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

KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

AKI in Pregnancy

Catherine Nelson-Piercy,
Professor of Obstetric Medicine

Athena SWAN
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

↑ RBF (70-80% in second trimester)

↑ GFR and Cr Cl 55%

↓ Cr and Urea

↑ 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

AKI in pregnancy

Creatinine rise >90μmol/l

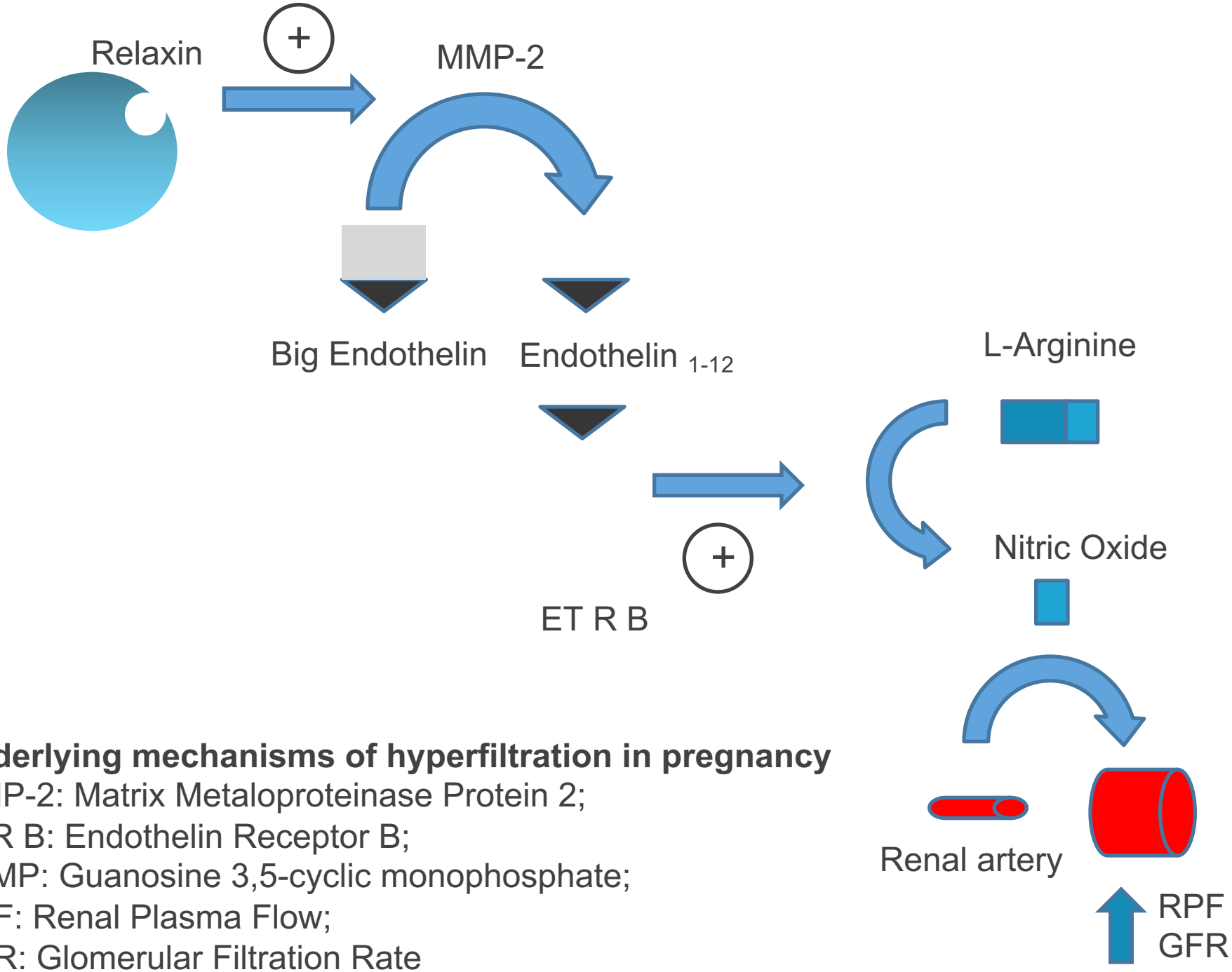
has been shown to be indicative of renal impairment in pregnancy

AKIN classification is not validated in pregnancy

AKIN classification

Severity of renal injury	Increase in serum creatinine	Urine output
Stage 1	1.5-2 x baseline	<0.5 ml/kg/h for >6h
Stage 2	2-3 x baseline	<0.5 ml/kg/hr >12h
Stage 3	> 3 x baseline	<0.3 ml/kg/min >24h Or anuria >12h

Girling 2000, Ganesan and Maynard 2011, Gurrieri et al 2012



Underlying mechanisms of hyperfiltration in pregnancy

MMP-2: Matrix Metaloproteinase Protein 2;
ETR B: Endothelin Receptor B;
cGMP: Guanosine 3,5-cyclic monophosphate;
RPF: Renal Plasma Flow;
GFR: Glomerular Filtration Rate

Pregnancy causes of AKI

- **Sepsis** (Pyelonephritis / abortion)
- **Pre-eclampsia** / HELLP syndrome
- ATN / pre-renal / **haemorrhage**
- NSAIDs
- Post renal (ureteric obstruction or trauma)
- Haemolytic uraemic syndrome (HUS) / TTP
- 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'

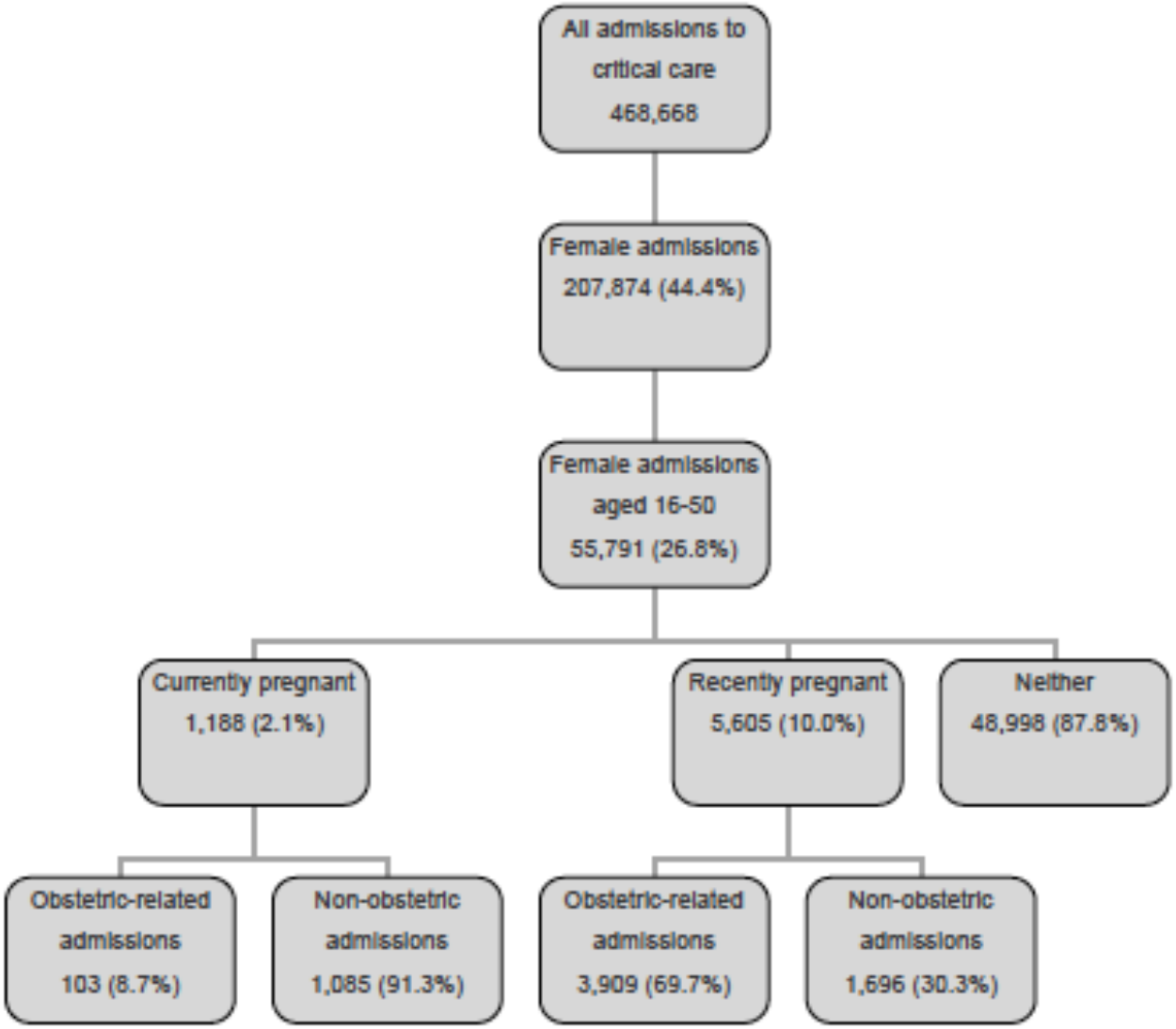
Report from the Intensive Care National Audit & Research Centre

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%

Table 6. Outcomes for female admissions to critical care aged 16-50 years reported as 'currently pregnant', 'recently pregnant' or neither on admission to the critical care unit

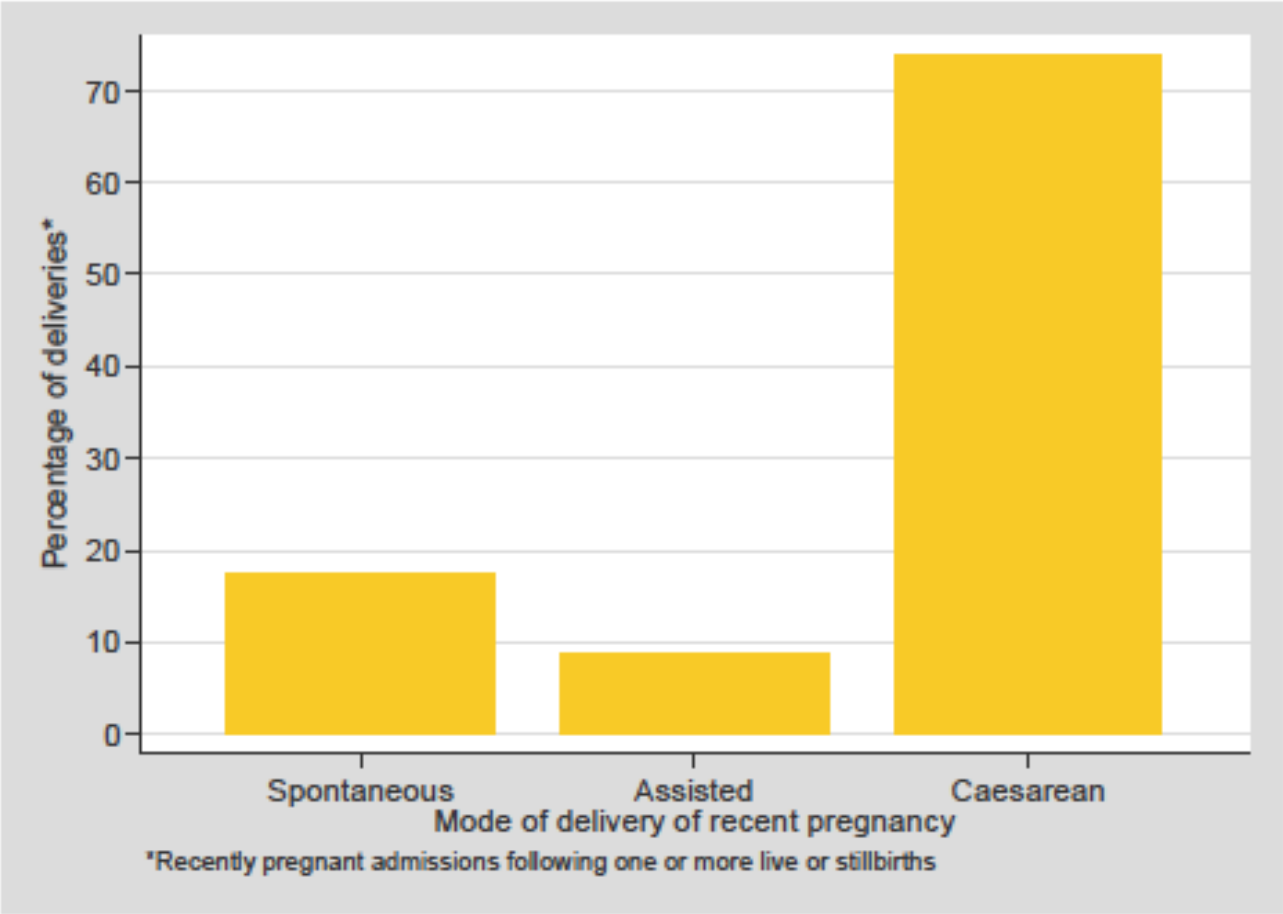
Female admissions aged 16-50 years		Currently pregnant	Recently pregnant	Neither
Number of admissions		1,188	5,605	48,998
Critical care unit mortality, deaths (%) [95% CI]		20 (1.7) [1.1, 2.6]	73 (1.3) [1.0, 1.6]	4,299 (8.8) [8.5, 9.0]
Acute hospital mortality*, deaths (%) [95% CI]		30 (2.7) [1.9, 3.8]	97 (1.8) [1.5, 2.2]	5,325 (11.6) [11.3, 11.9]
Location of death, n (% of deaths)	Original critical care unit admission	19 (63.3)	67 (69.1)	3,986 (74.9)
	Subsequent critical care unit admission†	7 (23.3)	22 (22.7)	552 (10.4)
	Acute hospital – following discharge from critical care‡	4 (13.3)	8 (8.2)	787 (14.8)

* Excluding readmissions to the critical care unit within the same acute hospital stay.

† Following transfer to another critical care unit or readmission to the original critical care unit.

‡ May include some deaths in other critical care units not participating in the CMP.

Figure 28. Mode of delivery for female admissions aged 16-50 reported as 'recently pregnant' on admission to the critical care unit (live and/or stillbirths only)



Estimated effects of prepregnancy renal function on pregnancy outcome and maternal renal function.

Values are the estimated percentage of women or neonates affected

Mean pre-pregnancy serum creatinine	Effects on pregnancy outcome				Loss of >25% renal function		
	FGR	Preterm	PET	PNM	During pregnancy	Persists post partum	ESRF after 1 yr
<125	25	30	22	1	2	0	
125-180	40	60	40	5	40	20	2
>180	65	>90	60	10	70	50	35
On dialysis	>90	>90	75	50	N/a	N/a	N/a

Williams, D. et al. BMJ 2008;336:211-215

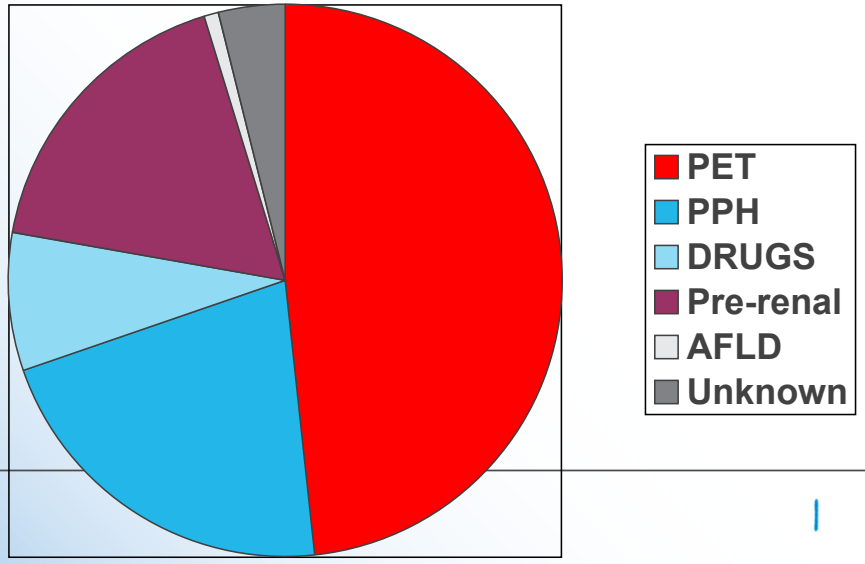
What was BP / urinalysis at booking?

Serum creatinine not routinely measured in pregnancy unless:

- **Hypertensive**
- **Proteinuric**
- **Known CKD**
- **Admitted / unwell**

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

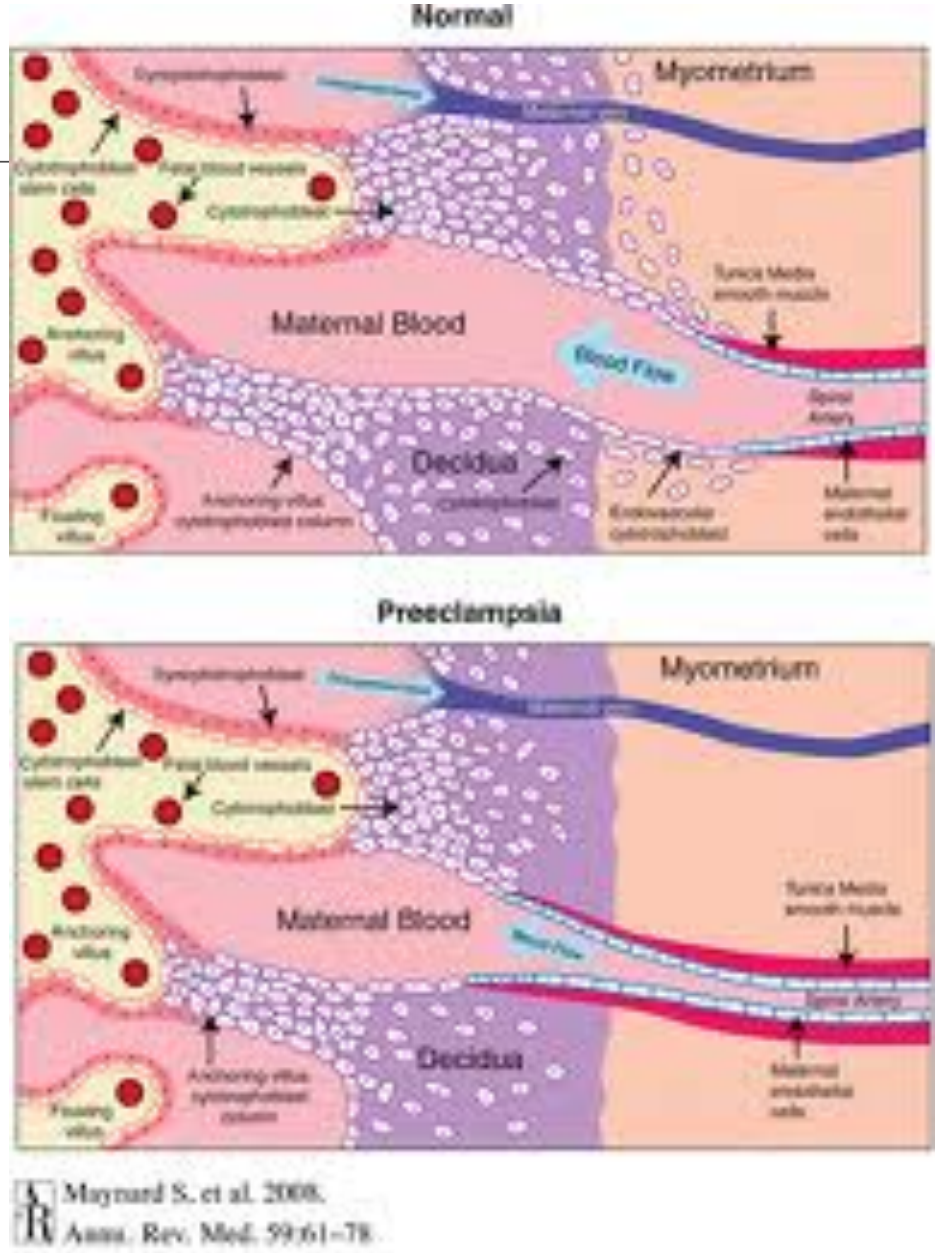
Pathophysiology of Pre-eclampsia

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

Pathophysiology: two stages in evolution pre-eclampsia

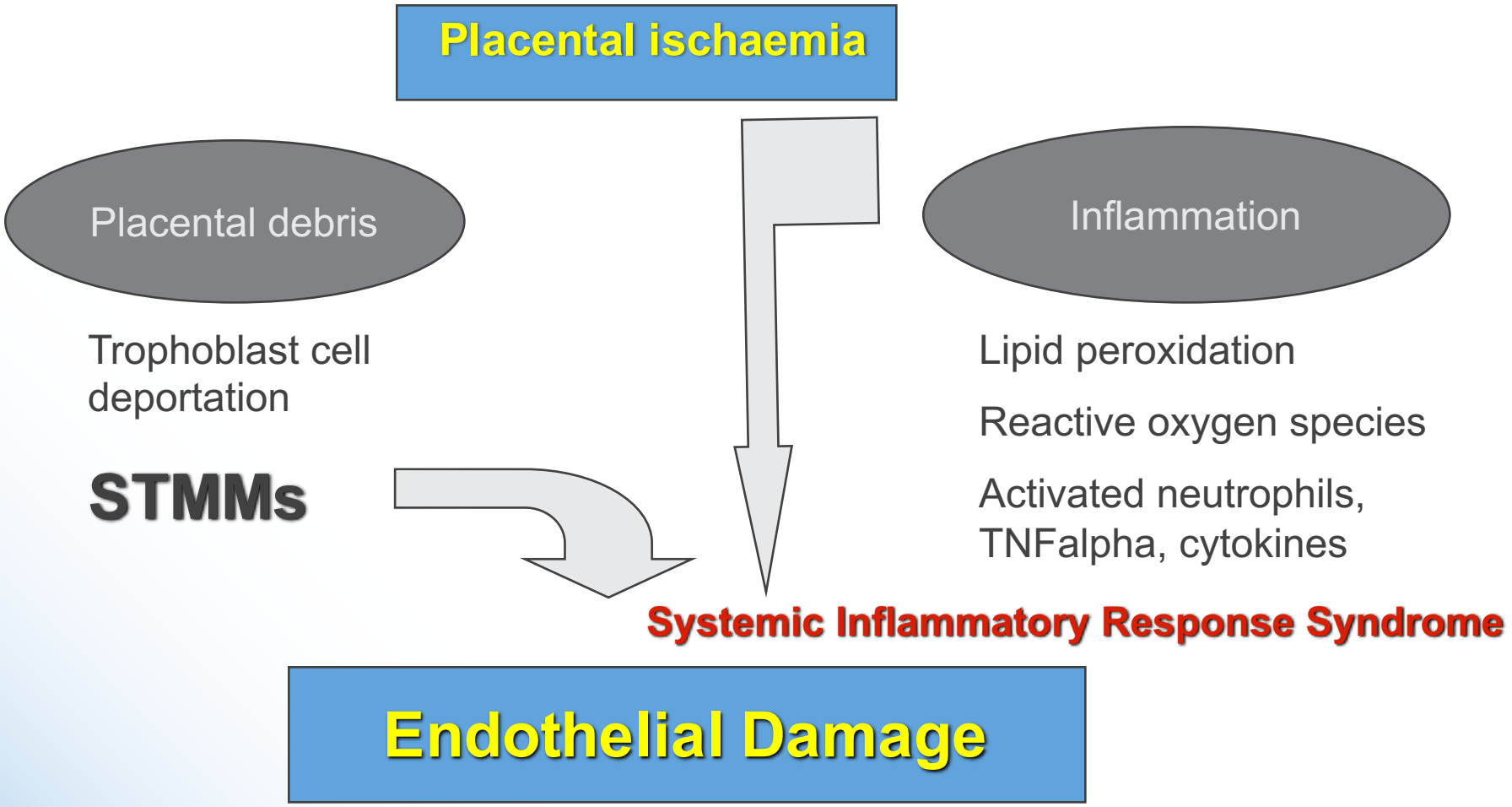
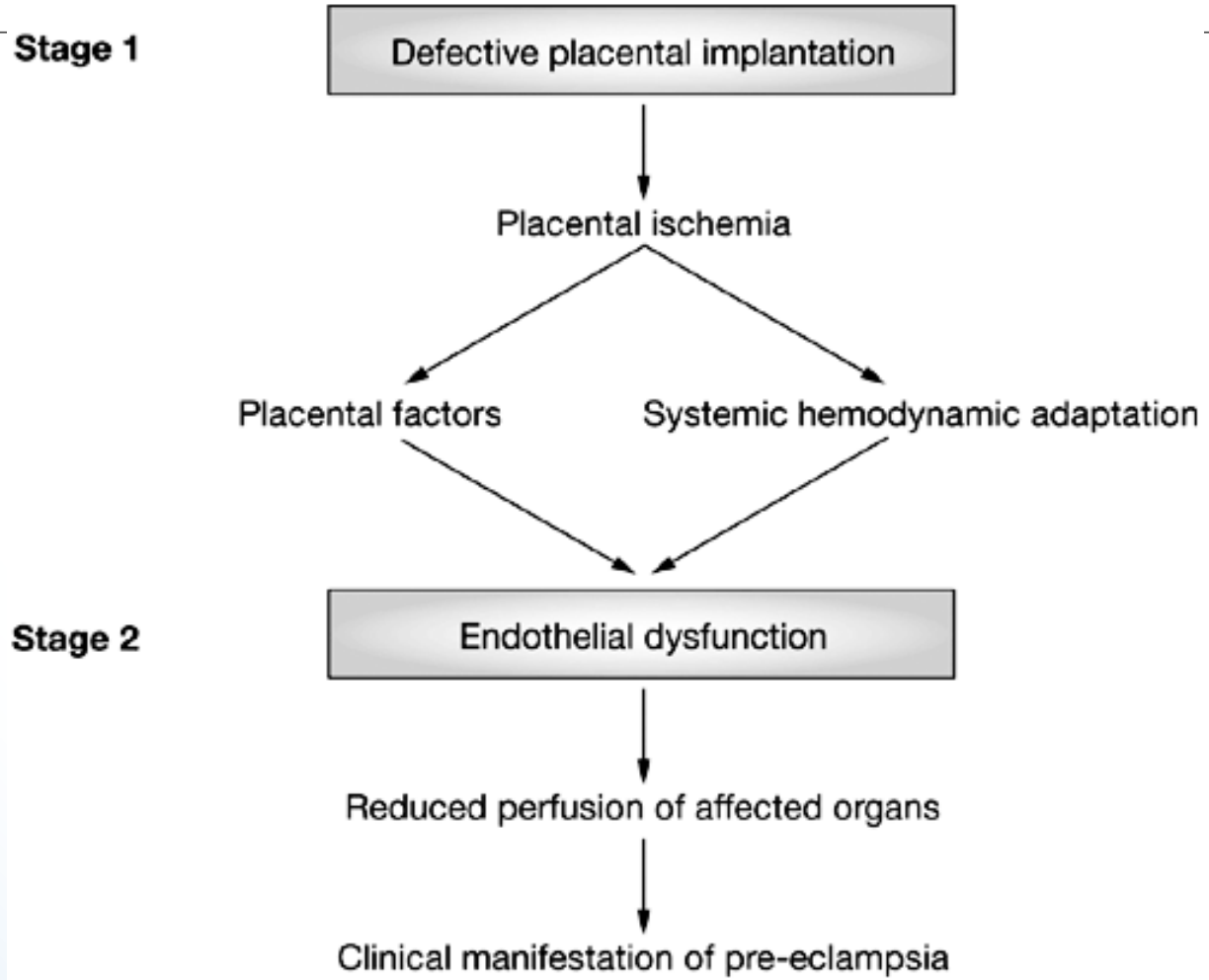


Figure 2 Pathophysiology of pre-eclampsia: the facts



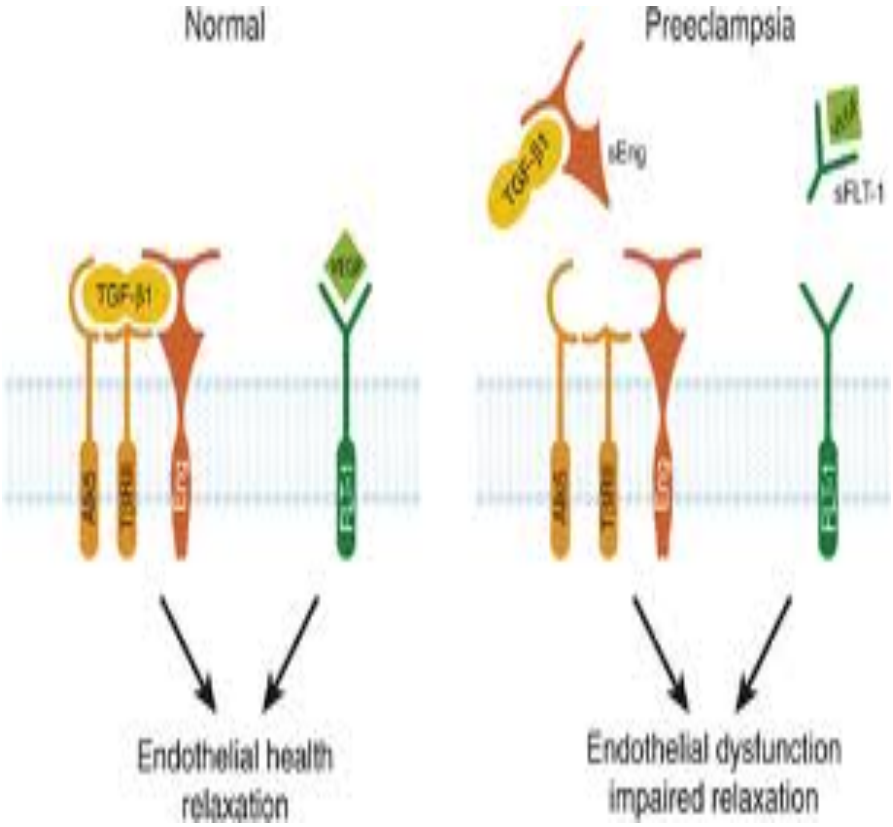
Noris M et al. (2005) Mechanisms of Disease: pre-eclampsia
Nat Clin Pract Neprol **1:** 98–114 doi:10.1038/ncpneph0035

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

↓PlGF – placental growth factor

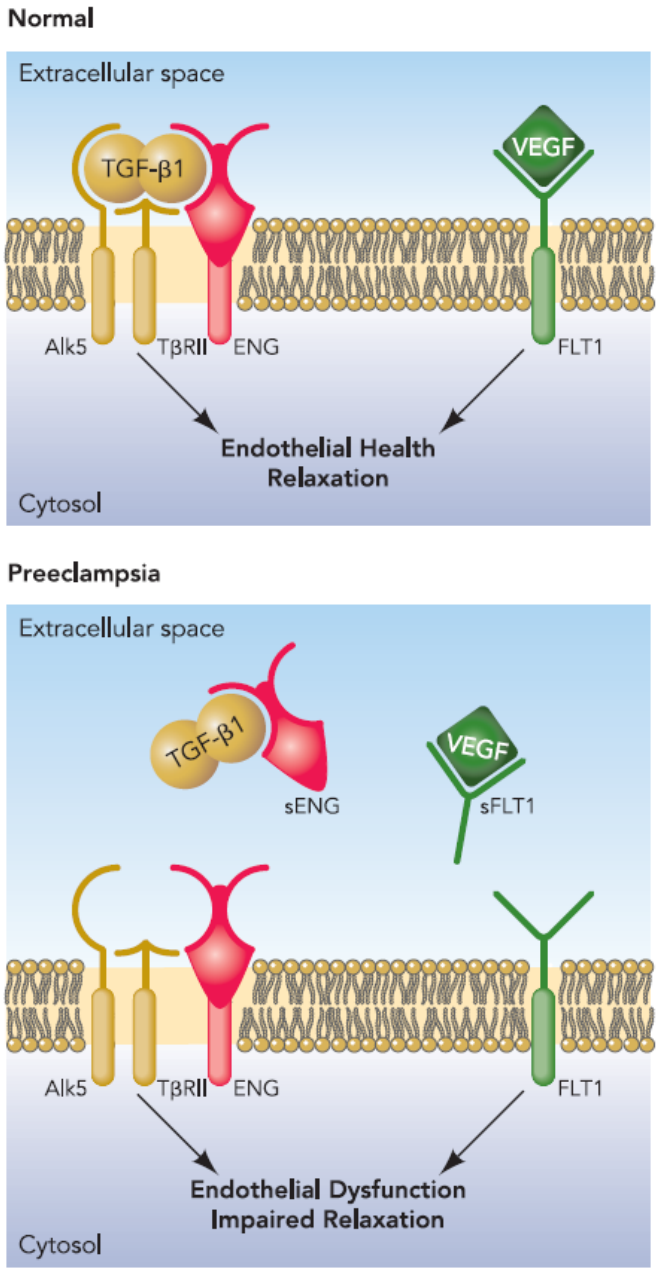
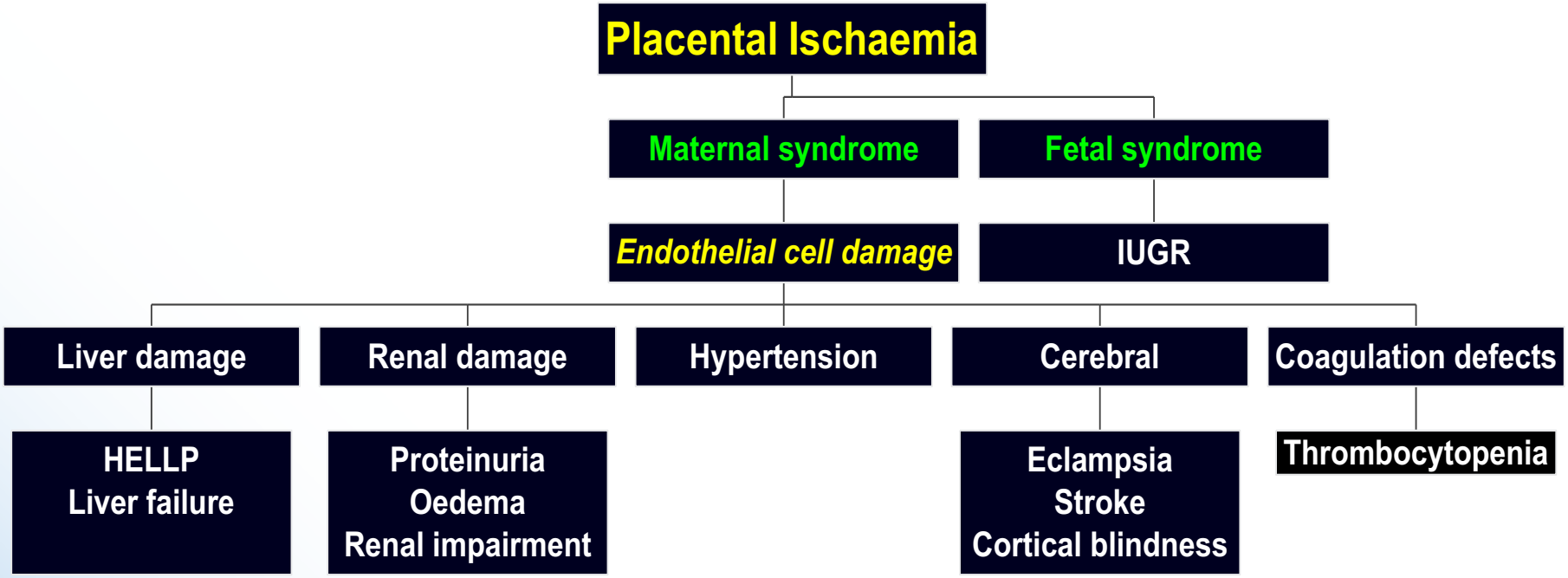
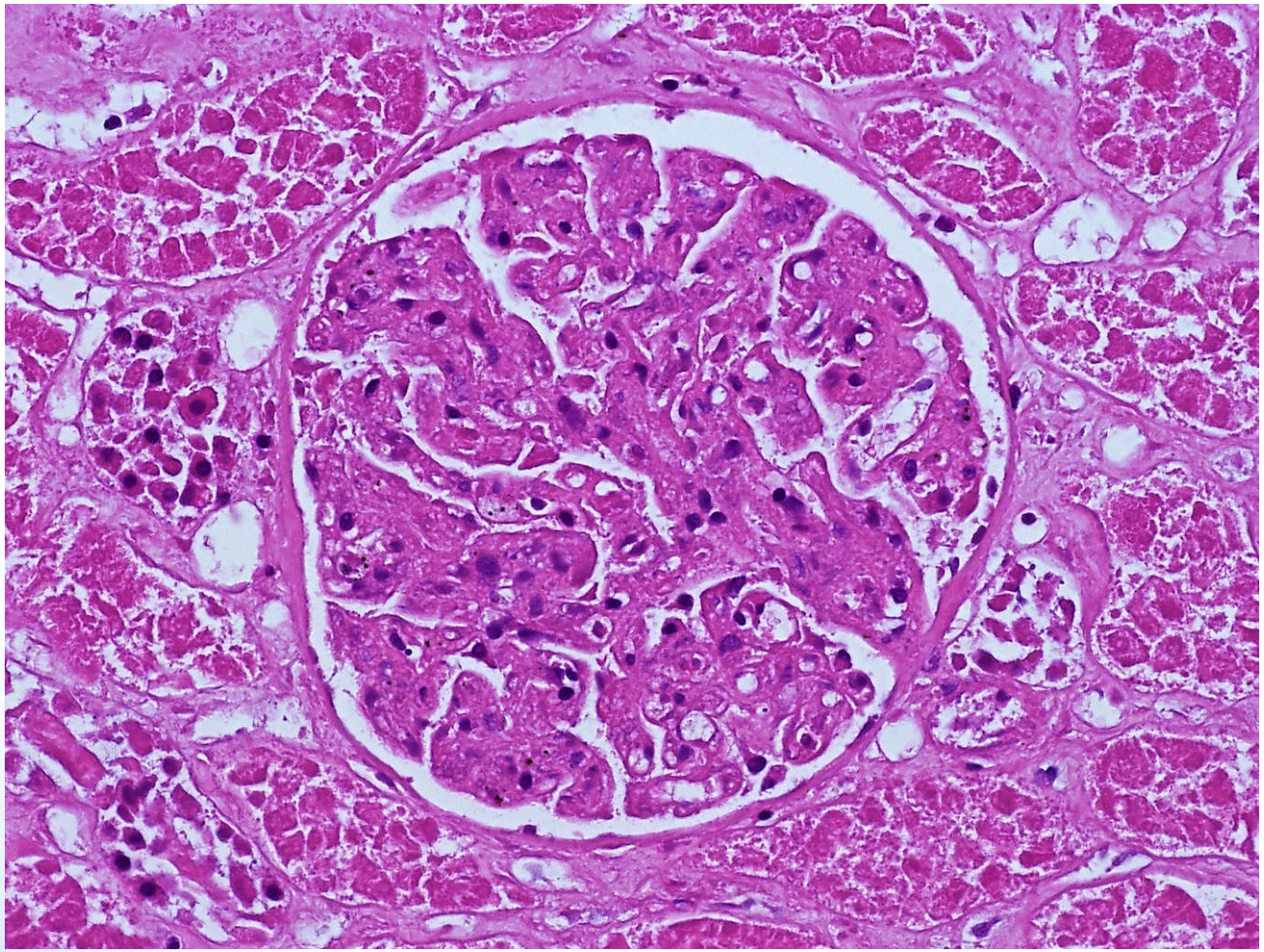


FIGURE 3. sFlt1 and sEng cause endothelial dysfunction by antagonizing VEGF and TGF-β signaling

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

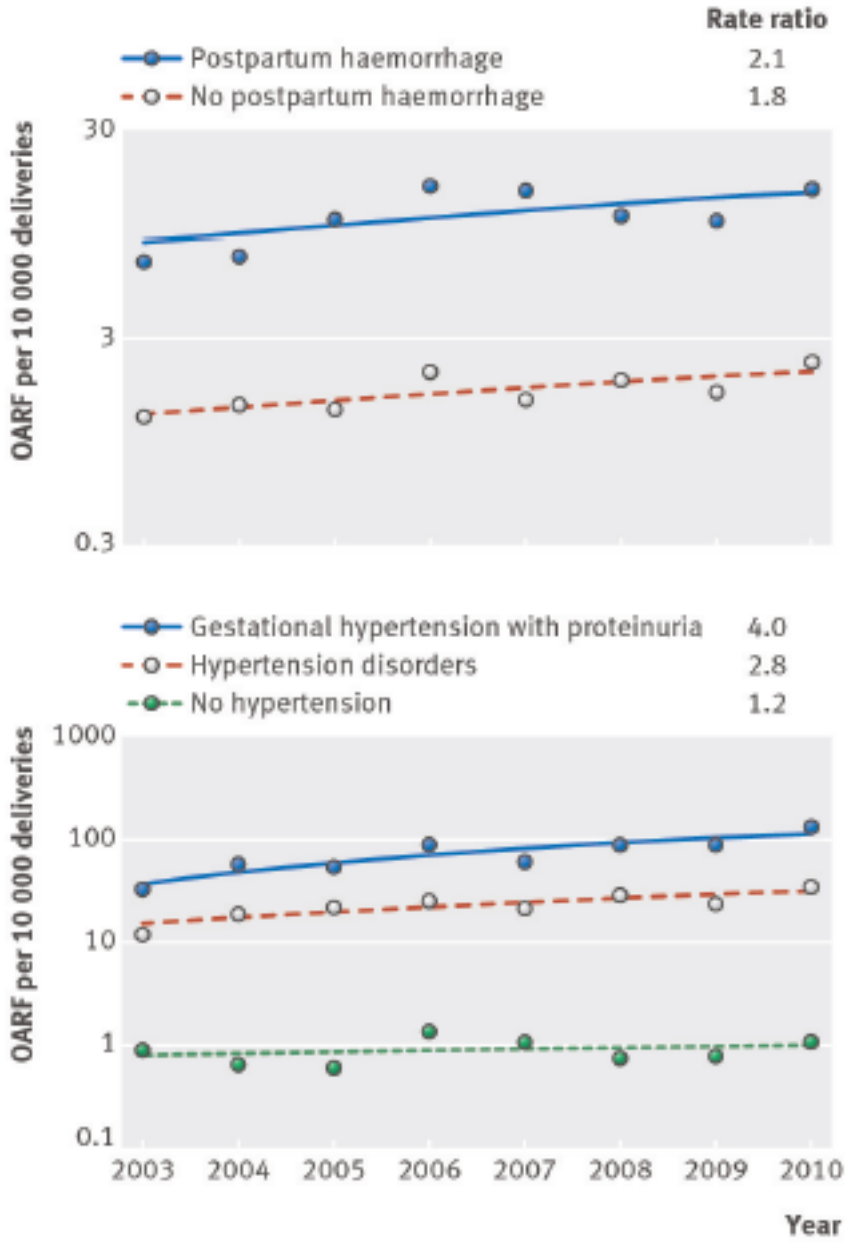
Azar Mehrabadi *PhD candidate*[1 2], Shiliang Liu *senior research scientist*[3], Sharon Bartholomew *senior epidemiologist*[3], Jennifer A Hutcheon *assistant professor*[1 2], Laura A Magee *clinical professor*[1 2 4], Michael S Kramer *professor*[5], Robert M Liston *professor emeritus*[1], K S Joseph *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

Deaths from HELLP Syndrome in UK

	HELLP	Pre-eclampsia
2006-2008	**8**	**19**
2003-2005	**8**	**14**
2000-2002	**8**	**14**
1997-1999	**5**	**15**

Maternal mortality < 1%

Perinatal mortality 9.4-16.2%

Rath & Bartz. Zentralb Gynakol 2004; 126: 294

Maternal mortality = 4.7%

Romero Arauz. Ginecol Obstet Mex 2001; 69: 189

HELLP - Clinical Features

Epigastric / RUQ pain (65%)

N & V (35%)

RUQ tenderness (may precede ↑ LFTs)

Hypertension and proteinuria (mild)

Low grade haemolysis (no anaemia)

Abnormal LFTs

- Raised transaminases
- Raised LDH
- Raised unconjugated bilirubin

Low / falling platelets (< 100,000)

DIC (20%)

Clinical Diagnosis

Platelet count < 100 x 10^9

AST ≥ 70 U/L

LDH > 600 U/L

Sibai AJOG 1990

Mississippi classification

Class 1 platelets ≤ 50 x 10^9

Class 2 platelets 50-100 x 10^9

Class 3 platelets 101-150 x 10^9

Sullivan AJOG 1994

Gestation

Romero Arauz et al. Ginecol Obstet Mex 2001; 69: 189

n = 170

92% antepartum

9%	< 27 weeks
66%	28-36 weeks
25%	term

8% postpartum

Postpartum worsening well described

30% arise postpartum

Liver enzymes recover before platelets

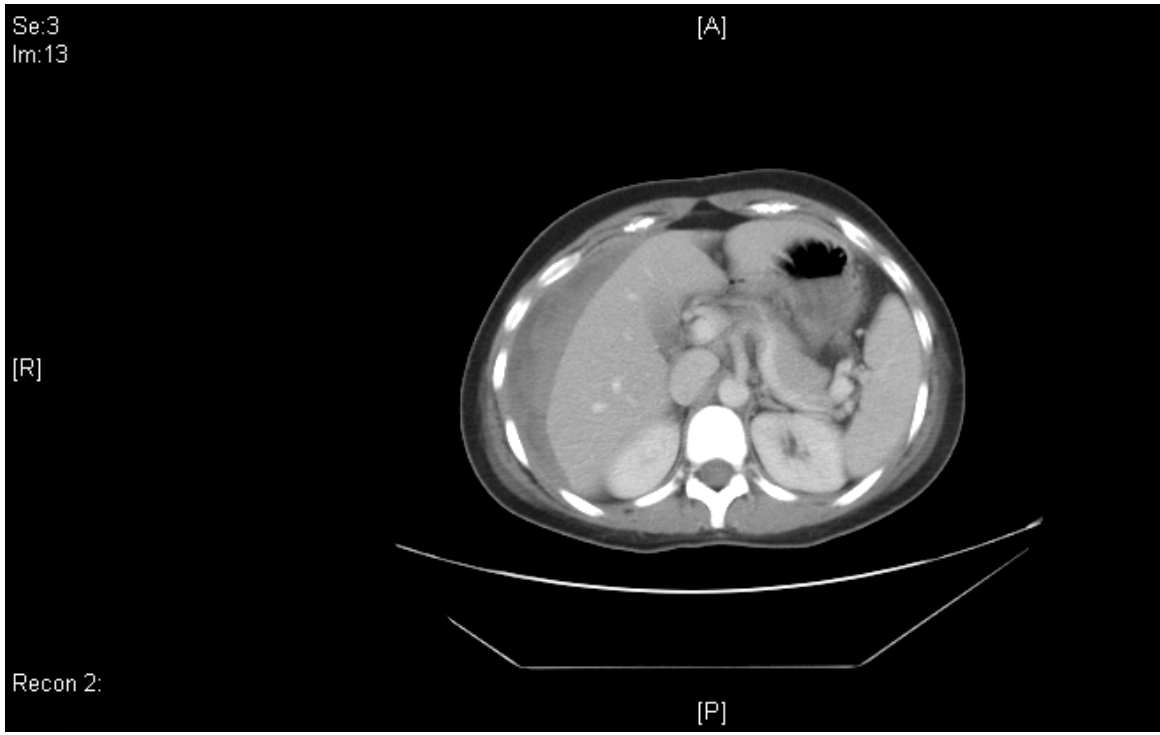
HELLP syndrome - CRISES

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

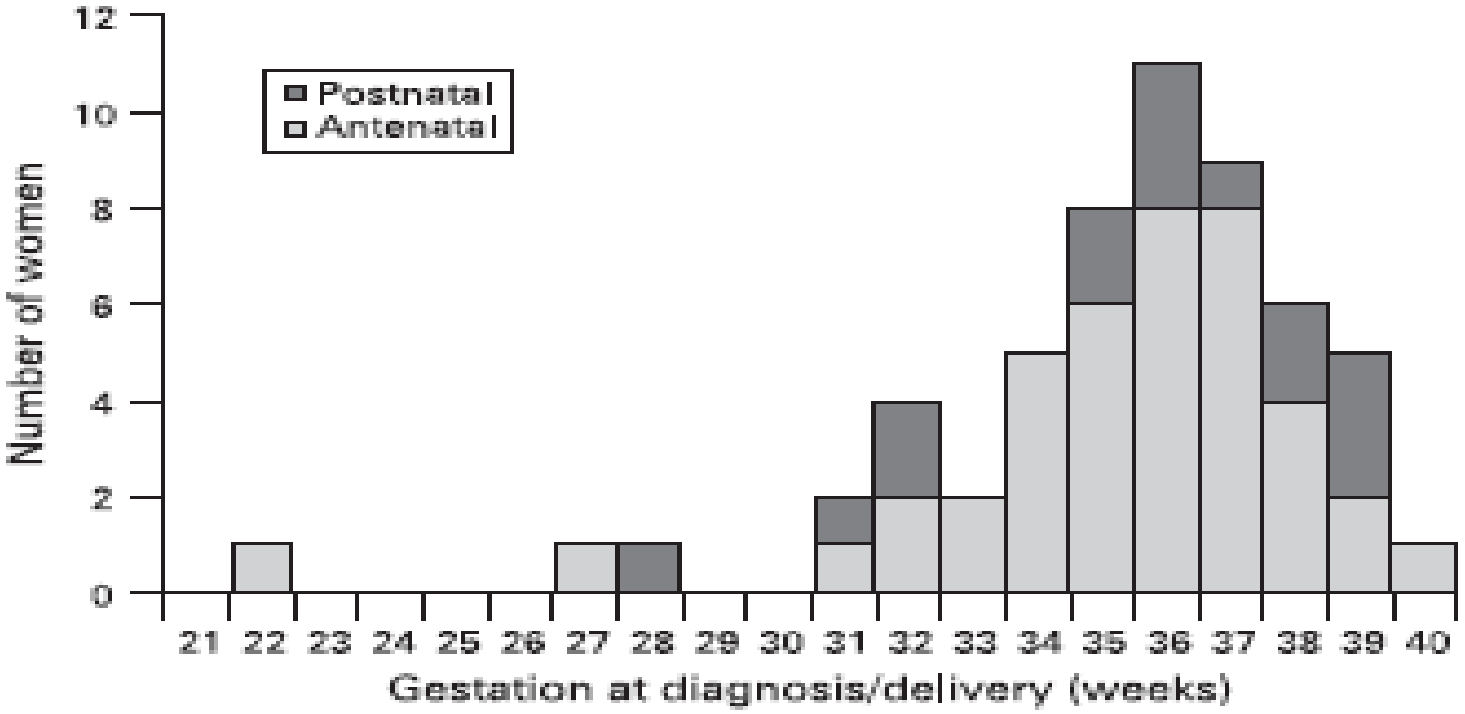


Figure 2 Gestation at diagnosis (antenatal cases) or delivery (postnatal cases).

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

Estimated Incidence

52 confirmed cases in 18 months

Incidence 1 in 21,000 deliveries (95% CI 1/16,000-1/28,100)

Incidence in SE Thames 1997-8
1 in 16,300 (95% CI 1/5,600-1/78,700)†

Incidence in SW Wales 1999-2000
1 in 880 (95% CI 1/380-1/2,700)††

† Waterstone M, Bewley S, Wolfe C (2001). BMJ 322:1089-93
†† Ch'ng et al (2002). Gut 51: 876-880

Acute fatty liver of pregnancy (AFLP)

Very rare (1/7000-1/16,000)

Microvesicular fatty infiltration due to defective beta oxidation of fat

?Variant of pre-eclampsia

Always third trimester (mean = 35 weeks)

Potentially lethal

- Maternal mortality 10%
- Fetal mortality 20-50%

AFLP - Clinical features

nausea, vomiting, malaise	(100%)
abdominal pain	(43%)
associated pre-eclampsia mild hypertension and proteinuria	(50-70%)
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

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%

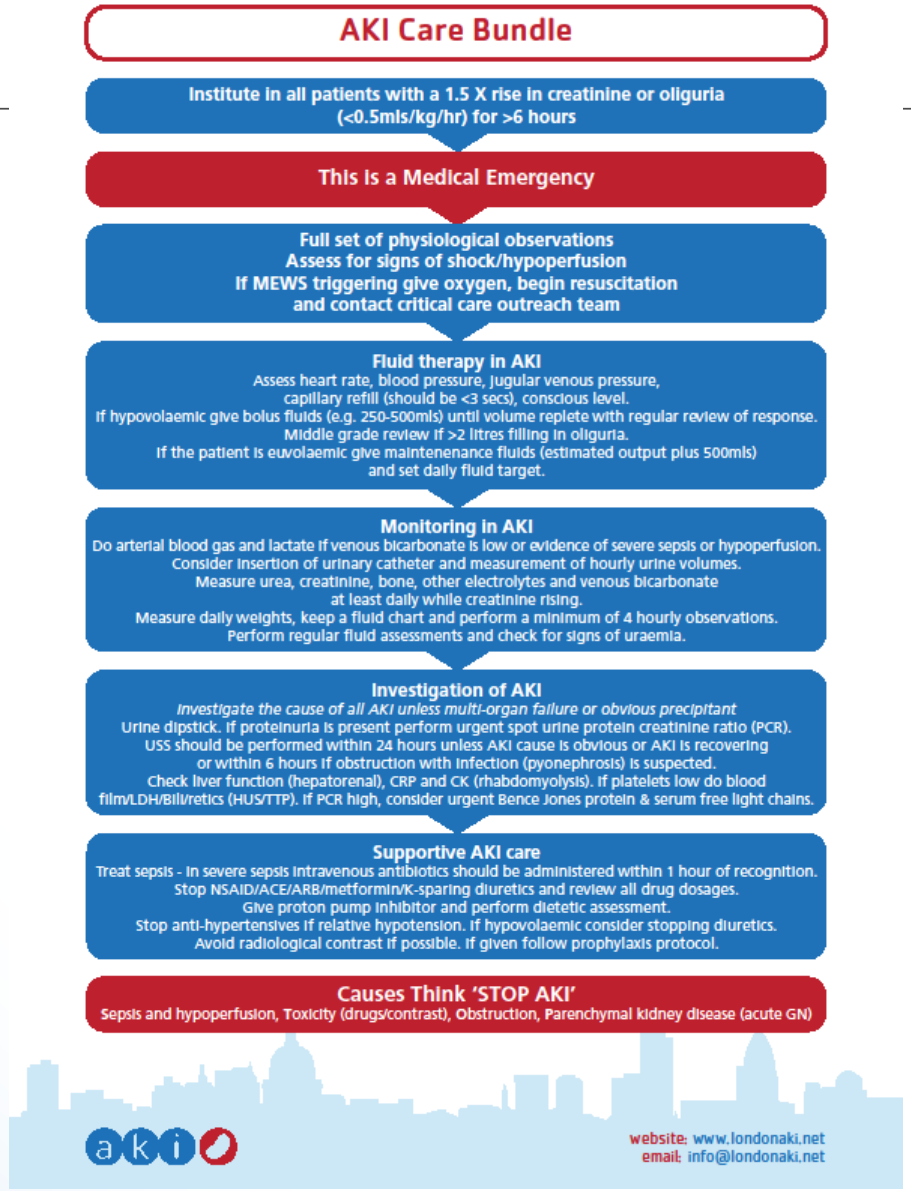
AFLP – Management; HDU / Critical care

- 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

Complications

ARDS	
Pulmonary oedema	**43%**
Pancreatitis	**43%**
AKI	**56%**
Encephalopathy	**50%**
Ascites	**30%**
Wound seroma	**40%**

- Broad spectrum antibiotics and antifungal agents


AKI Care Bundle
Institute in all patients with a 1.5 X rise in creatinine or oliguria (<0.5mls/kg/hr) for >6 hours
This is a Medical Emergency
Full set of physiological observations
Assess for signs of shock/hypoperfusion
If MEWS triggering give oxygen, begin resuscitation and contact critical care outreach team
Fluid therapy in AKI
Assess heart rate, blood pressure, jugular venous pressure, capillary refill (should be <3 secs), conscious level.
If hypovolaemic give bolus fluids (e.g. 250-500mls) until volume replete with regular review of response. Middle grade review if >2 litres filling in oliguria.
If the patient is euvolaemic give maintenenance fluids (estimated output plus 500mls) and set daily fluid target.
Monitoring in AKI
Do arterial blood gas and lactate if venous bicarbonate is low or evidence of severe sepsis or hypoperfusion.
Consider insertion of urinary catheter and measurement of hourly urine volumes.
Measure urea, creatinine, bone, other electrolytes and venous bicarbonate at least daily while creatinine rising.
Measure daily weights, keep a fluid chart and perform a minimum of 4 hourly observations.
Perform regular fluid assessments and check for signs of uraemia.
Investigation of AKI
Investigate the cause of all AKI unless multi-organ failure or obvious precipitant
Urine dipstick. If proteinuria is present perform urgent spot urine protein creatinine ratio (PCR).
USS should be performed within 24 hours unless AKI cause is obvious or AKI is recovering or within 6 hours if obstruction with infection (pyonephrosis) is suspected.
Check liver function (hepatorenal), CRP and CK (rhabdomyolysis). If platelets low do blood film/LDH/Bili/retics (HUS/TTP). If PCR high, consider urgent Bence Jones protein & serum free light chains.
Supportive AKI care
Treat sepsis - in severe sepsis intravenous antibiotics should be administered within 1 hour of recognition.
Stop NSAID/ACE/ARB/metformin/K-sparing diuretics and review all drug dosages.
Give proton pump inhibitor and perform dietetic assessment.
Stop anti-hypertensives if relative hypotension. If hypovolaemic consider stopping diuretics.
Avoid radiological contrast if possible. If given follow prophylaxis protocol.
Causes Think 'STOP AKI'
Sepsis and hypoperfusion, Toxicity (drugs/contrast), Obstruction, Parenchymal kidney disease (acute GN)
website: www.londonaki.net
email: info@londonaki.net

OBSTETRIC AKI CARE BUNDLE

Institute in all cases with creatinine >90mmol/L
or doubling of baseline creatinine or anuria for 1 hour

THIS IS POTENTIALLY A MEDICAL EMERGANCY

Full set of physiological observations BP/HR/RR/SATS/TEMP
Assess for signs of shock/hypoperfusion- low BP/high HR/confusion/pale & cold skin
Review history and past results If MEOWS triggering- high flow oxygen, Review senior/HDU/ITU

Fluid therapy in AKI

If hypovolaemic give crystalloid 250ml. Followed by 125 ml/hr* Assess BP, HR every 15mins
If MEOWS score > 4 middle grade review
Catheterise if obstruction and measure hourly urine output

Monitoring in AKI

Venous blood gas & lactate, U&E twice a day while creatinine rising
Fluid chart, regular fluid assessment and observations

Investigations in AKI

Review drug chart-STOP NSAIDS. Review drug dosages. If proteinuria URGENT spot PCR
Ultrasound (obstruction), Liver Function,
Low platelets blood film (fragmented RBC/PLT), LDH, Bilirubin, Reticulocytes

Supportive AKI care

Sepsis- ANTIBIOTICS within an hour. Review thromboprophylaxis

Causes Think STOP AKI
Prerenal Sepsis/hypovolaemia (PPH)
Renal Toxicity NSAIDS, PET, HELLP, HUS,TTP
Postrenal Obstruction or ureteric damage during delivery

* Caution with PET

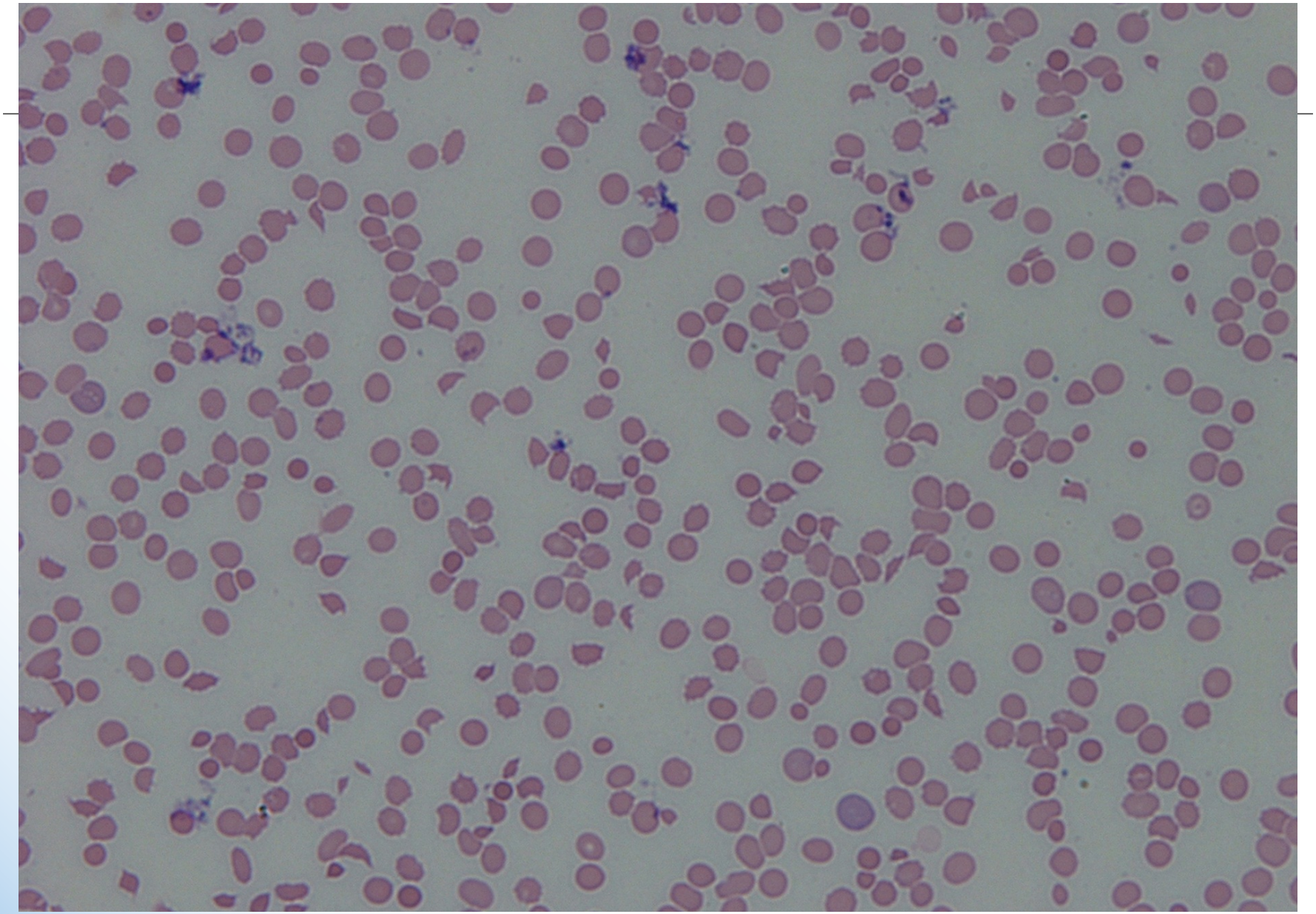
Haemolytic Uraemic Syndrome

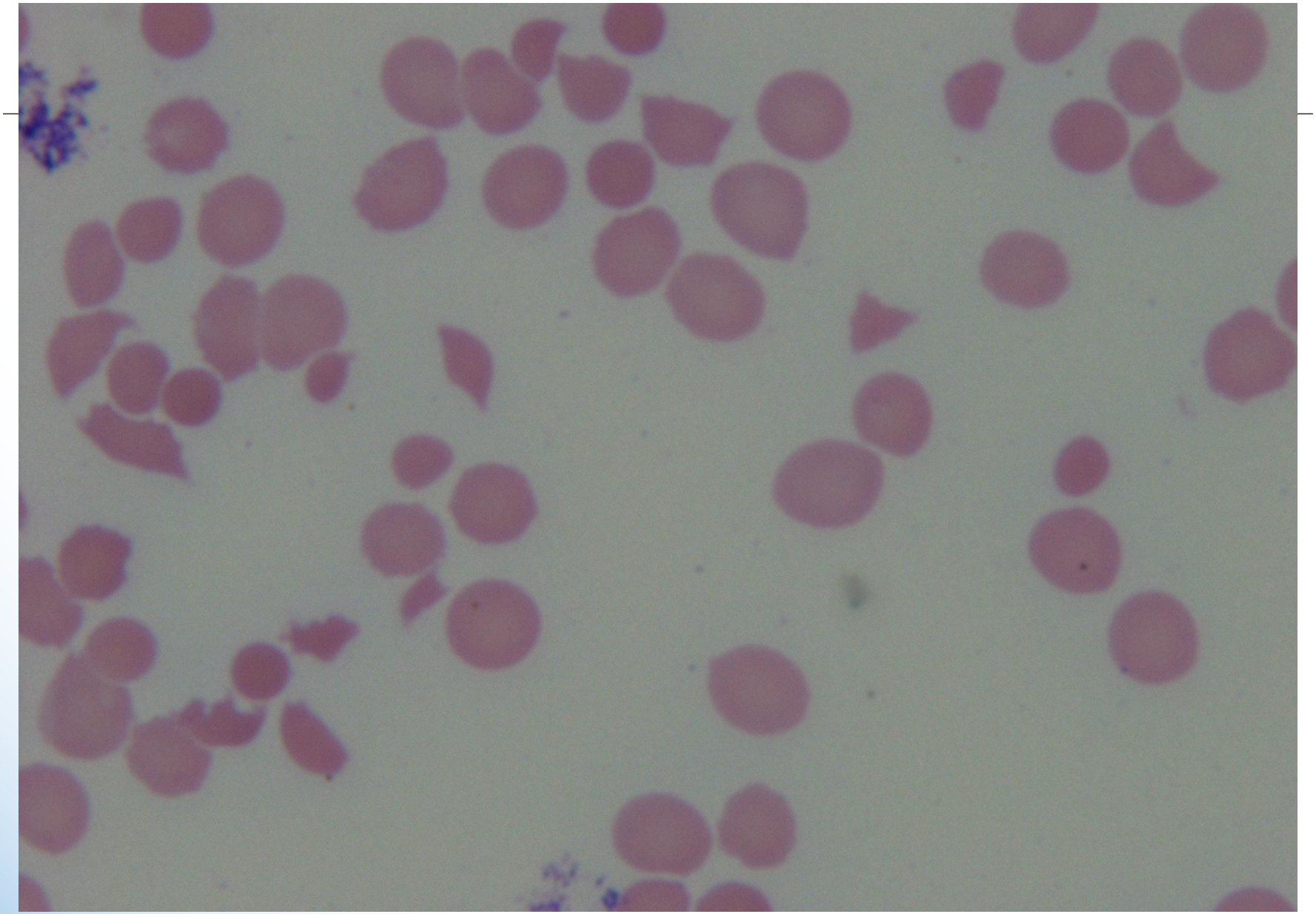
Microangiopathic haemolytic anaemia (MAHA)

Thrombocytopenia (normal clotting)

AKI

Closely related to Thrombotic thrombocytopenic purpura (TTP)





Thrombotic Thrombocytopenic Purpura

Classic pentad (only seen in 1/3)

Fever

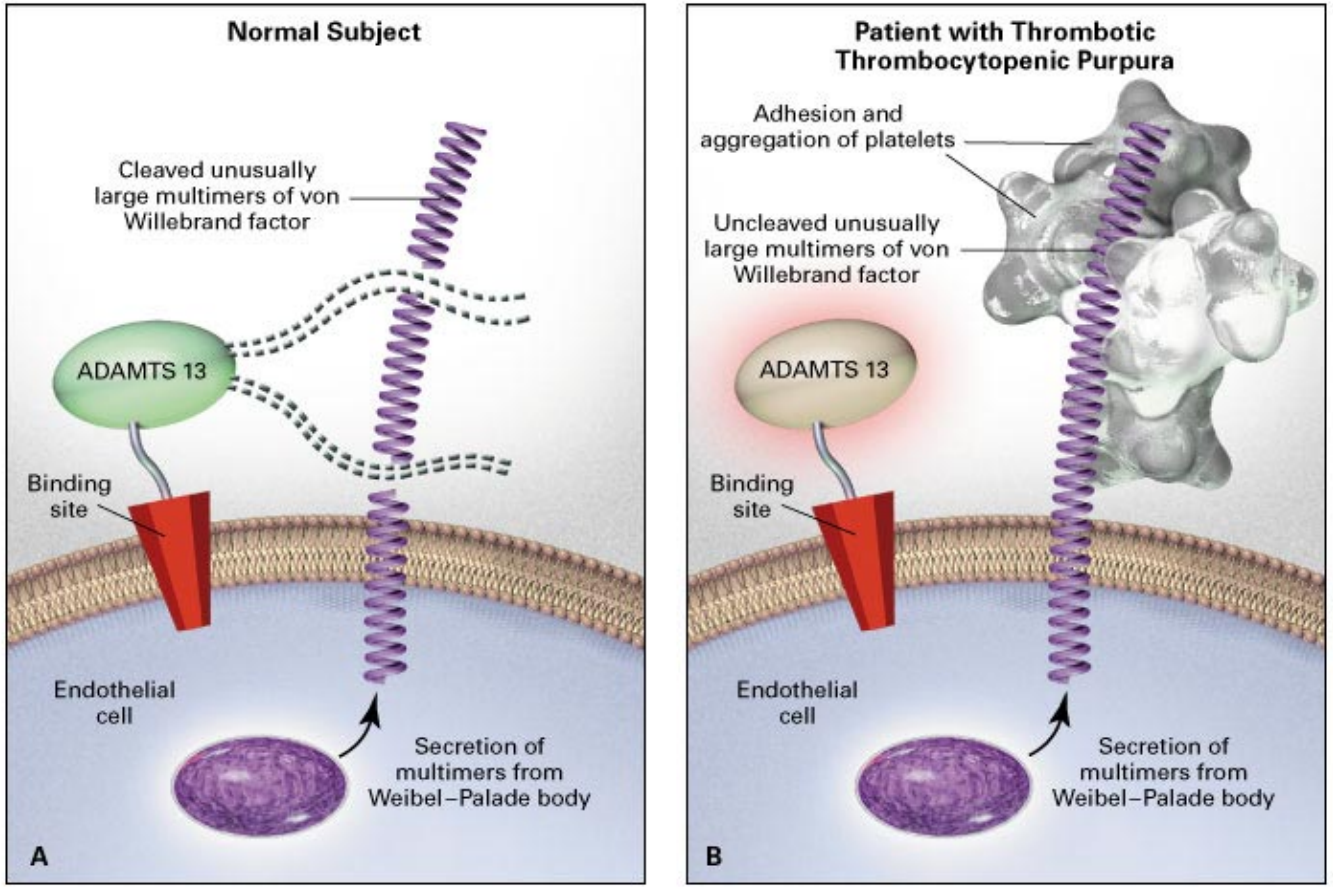
Thrombocytopenia*

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!

Summary

The incidence of AKI is 1.4% in our obstetric unit

The common causes of AKI are Pre-eclampsia and PPH

AKI was recognised in <50% cases

Not all AKI had improved prior to discharge

The development of an AKI Obstetric Bundle is in place