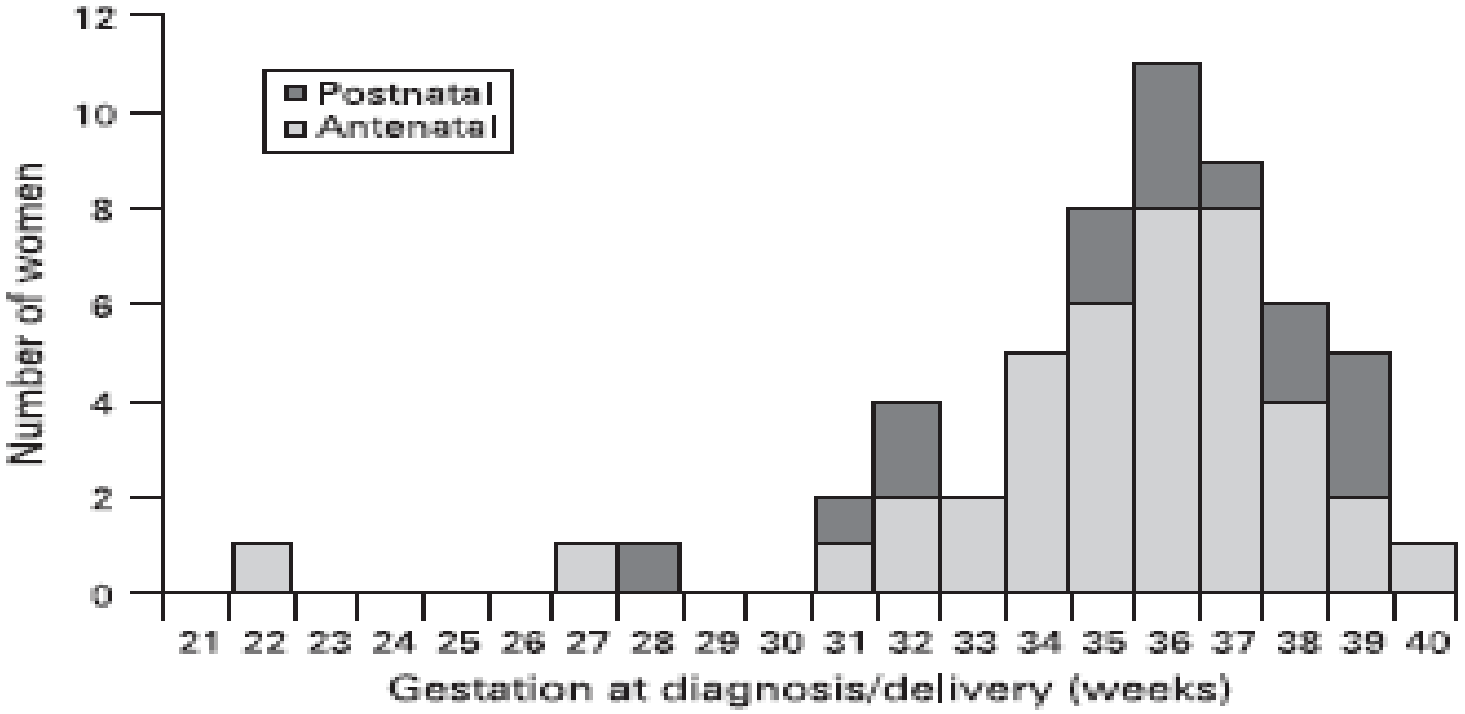


Figure 2 Gestation at diagnosis (antenatal cases) or delivery (postnatal cases).

N = 57; 5/100,000 Feb 05-Aug 06

AFLP - Clinical features

nausea, vomiting, malaise	(100%)
abdominal pain	(43%)
associated pre-eclampsia	(50-70%)
mild hypertension and proteinuria	
Jaundice	(37%)
Pruritus	(10%)
fulminant liver failure / hepatic encephalopathy / coagulopathy / hypoglycaemia	
AKI	(90%)
Diabetes insipidus	

AFLP: Swansea Criteria

Any six of the following:

Vomiting

Abdominal pain

Polydipsia/polyuria

Encephalopathy

Elevated bilirubin levels

Hypoglycaemia

Elevated urate

Elevated white cell count

OR Confirmed by Post Mortem

Elevated transaminases

Elevated Ammonia levels

Renal impairment

Coagulopathy

Ascites or bright liver on scan

Microvesicular steatosis on liver biopsy

Ch'ng et al (2002). Gut 51: 876-880

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Renal impairment

Coagulopathy

Ascites or bright liver on scan

Microvesicular steatosis on liver biopsy

Metabolic acidosis / raised lactate

Ch'ng et al (2002). Gut 51: 876-880

Associated Diabetes Insipidus

- Xs vasopressinase activity, a placental enzyme that degrades arginine-vasopressin (AVP), but not 1-deamino-8-D: -arginine vasopressin (dDAVP), [synthetic form].
- Impaired liver function means vasopressinase is not degraded, leading to further breakdown of AVP / ADH
- Polyuria / polydipsia affect up to 80%

AFLP – Management; HDU / Critical care

- Treat hypoglycaemia
  - 10 / 50% dextrose
- Treat coagulopathy
  - 10mg Vit K IV X 3 days
  - FFP
- Deliver
  - close fetal surveillance
- N acetyl cysteine (as for paracetemol OD)
  - 150mg/kg over 15 mins in 200mls 5% dextrose
  - 50mg/kg over 4 hours in 500mls
  - 100mg/kg over 16hours in 1000mls and continue
- Supportive Rx of AKI / liver failure / Transplantation

Haemolytic Uraemic Syndrome

Microangiopathic haemolytic anaemia (MAHA)

Thrombocytopenia (normal clotting)

AKI

Closely related to Thrombotic thrombocytopenic purpura (TTP)

Thrombotic Thrombocytopenic Purpura

Classic pentad (only seen in 1/3)

Fever

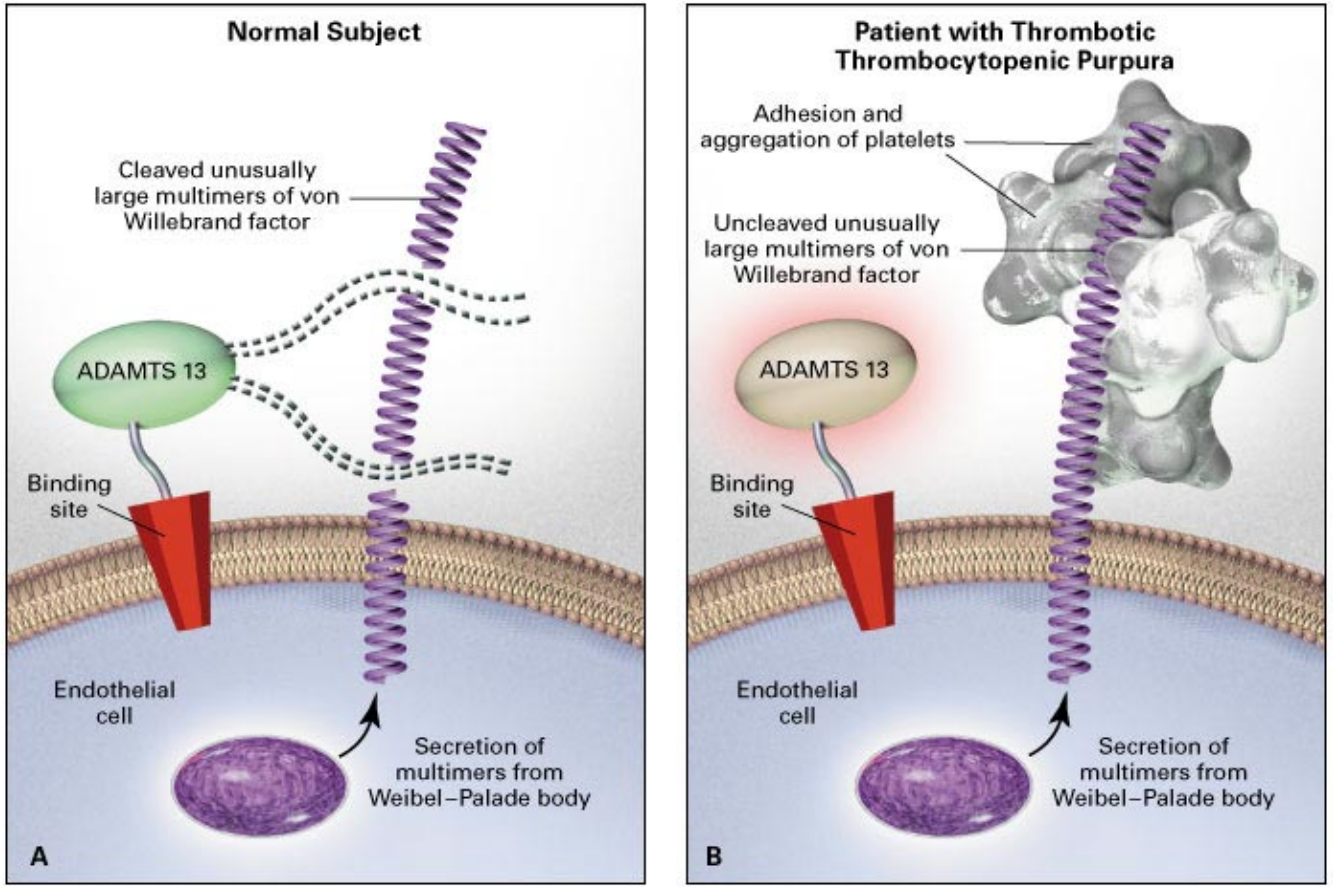
Thrombocytopenia*

Microangiopathic hemolytic anemia (MAHA)*

Elevated creatinine*

Neurologic symptoms

- Headache
- Irritability
- Drowsiness / Coma
- Seizure



Moake J. N Engl J Med 2002

TABLE IV
SEVERE PREECLAMPSIA, HELLP SYNDROME, ACUTE FATTY LIVER OF PREGNANCY AND THROMBOTIC MICROANGIOPATHY: DIFFERENTIAL DIAGNOSIS

	Severe preeclampsia	HELLP	AFLP	TTP	aHUS
Time of diagnosis	Usually 3T	3T		Usually 2T/3T	Postpartum
Frequency of hypertension	100%	80%	25%-50%	0/+	+
Fever / neurologic symptoms	no	no	no	yes	no
Acute kidney Injury	mild	mild / moderate	moderate	mild / moderate	severe
Hemolytic anemia	0	+	0/+	++	+
Thrombocytopenia	0/+	+	0	++	++
Liver transaminase increase	0/+	+	++	0	0
Partial thromboplastin time increase	0/+	0/+	+	0	0
ADAMTS-13 activity <10%	0	0	0	++	+
Recovery after delivery	2-3 days	1 week	1-2 days	No recovery	
Treatment	Delivery; Support measures			Plasma infusion /exchange	

0 = absence; 0/+ = occasionally present; + = sometimes present; ++ = always present; AFLP = acute fatty liver of pregnancy; aHUS = atypical hemolytic uremic syndrome; HELLP = hemolysis, elevated liver enzymes and low platelet count, TTP = thrombotic thrombocytopenic purpura; 2T = second trimester of gestation; 3T = third trimester of gestation.

Remember

AKI is rare in pregnancy in the absence of HELLP, DIC, NSAID or missed haemorrhage

DO not prescribe NSAIDs in Pre-eclampsia

Thank you for your attention!