Brigham and Women's Hospital
Founding Member, Mass General Brigham

Pregnancy and Renal Disease

Jessica Sheehan Tangren, MD, MPH
Assistant Physician
Division of Nephrology & Department of Medicine
Massachusetts General Hospital
Assistant Professor
Harvard Medical School

Jessica Sheehan Tangren, MD, MPH

University of Pennsylvania School of Medicine
Medicine Residency @ BWH
Nephrology Fellowship @MGH/BWH
Assistant Professor of Medicine@ HMS

- Clinical focus: Women's Health in Nephrology/ Obstetric Nephrology
- Research focus: Obstetric Nephrology, Preeclampsia

Disclosures

- None

Lecture Objectives

Renal Function Changes in Pregnancy

Approach to AKI during pregnancy

Management of chronic hypertension in pregnancy (new data!)

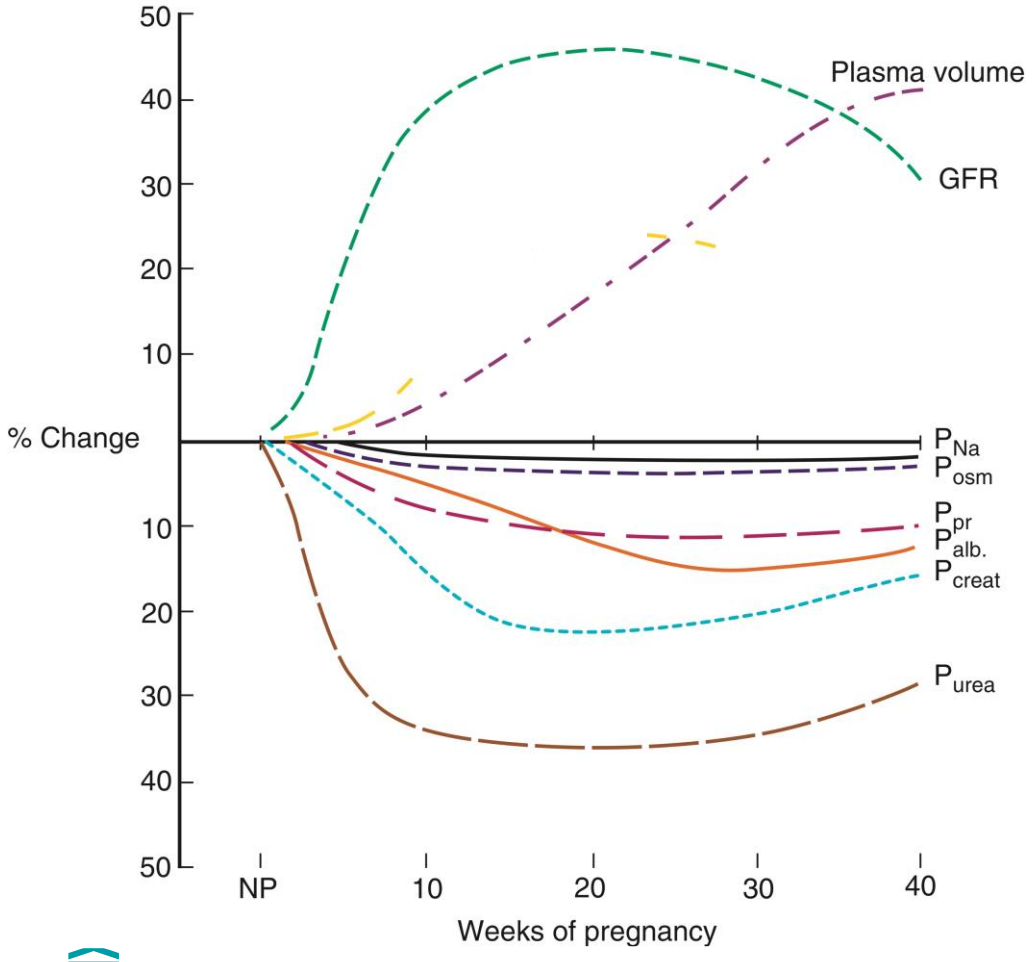
Case Example

25 y/o G1P0 admitted at 37 weeks gestation

- Developed abdominal pain 24 hours prior, poor PO intake
- Noted to be hypertensive with 2+ protein on dipstick and admitted to L+D
- Fetal monitoring was reassuring
- Due to term dates, she underwent induction of labor
- ***Labs return notable for serum creatinine of 1.3 mg/dl***
- 24 hours later she delivered a healthy baby girl

Is this serum creatinine normal in pregnancy?

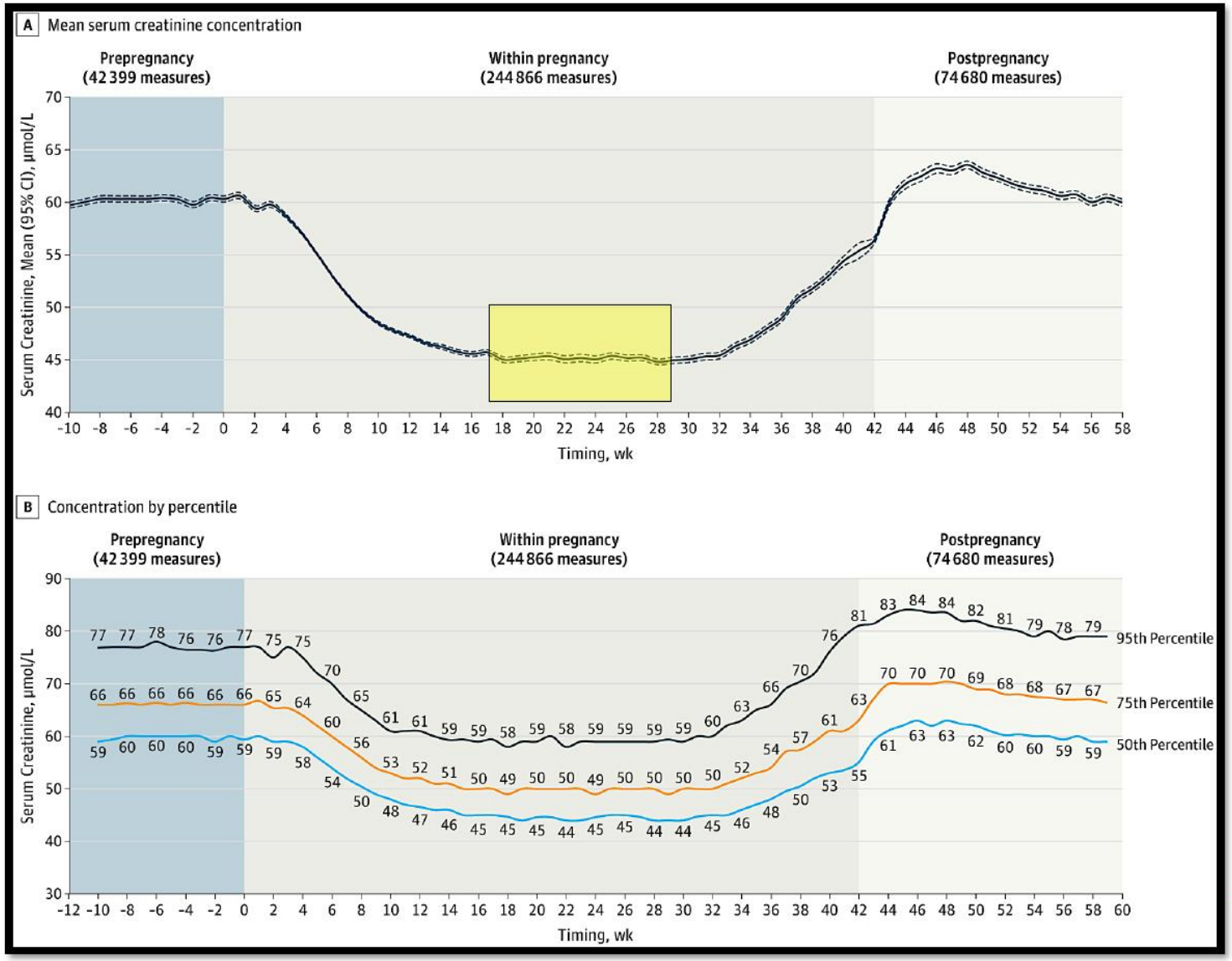
Renal Physiology in Pregnancy



Plasma volume	Increases by 30-50%
Blood Pressure	Decreases by ~10 mm Hg with nadir in mid pregnancy followed by slow rise to pre-pregnancy levels at delivery
Cardiac Output	Increases by 30-40%
Renal Blood Flow	Increases by 80%
Glomerular filtration rate	Increases by 40-50% above baseline
Osmolality	Falls to new osmotic setpoint ~ 270 mOsm//kg

Tangren and Hladunewich, *NKF Primer* 2018

Estimating GFR in Pregnancy



Harel JAMA *2019*

How to Define AKI in Pregnancy?

- Given the dynamic changes in GFR longitudinally across pregnancy, defining AKI can be challenging

- A “normal” creatinine can reflect significant compromise in renal function in a pregnant woman.

- Standard definitions of AKI, including the RIFLE and AKIN criteria, have not been validated in pregnant populations, however in general these definitions are used to define AKI in this population.

How to Define AKI in Pregnancy?

Timing	Creatinine Range (mg/dL)
Pre-Pregnancy	0.68-0.88
1st Trimester (12 weeks)	0.53-0.69
2nd Trimester (24 weeks)	0.51-0.68
3rd Trimester (36 weeks)	0.54-0.63
Post-Partum	0.71-0.95

Harel JAMA *2019*

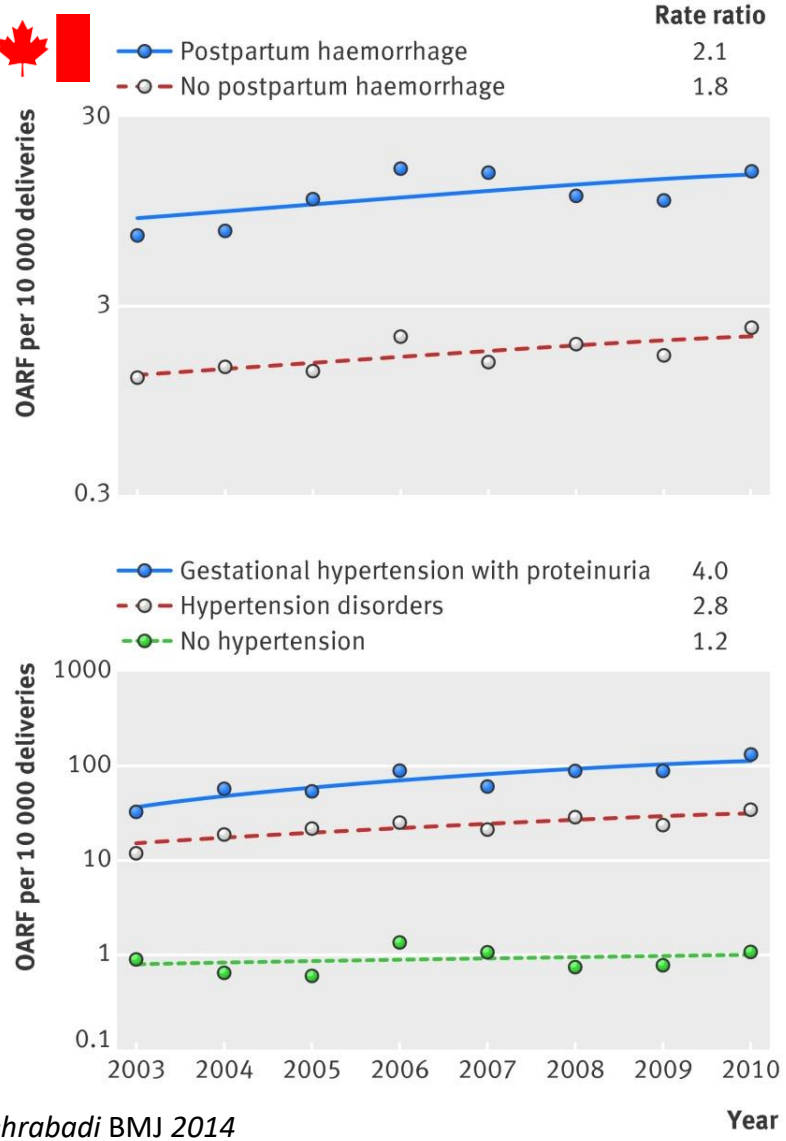
AKI Epidemiology in Pregnancy

In general, rates of pregnancy-associated AKI (P-AKI) have decreased over the past 30 years.

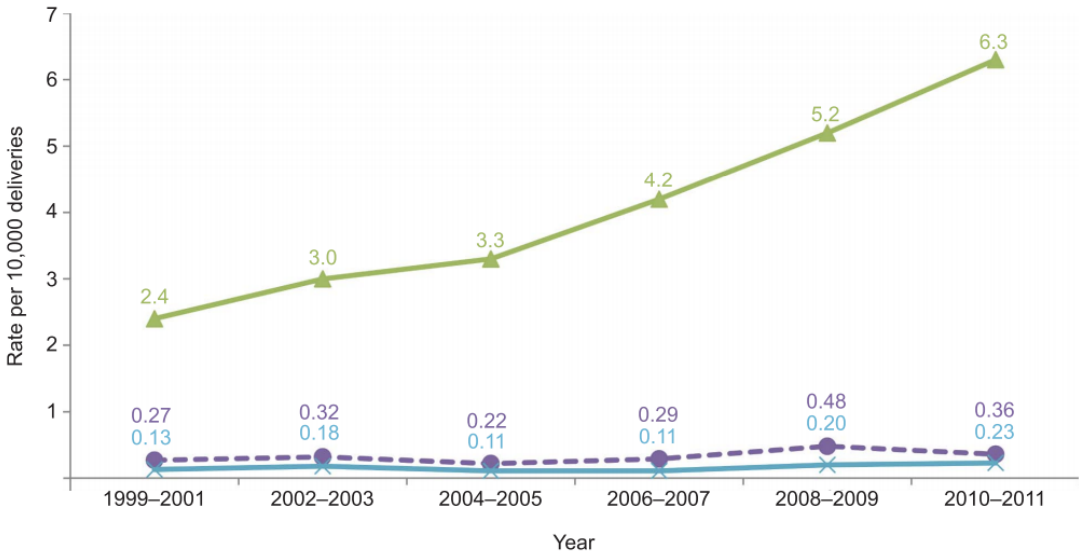
- Italy 1:3,000 births → 1:18,000 from 1950s to 1990s
- India 15% → 1.5% from 1980s to 2010s
- Associated mortality >20% → 4-6%

Improved care of sepsis, post-partum hemorrhage and placental abruption

AKI Epidemiology in Pregnancy



Mehrabadi BMJ *2014*



	2010–2011 compared with 1999–2001 OR (95% CI)	*P* value for trend
Acute renal failure	2.64 (2.31–3.01)	*P*<.01
Acute renal failure with dialysis	1.31 (0.91–1.90)	*P*=.01
Acute renal failure with maternal death	1.73 (1.00–3.01)	*P*=.01

Fig. 1. Unadjusted rates of obstetric acute renal failure, acute renal failure with dialysis, and acute renal failure with maternal death, United States, 1999–2011. Odds ratios (ORs) (95% confidence interval [CI]) express the temporal increase in rates of obstetric acute renal failure in 2010–2011 compared with 1999–2001, and the *P* value for trend expresses the significance of these changes.

Mehrabadi. Rise in Obstetric Acute Renal Failure. Obstet Gynecol 2016.

Case Example

25 y/o G1P0 admitted at 37 weeks gestation

- Developed abdominal pain 1 day prior
- Noted to be hypertensive with 2+ protein on dipstick and admitted to L+D
- Fetal monitoring was reassuring
- Due to term dates, she underwent induction of labor
- ***Labs return notable for serum creatinine of 1.3 mg/dl***
- 24 hours later she delivered a healthy baby girl

Additional lab evaluation

- **Hemoglobin 5.3 g/dL, LDH >1,000, AST 114, platelets 50**

How to approach differential diagnosis of AKI in pregnancy?

Differential Diagnosis of AKI in Pregnancy

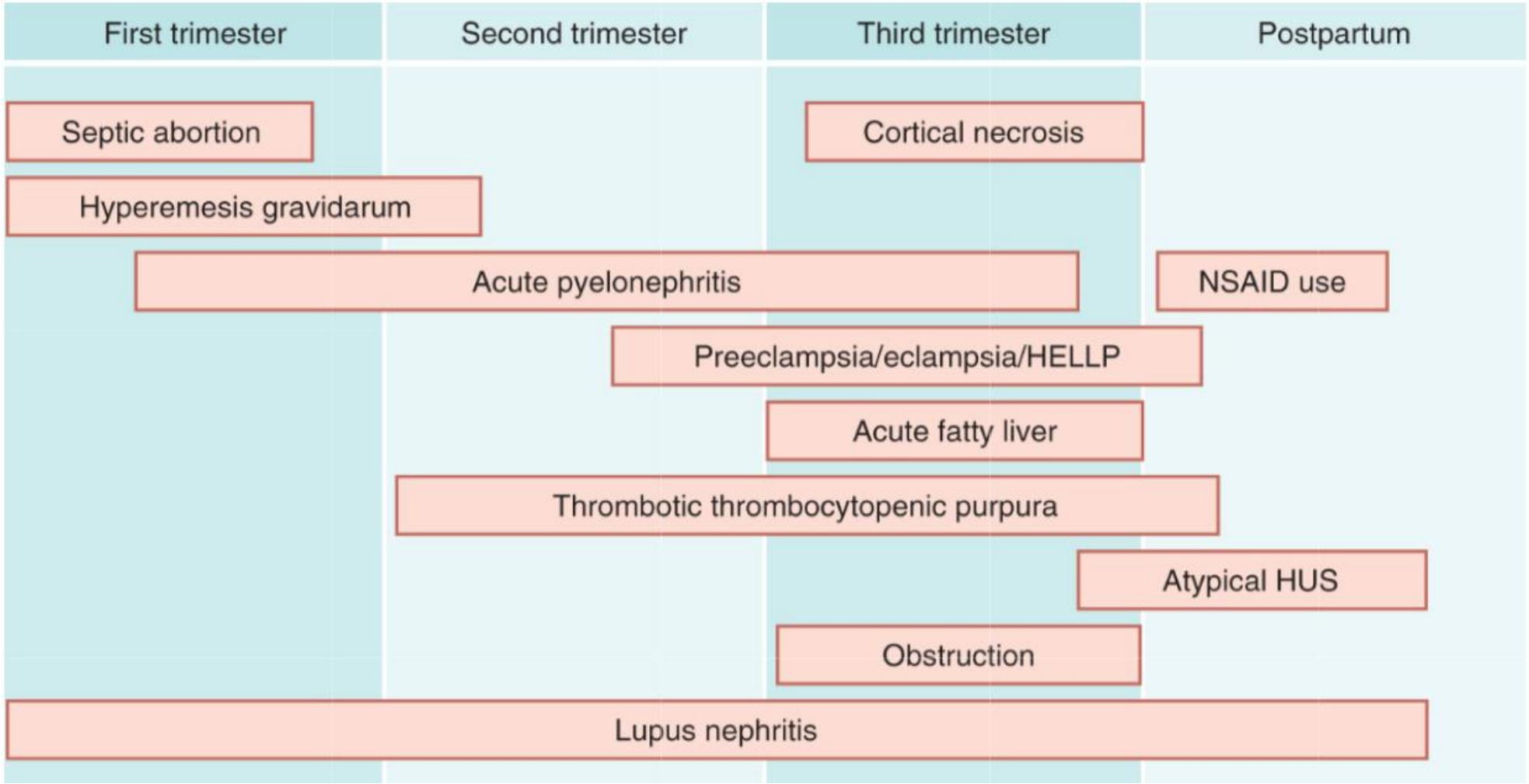
Pregnancy-specific "placental" syndromes – ***severe preeclampsia or HELLP syndrome***

- Symptoms should resolve with delivery

Primary renal syndromes –***glomerular disease/thrombotic microangiopathy***

- Diagnosis and appropriate treatment based on underlying cause (immunosuppression, plasma exchange, B-cell depletion, complement inhibitors)

Major Causes of AKI by Trimester



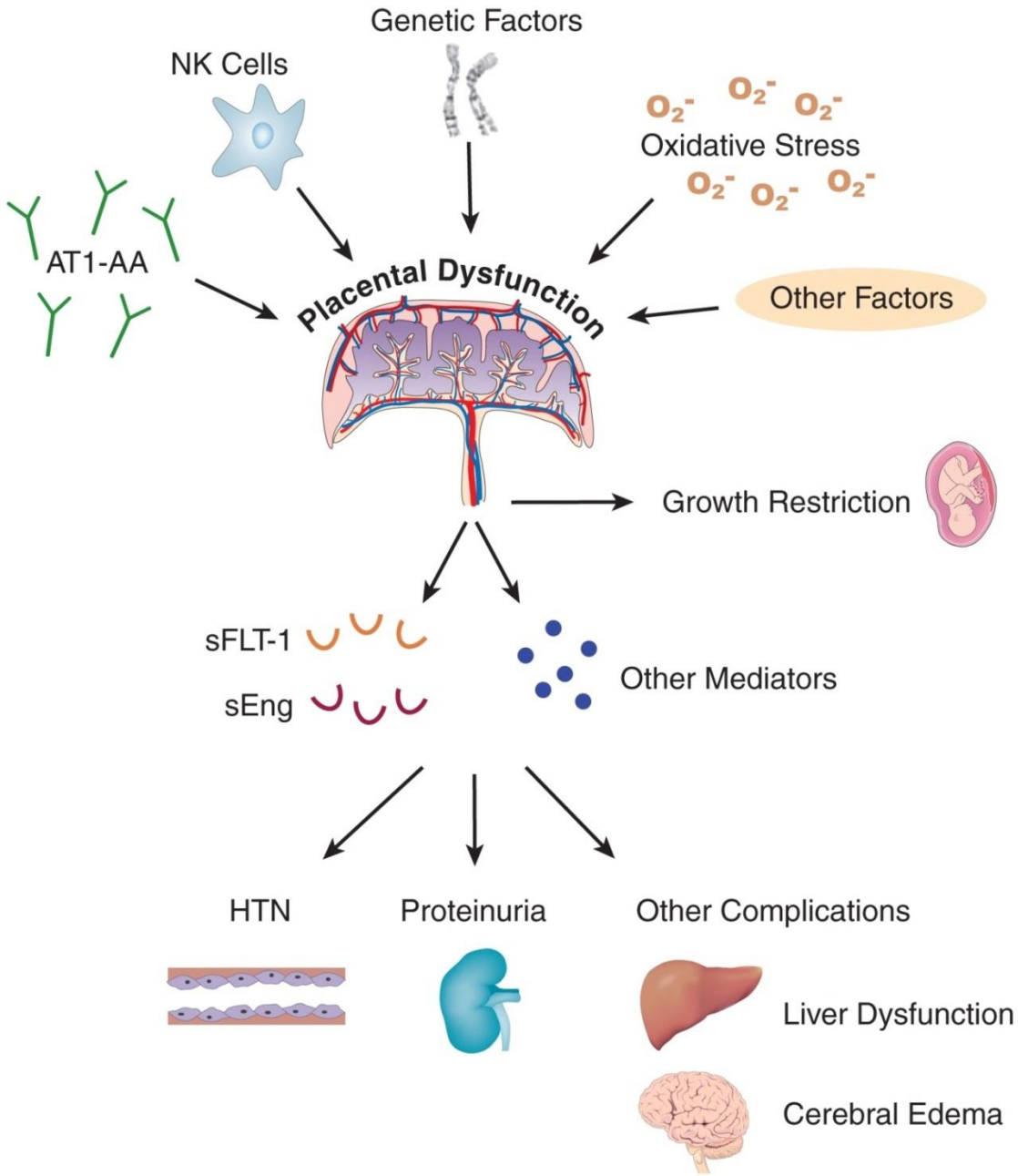
Tangren and Hladunewich, *NKF Primer* 2018

TABLE 2-1. Diagnostic Criteria for Preeclampsia

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	• Greater than or equal to 300 mg per 24 hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio greater than or equal to 0.3* • Dipstick reading of 1+ (used only if other quantitative methods not available)
Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	• Platelet count less than 100,000/microliter
Renal insufficiency	• Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
Impaired liver function	• Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual symptoms	

* Each measured as mg/dL.

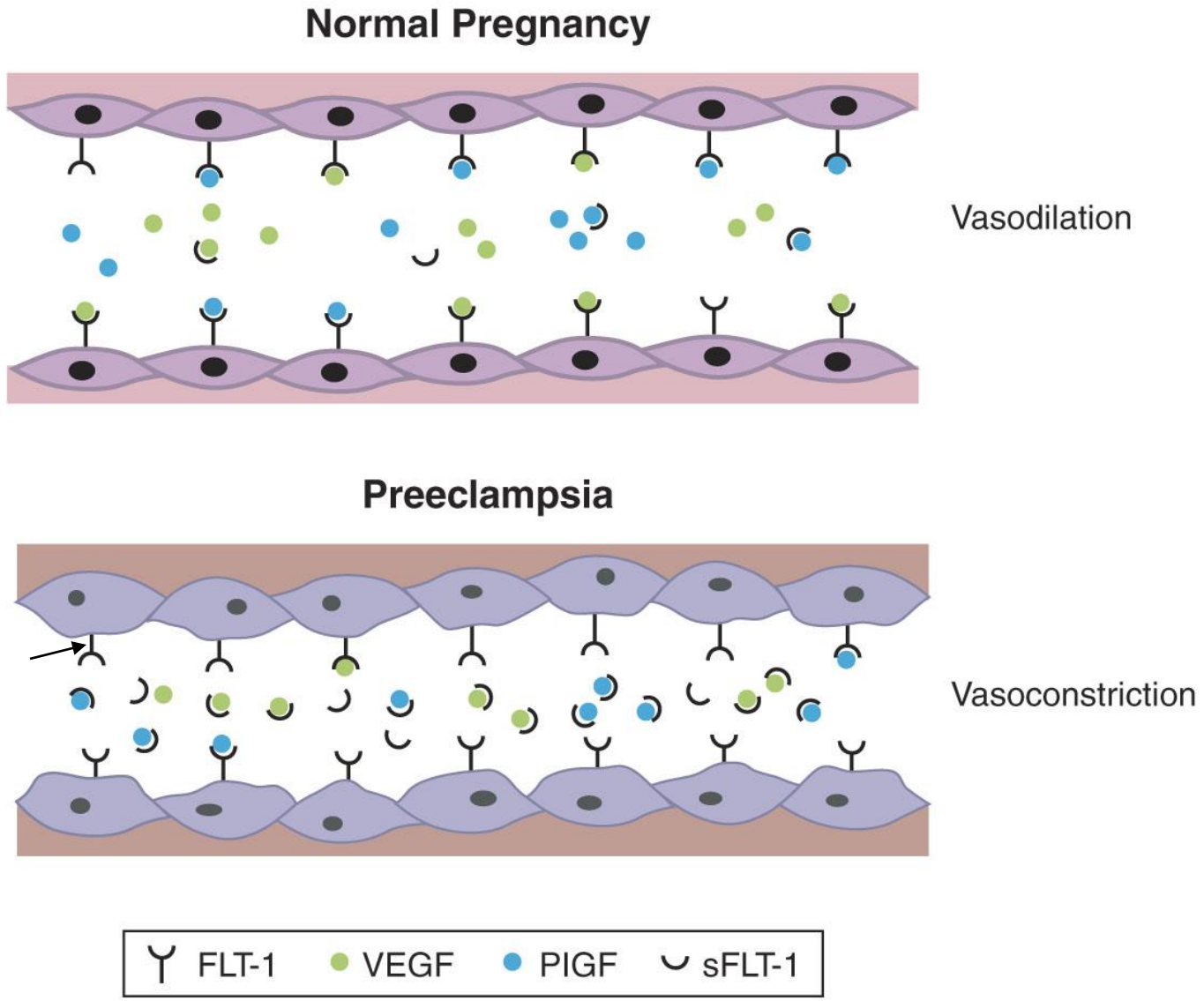
ACOG 2013



Parikh S & Karumanchi SA, Nature Medicine, 2008

Blood vessel

Sick endothelium



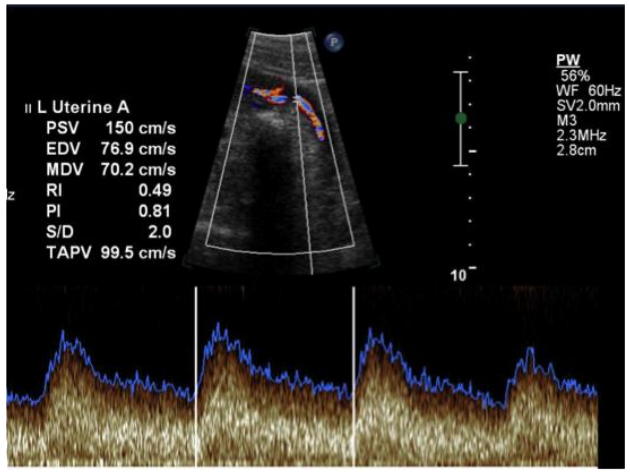
Bdolah *Seminars in Nephrology* 2004

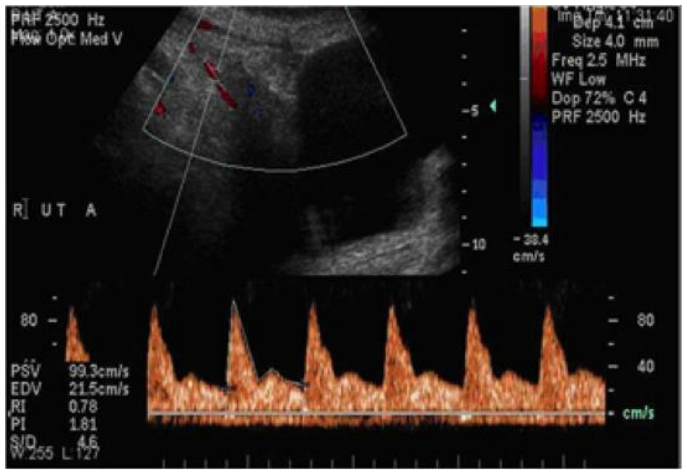
Risk Factors for Preeclampsia

Risk Factor	OR or RR (95% CI)
Antiphospholipid antibody syndrome	9.7 (4.3 – 21.7)
Renal Disease	7.8 (2.2 – 28.2)
Prior Preeclampsia	7.2 (5.8 - 8.8)
Systemic lupus erythematosis	5.7 (2.0 – 16.2)
Nulliparity	5.4 (2.8 – 10.3)
HIV positive, untreated	4.9 (2.4-10.1)
HIV+ on HAART	5.6 (1.7-18.1)
Chronic hypertension	3.8 (3.4 – 4.3)
Diabetes Mellitus	3.6 (2.5 - 5.0)
Multiple Gestations	3.5 (3.0 - 4.2)
Strong family history of cardiovascular disease (heart disease or stroke in ≥2 first degree relatives)	3.2 (1.4 – 7.7)
Obesity	2.5 (1.7-3.7)
Family history of preeclampsia in first degree relative	2.3-2.6 (1.8 – 3.6)
Advanced Maternal Age (>40)	1.68 (1.23-2.29) for nulliparas 1.96 (1.34-2.87) for multips

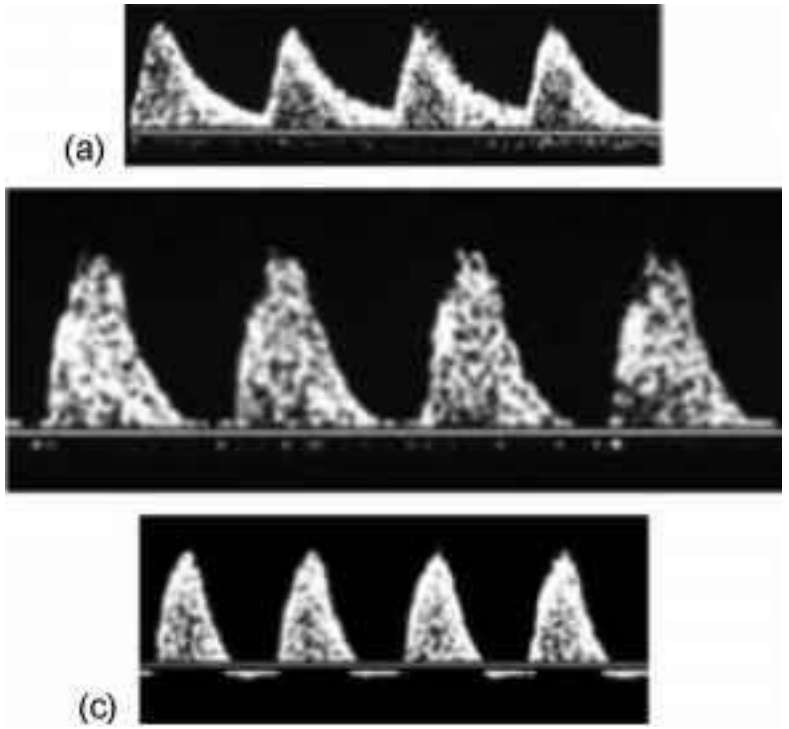
Placental Evaluation

- Uterine artery dopplers



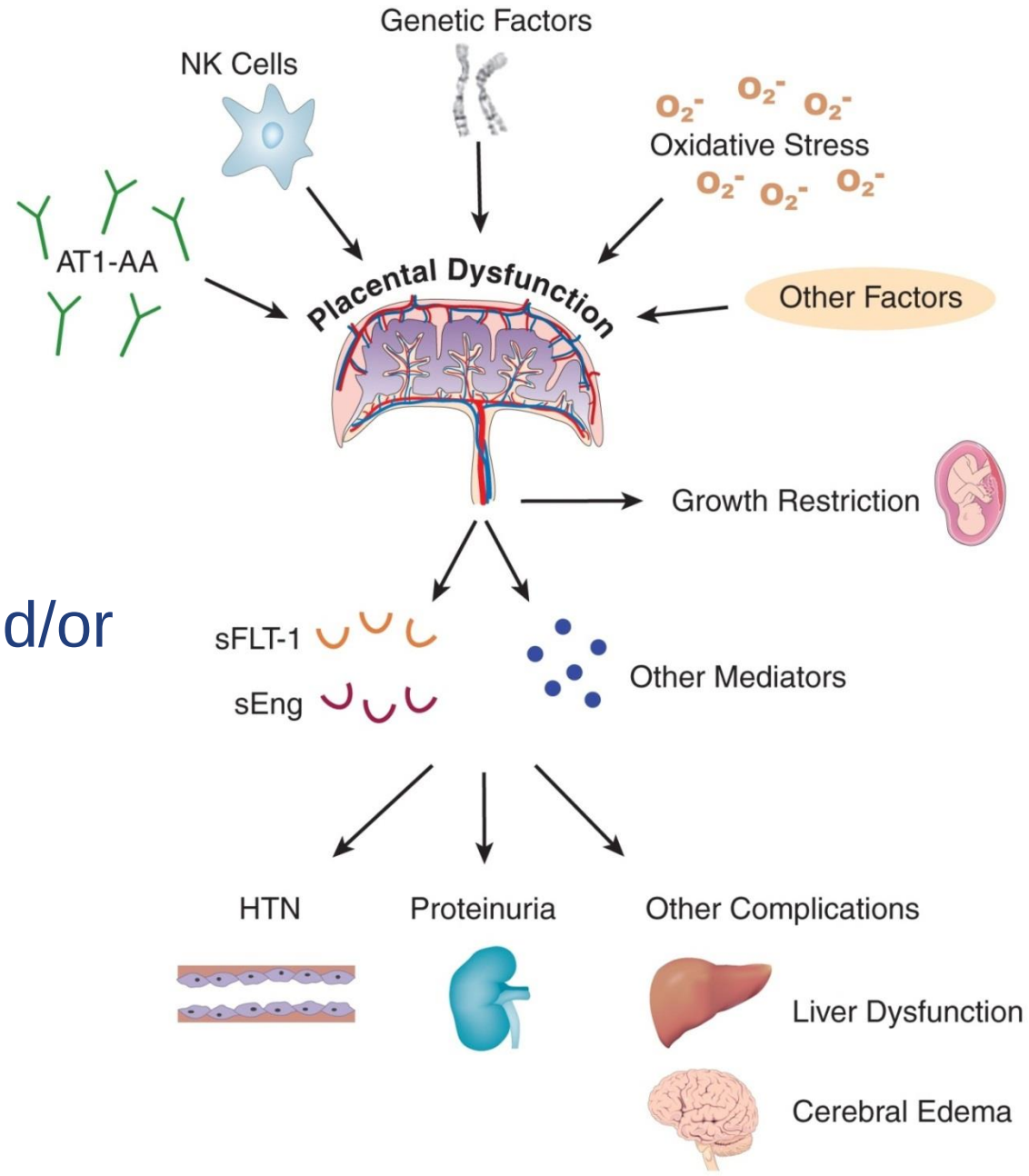


- Umbilical artery dopplers



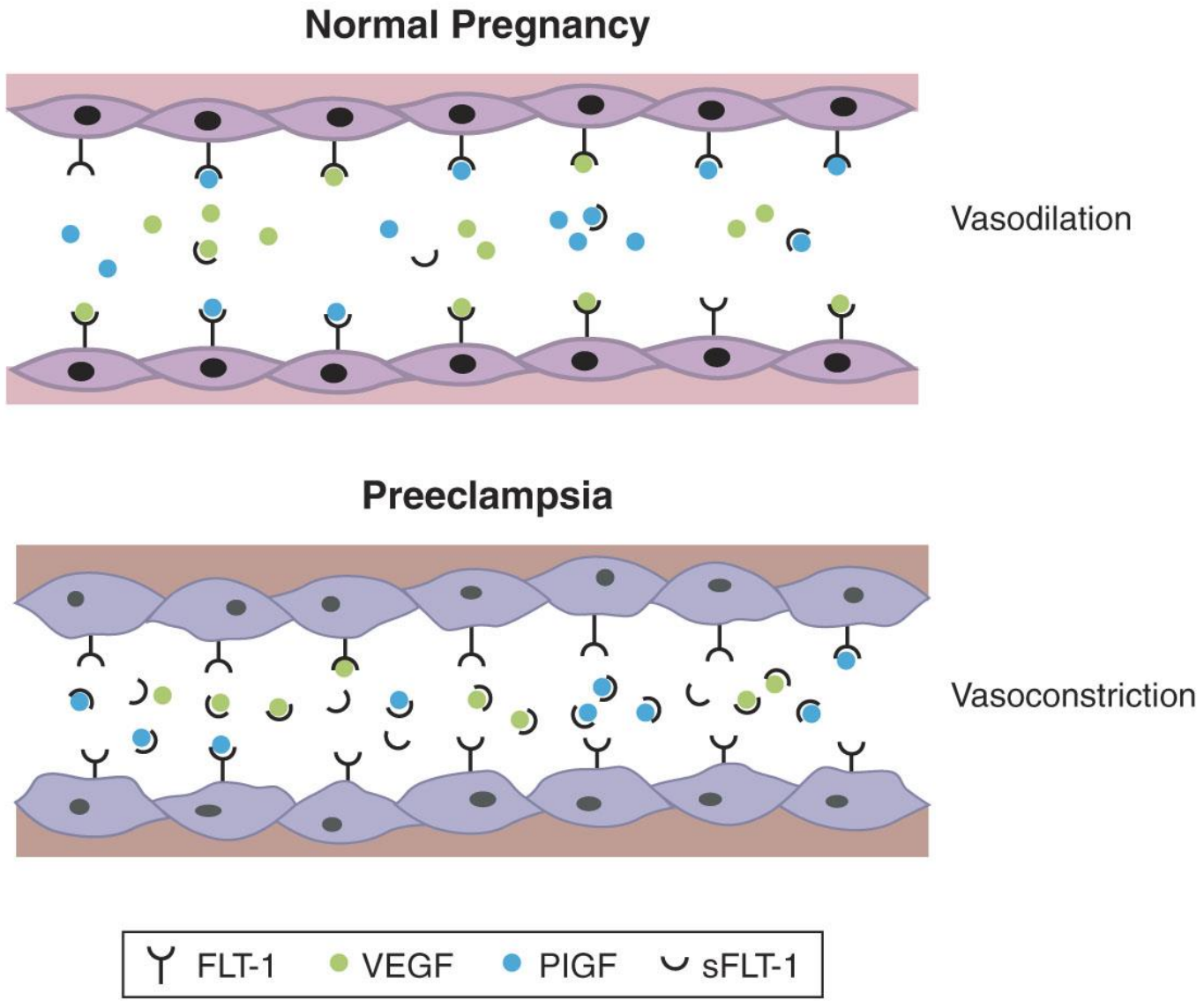
http://womensandinfantshealth.ca/fetal-medicine/placenta/placental-function-testing/

Preeclampsia is a *clinical syndrome* characterized by hypertension, proteinuria and/or end-organ dysfunction



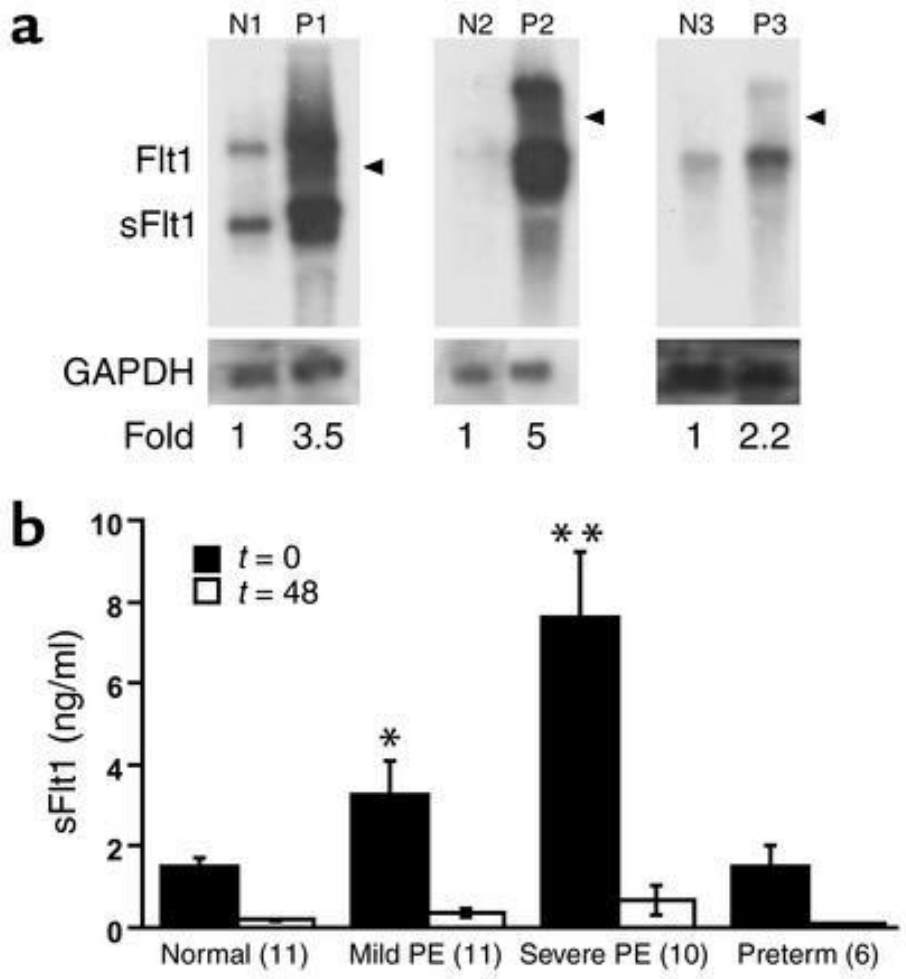
Parikh S & Karumanchi SA, Nature Medicine, 2008

- sFlt1 is a soluble spice variant of the VEGF receptor Flt1
- sFlt1 is secreted by the placenta and antagonizes VEGF and PlGF in the circulation
- sFlt administered to pregnant rats results in a preeclampia syndrome



Bdolah *Seminars in Nephrology* 2004

Angiogenic Imbalance in Preeclampsia



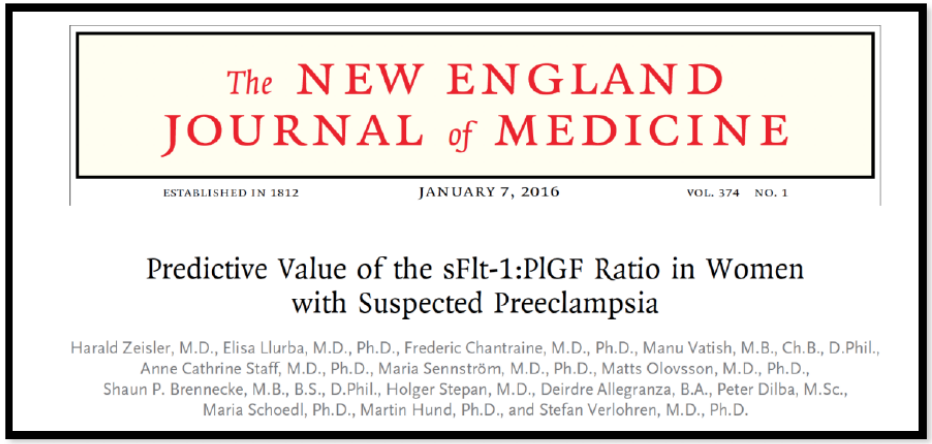
Maynard *JCI* 2003

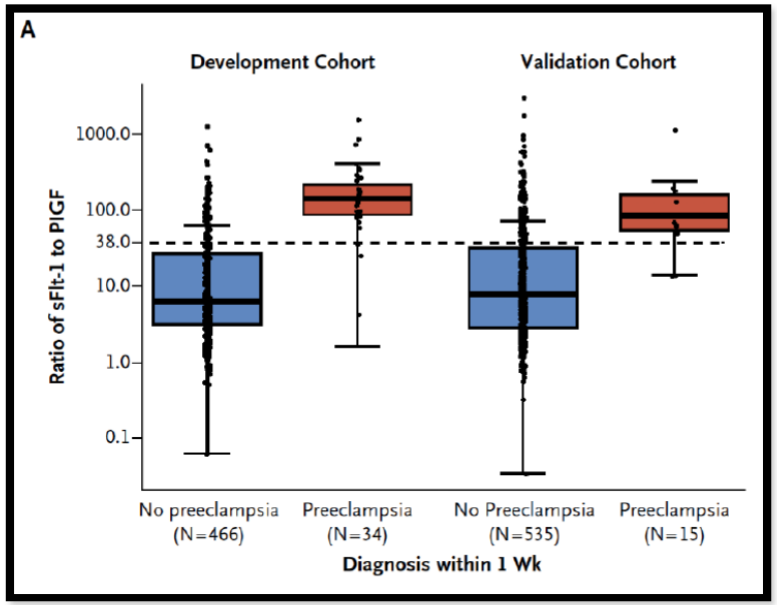
PROGNOSIS Study

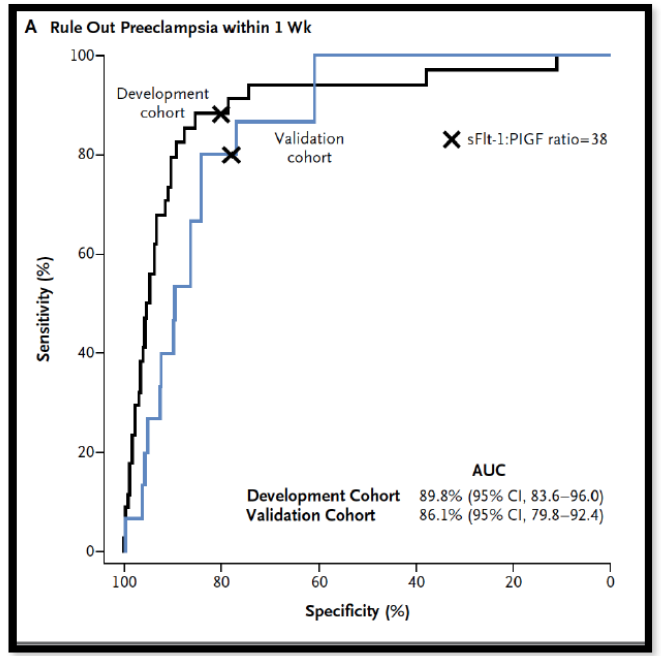
Population: ‘Suspected preeclampsia’
Europe/Australia/NZ/Canada/S. America
90% Caucasian

Outcome: s-Flt1:PlGF cut-off <38 ruled out preeclampsia in next week

99.3% negative predictive value







PRAECIS Study

NEJM Evidence

Published November 9, 2022
NEJM Evid 2022; 1 (12)
DOI: 10.1056/EVIDoa2200161

ORIGINAL ARTICLE

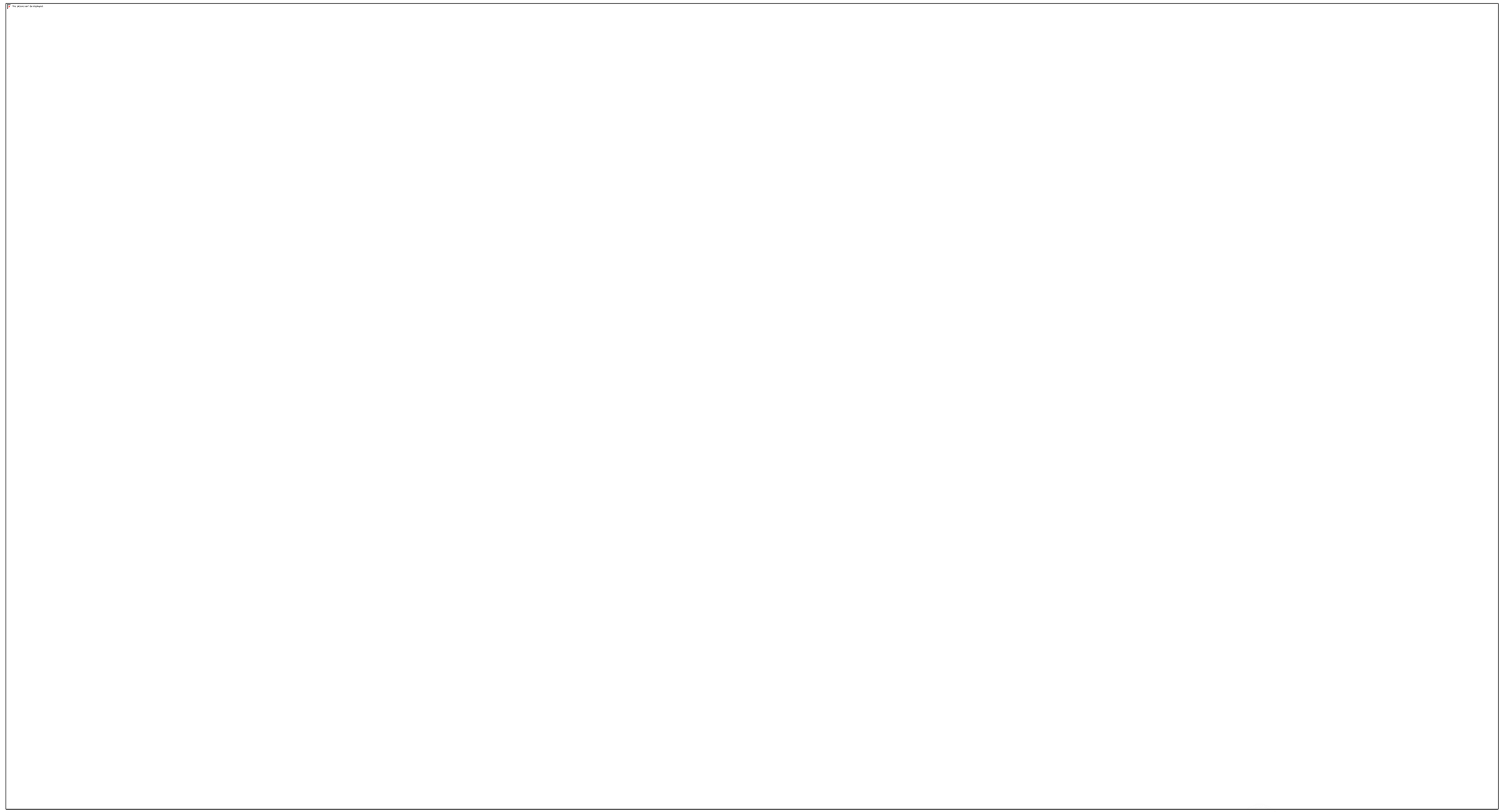
Circulating Angiogenic Factor Levels in Hypertensive Disorders of Pregnancy

Ravi Thadhani, M.D., M.P.H.,[1,2] Elizabeth Lemoine, M.D.,[1,3] Sarosh Rana, M.D., M.P.H.,[4] Maged M. Costantine, M.D.,[5] Vinicius F. Calsavara, Ph.D.,[1] Kim Boggess, M.D.,[3] Blair J. Wylie, M.D., M.P.H.,[6] Tiffany A. Moore Simas, M.D., M.P.H., M.Ed.,[7] Judette M. Louis, M.D., M.P.H.,[8] Jimmy Espinoza, M.D., M.Sc.,[9] Stephanie L. Gaw, M.D., Ph.D.,[10] Amy Murtha, M.D.,[10] Samantha Wiegand, M.D.,[11] Yvonne Gollin, M.D.,[12] Deepjot Singh, M.D., M.M.M.,[13] Robert M. Silver, M.D.,[14] Danielle E. Durie, M.D., M.P.H.,[15] Britta Panda, M.D.,[16] Errol R. Norwitz, M.D., Ph.D.,[16,17] Irina Burd, M.D., Ph.D.,[18] Beth Plunkett, M.D., M.P.H.,[19] Rachel K. Scott, M.D., M.P.H.,[20] Anna Gaden, B.S.,[1] Martha Bautista, B.S.,[1] Yuchiao Chang, Ph.D.,[2] Marcio A. Diniz, Ph.D.,[1] S. Ananth Karumanchi, M.D.,[1] and Sarah Kilpatrick, M.D., Ph.D.[1]

Population:
18 US Centers (tertiary and community with level 3 NICU)
Hospitalized singleton women 23-34 weeks gestational age with a hypertensive disorder of pregnancy

Outcome: Preeclampsia with **severe features (sPE) -** adjudicated by MFMs

Derivation and validation cohort for sFlt-1:PlGF ratio to predict developing sPE within 2 weeks


The picture can't be displayed.

sFLT-1/PlGF improves diagnostic classification

NEW in 2023 – sFlt1/PlGF FDA cleared

◆ WSJ NEWS EXCLUSIVE | HEALTH

Preeclampsia Blood Test Wins FDA Clearance

Thermo Fisher's blood test is the first cleared to predict life-threatening preeclampsia during pregnancy

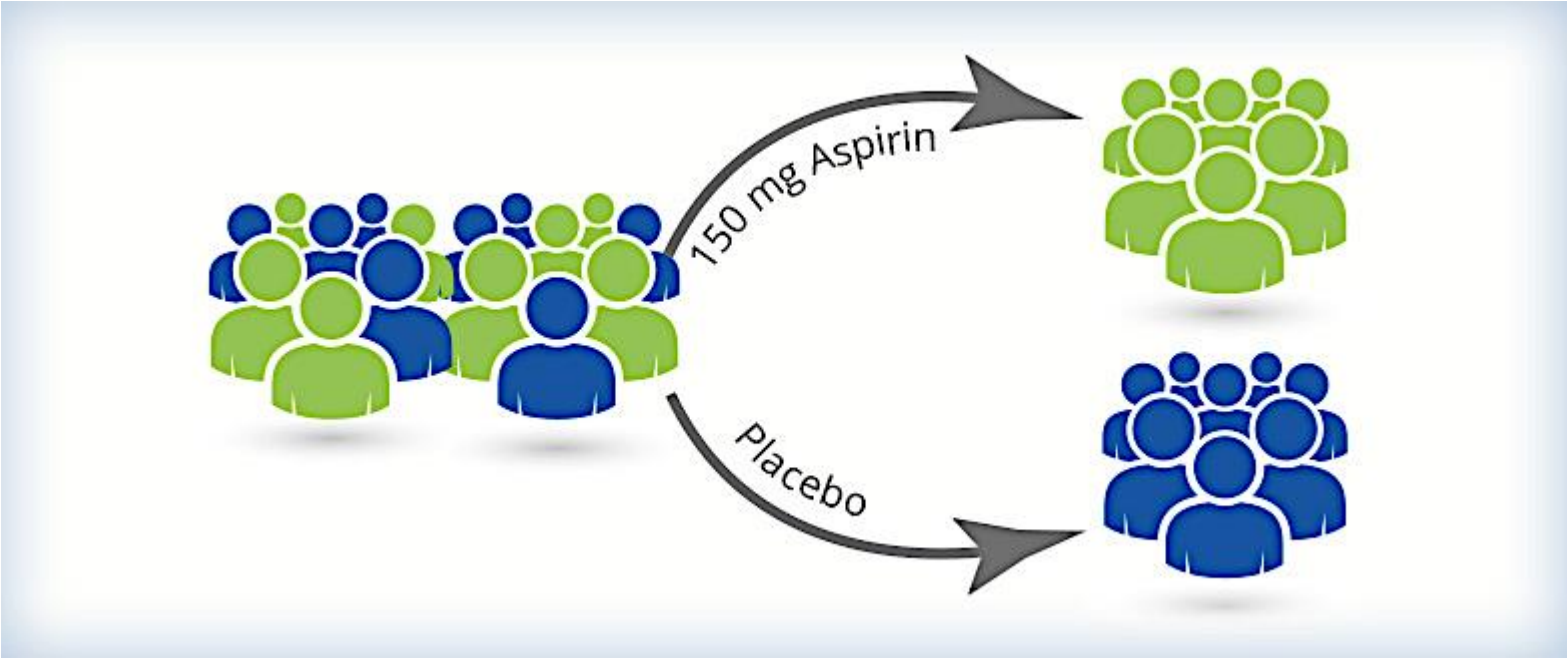
By *Sarah Toy* Follow

Updated May 18, 2023 4:51 pm ET

Share Resize

Preeclampsia occurs when something goes wrong with a woman's placenta during pregnancy, and it can lead to organ damage or death. PHOTO CREDIT: Getty Images/Tetra images RF PHOTO: GETTY IMAGES/TETRA IMAGES RF

ASPRE Study: NEJM 2017



Preterm preeclampsia occurred in **13 participants (1.6%) in the aspirin group**, as compared **with 35 (4.3%) in the placebo group** (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004).

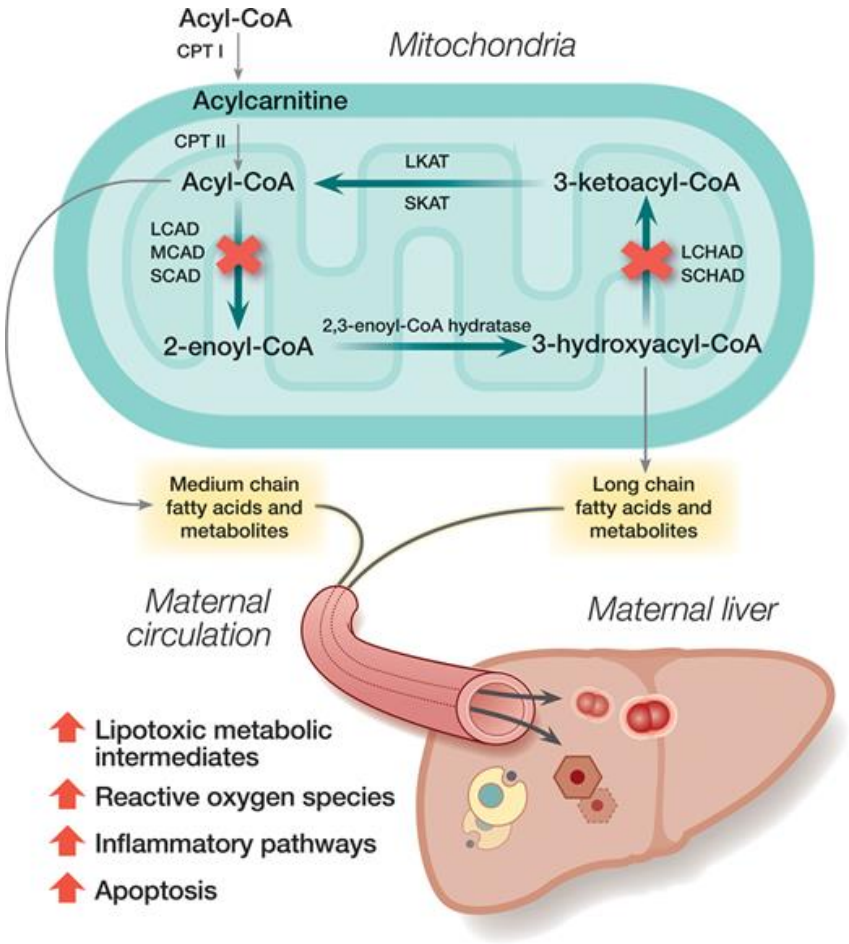
AKI in Preeclampsia/HELLP

- AKI develops in ~1% of patients with preeclampsia

- AKI more common in *HELLP syndrome* (Hemolysis, Elevated Liver Enzymes, Low Platelets) (~7-15%).
  - Most common cause of pregnancy-associated AKI in developed world

- s-Flt1/PlGF ratio can help differentiate preeclampsia/HELLP from other conditions including:
  - Chronic hypertension
  - Chronic kidney disease
  - Lupus nephritis
  - Dialysis patients

Acute Fatty Liver of Pregnancy



Most women also meet criteria for preeclampsia with hypertension and proteinuria

AFLP: malaise, nausea/vomiting, abdominal pain. Hypoglycemia, low ATIII, DIC. ***AKI more common***

HELLP: Headache, abdominal pain, hypertension. Higher transaminase levels.

Naoum *Anesthesology* 2019

Renal Thrombotic Microangiopathies

Thrombotic Thrombocytopenia Purpura (TTP)

Pregnancy associated with decreases in ADAMTS-13 levels and can be trigger for new onset or relapse of TTP

Second or third trimester onset

Neurologic symptoms predominate

Hemolytic Uremic Syndrome (HUS)

Complement dysregulation 2/2 genetic mutations in regulatory proteins.

2/3 of cases develop post-partum.

Renal involvement severe

High overlap with preeclampsia criteria

Lupus Nephritis + Other Glomerular Diseases

- SLE common in women of childbearing age
- Maternal immunologic and hormonal changes make pregnancy a common trigger for flares or de novo lupus nephritis
- Low or low-normal complement levels, serologic markers and extrarenal lupus manifestations can aid in diagnosis
- Renal biopsy often deferred if serologies positive

Hemodynamic Injury + Renal Cortical Necrosis

- Spectrum of pre-renal → ATN → bilateral renal cortical necrosis
- Catastrophic pregnancy complications such as sepsis, obstetric hemorrhage, amniotic fluid embolism
- Cortical necrosis is rare (~ 0.5% of obstetric AKI cases)
  - More likely to develop in pregnancy compared to general population
  - Mechanisms unknown but likely related to hypercoagulability of late-pregnancy

Renal Biopsy in Pregnancy

- Decision on renal biopsy depends on:
  - Age of gestation
  - Severity of renal disease
  - Suspected underlying diagnosis → **NOT a good way to dx preeclampsia**

- Higher risk of bleeding antepartum postpartum (7% vs 1%)

- <32 weeks expert opinion cut off

Case Example

25 y/o G1P0 admitted at 37 weeks gestation

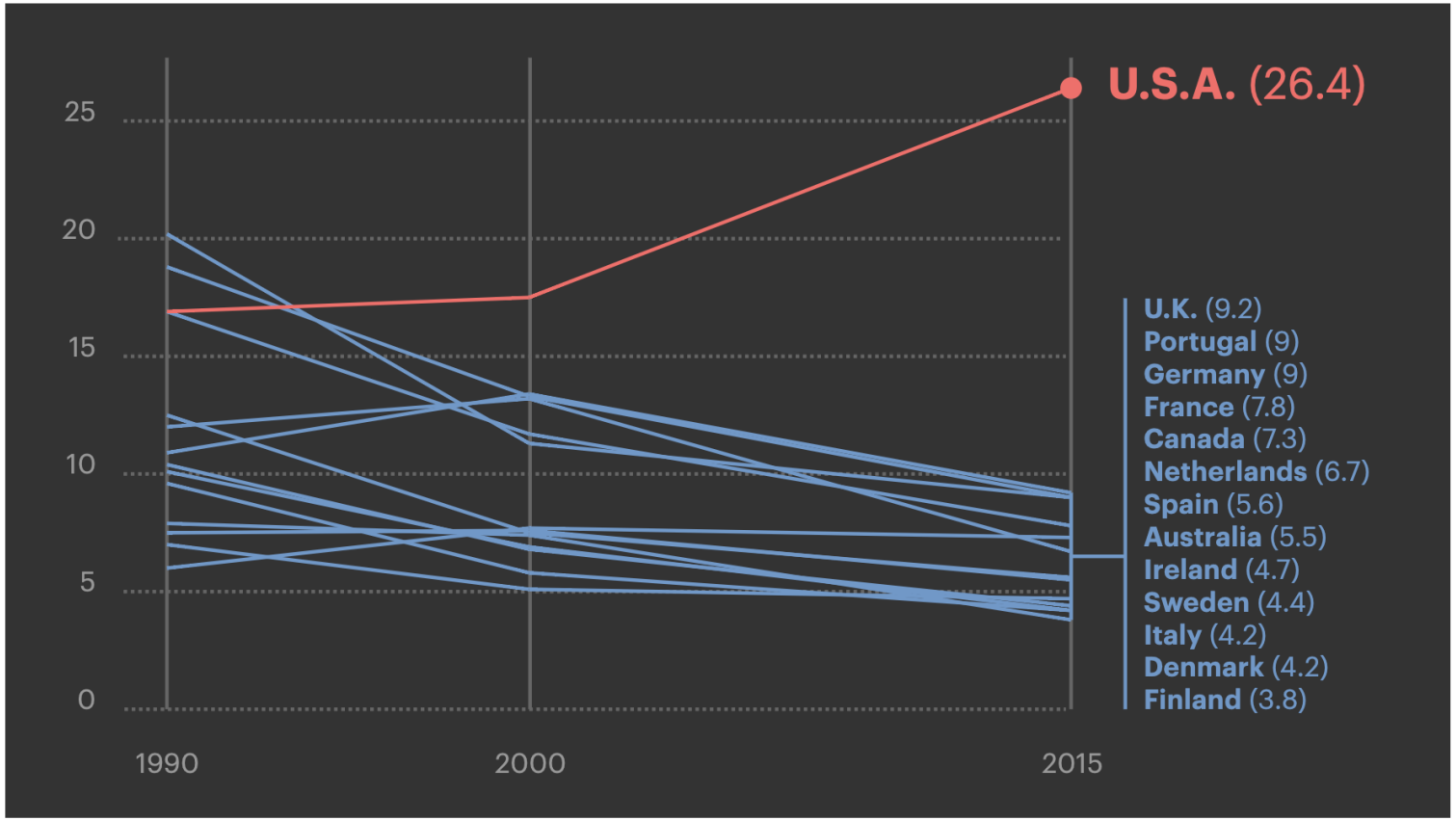
- Developed abdominal pain 1 day prior
- Noted to be hypertensive with 2+ protein on dipstick and admitted to L+D
- Fetal monitoring was reassuring
- Due to term dates, she underwent induction of labor
- **Labs return notable for serum creatinine of 1.3 mg/dl**
- 24 hours later she delivered a healthy baby girl
- **Hemoglobin 5.3 g/dL, LDH >1,000, AST 114, platelets 50**
- **Extensive schistocytes on peripheral smear**

Postpartum hemorrhage, developed hypotension during emergent hysterectomy, DIC/shock. Transferred to SICU at tertiary care institution

- **AKI-D 2/2 ATN was working diagnosis until an astute nephrologist made the diagnosis.**
- **PLEX → Eculizumab. Off HD.**

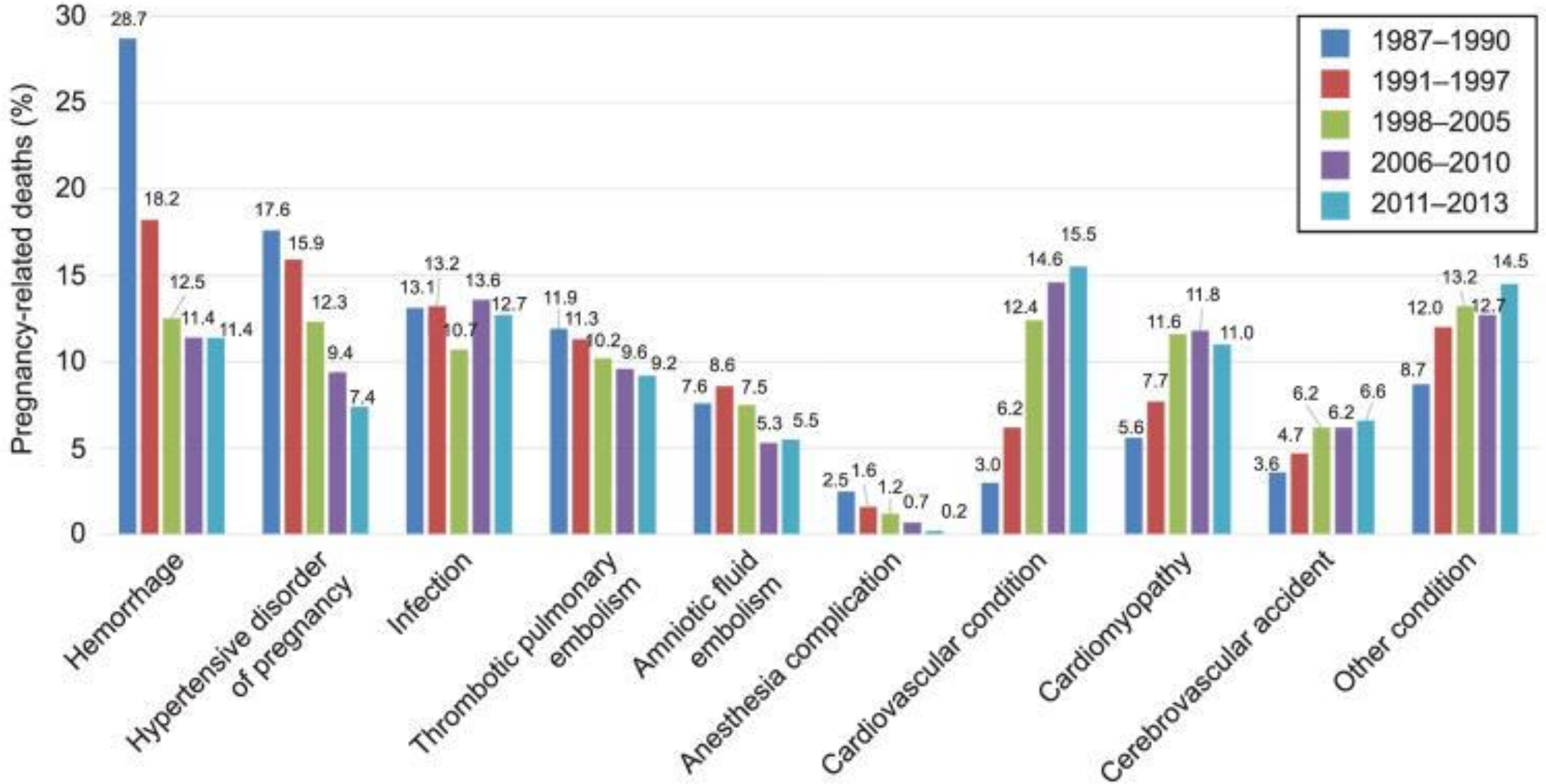
Maternal Morbidity Crisis

Maternal Mortality Is Rising in the U.S. As It Declines Elsewhere



Per 100,000 live births. Source: "Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015," The Lancet. Note: Only data for 1990, 2000 and 2015 was made available in the journal.

Cause of Maternal Death is Changing



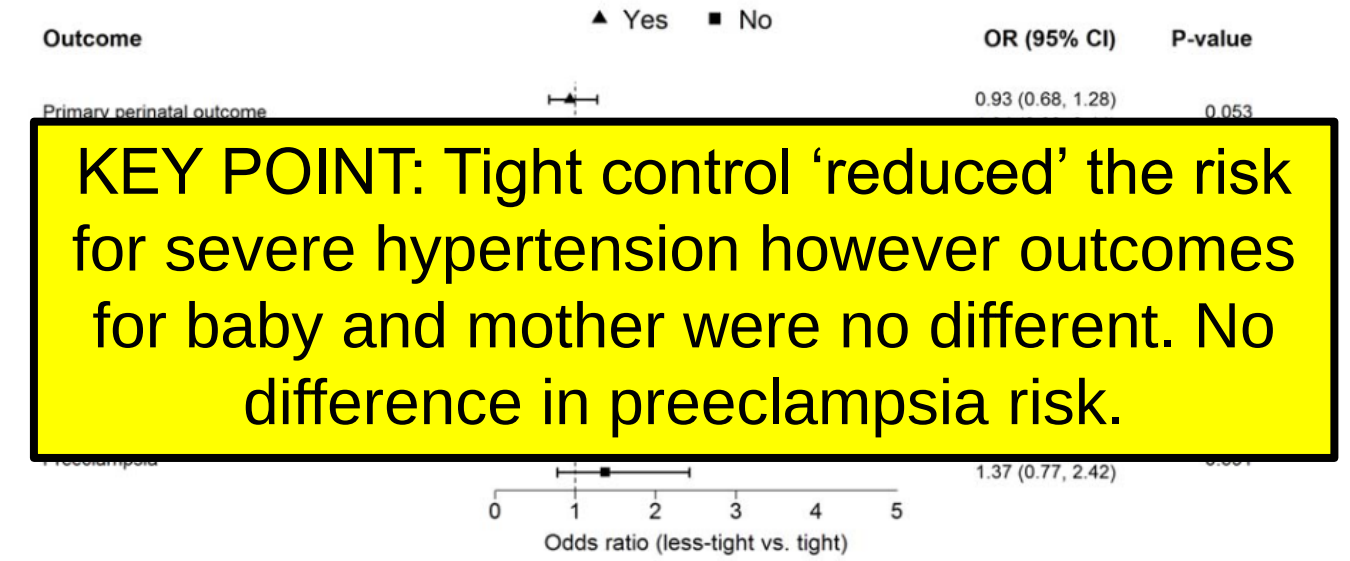
Creanga, *Obstetrics and Gynecology* 2017

Management of Chronic Hypertension in Pregnancy

- ~2-3% of pregnancies in US with pre-existing hypertension
- Associated with significant maternal morbidity
  - 3-5x risk of preeclampsia
  - 5-10x risk maternal death, CHF, stroke, AKI
- Blood pressure target historically controversial
  - ACOG 2019 Recommendations – pharmacotherapy for > 160/110

Table 2. Primary and Other Perinatal Outcomes.*

Figure S2: Perinatal and maternal outcomes according to 'clinically reasonable' adherence (see Table S2 for definition)*



KEY POINT: Tight control 'reduced' the risk for severe hypertension however outcomes for baby and mother were no different. No difference in preeclampsia risk.

CI (confidence interval), OR (odds ratio), SGA (small for gestational age)

** Comparisons of OR and 95% CI for less tight vs. tight control were made using the Breslow-Day test of homogeneity.*

At least one serious neonatal complication — no./total no. (%)‖	40/480 (8.3)	40/479 (8.4)	0.96 (0.60–1.52)

Treatm nancy

A.T. Tita gaard,
R.K. Edward .R. Saade,
K.K. Hoppe, P. August,
U.M. Red unyemi,
Z.S. Galis, e Chronic

KEY POINT: **ACOG/SMFM now recommend <140/90 for pharmacotherapy.**

Reduced incidence of preeclampsia in the active-treatment group is novel and requires more study

The primary ou group than in the control group (of 0.82 (95% confidence interval, 0.74 to 0.92; P<0.001)

Drug	Advantages	Disadvantages
First-line Agents: Oral		
Methyldopa	First-line, extensive safety data.	Short duration of action/BID or TID dosing.
Labetalol	Appears to be safe. Labetalol is preferred over other beta-blockers due to theoretical beneficial effect of alpha-blockade on uteroplacental blood flow.	Short duration of action/TID dosing.
Long-acting nifedipine	Appears to be safe. Available in a slow-release preparation, allowing once daily dosing.	
First-line agents: Intravenous		
Labetalol	Good safety data.	
Nicardipine	Extensive safety data as a tocolytic during labor. Effective.	
Second-line agents		
Hydralazine (PO or IV)	Extensive clinical experience	Increased risk of maternal hypotension and placental abruption when used acutely.
Metoprolol	Potential for once-daily dosing using long-acting formulation.	Safety data less extensive than for labetalol.
Verapamil, Diltiazem	No evidence of adverse fetal effects.	Limited data
Generally Avoided		
Diuretics	No clear evidence of adverse fetal effects.	Theoretically may impair pregnancy-associated expansion in plasma volume
Atenolol		May impair fetal growth
Nitroprusside		Risk of fetal cyanide poisoning if used for more than 4 hours.
Contraindicated		
ACE inhibitors		Multiple fetal anomalies, see text.
Angiotensin receptor antagonists		Similar risks as ACE inhibitors.

Summary

Renal Function Changes in Pregnancy

Approach to AKI during pregnancy

Management of chronic hypertension in pregnancy (new data!)

Relevant Clinical Trials

The CHAPS Trial	N Engl J Med 2022; 386:1781-1792
The PRAECIS Trial	NEJM Evid 2022;1(12)

Contact if questions: jtangrern@mgh.harvard.edu