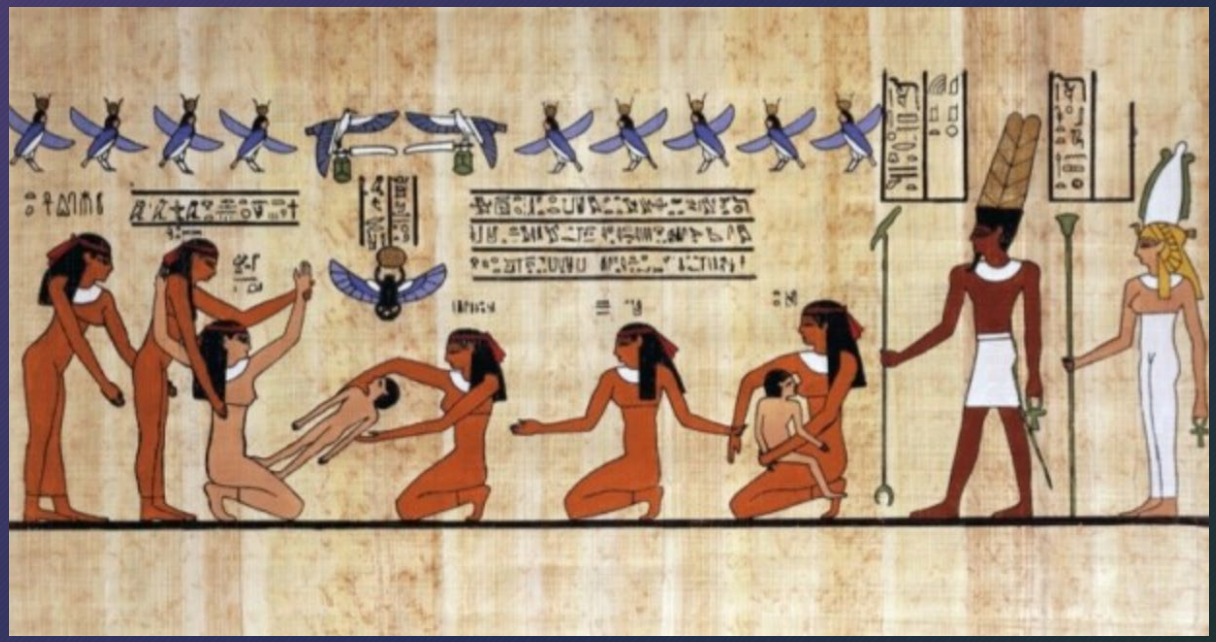
Pregnancy: What the non-Ob needs to know



Nicole Smith, M.D., M.P.H.
Associate Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Medical Director, Maternal Fetal Medicine
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology
Brigham & Women's Hospital

Disclosures

I have no disclosures

Overview

- Hot topics in Obstetrics
  - The maternal mortality crisis
  - Rising CS rates
  - Doulas
- Common complications in Pregnancy
  - Cardiovascular changes and hypertensive disorders of pregnancy
  - Gestational diabetes
- Breastfeeding: impacts on CV disease and DM

Pregnancy: A time of joy and apprehension

Martha Jefferson

Maternal Mortality by State, 2021

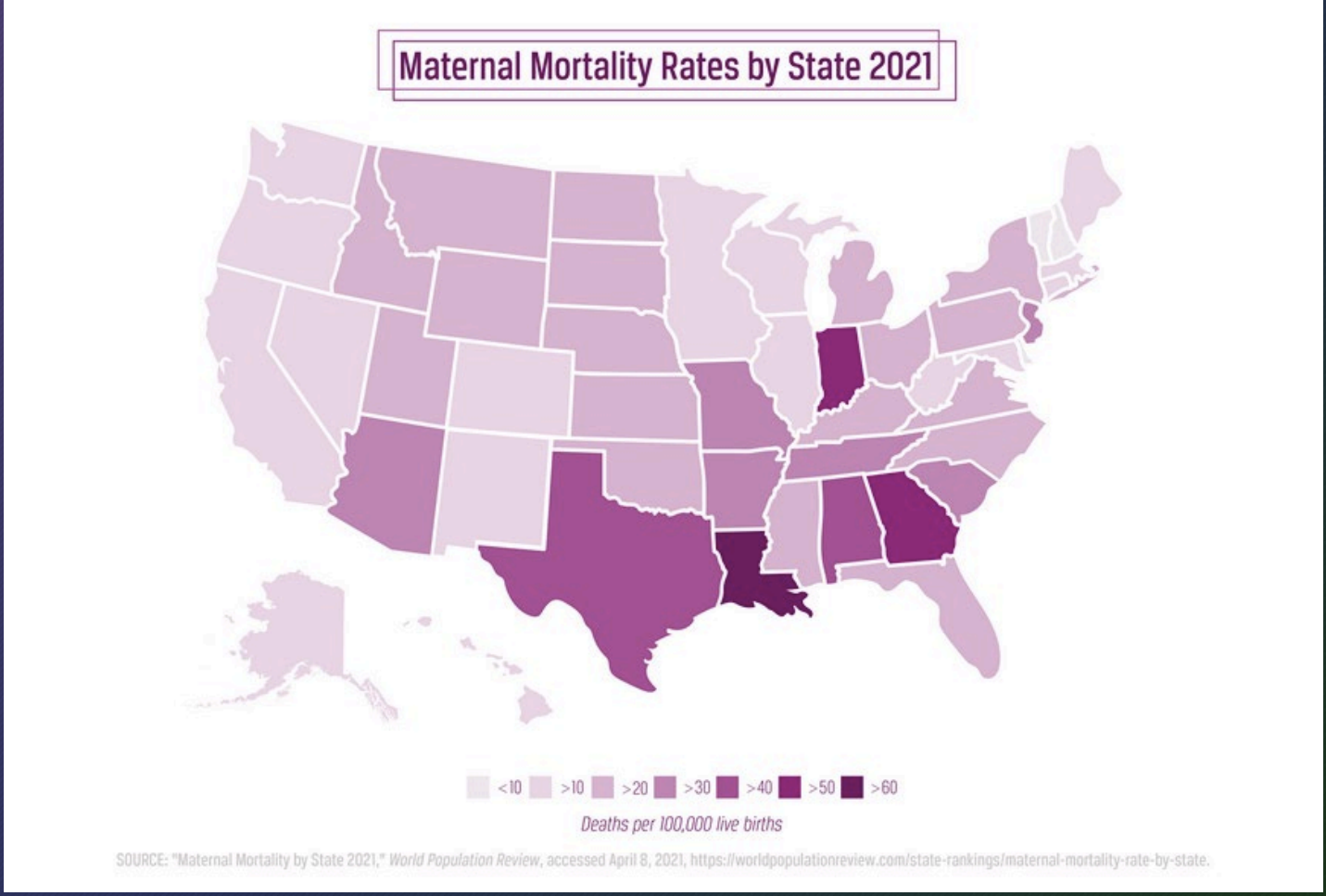
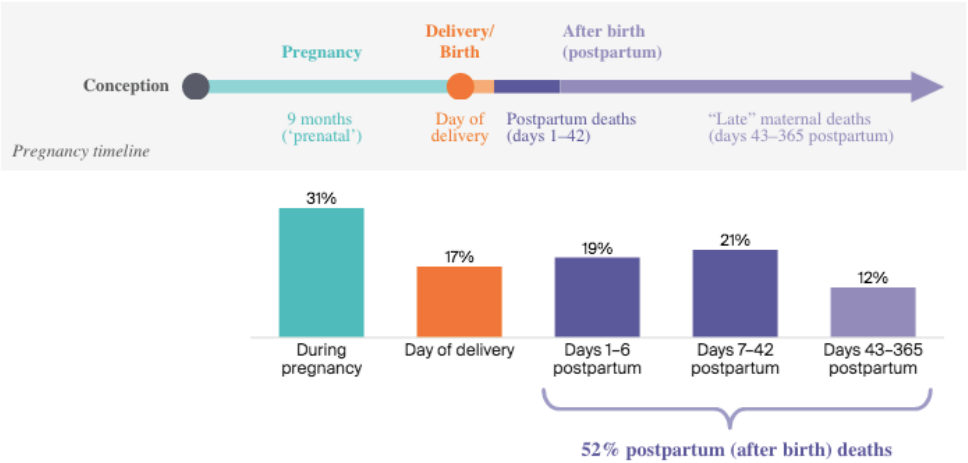


Exhibit 2

Timing of U.S. Maternal and Pregnancy-Related Deaths, 2011–2015

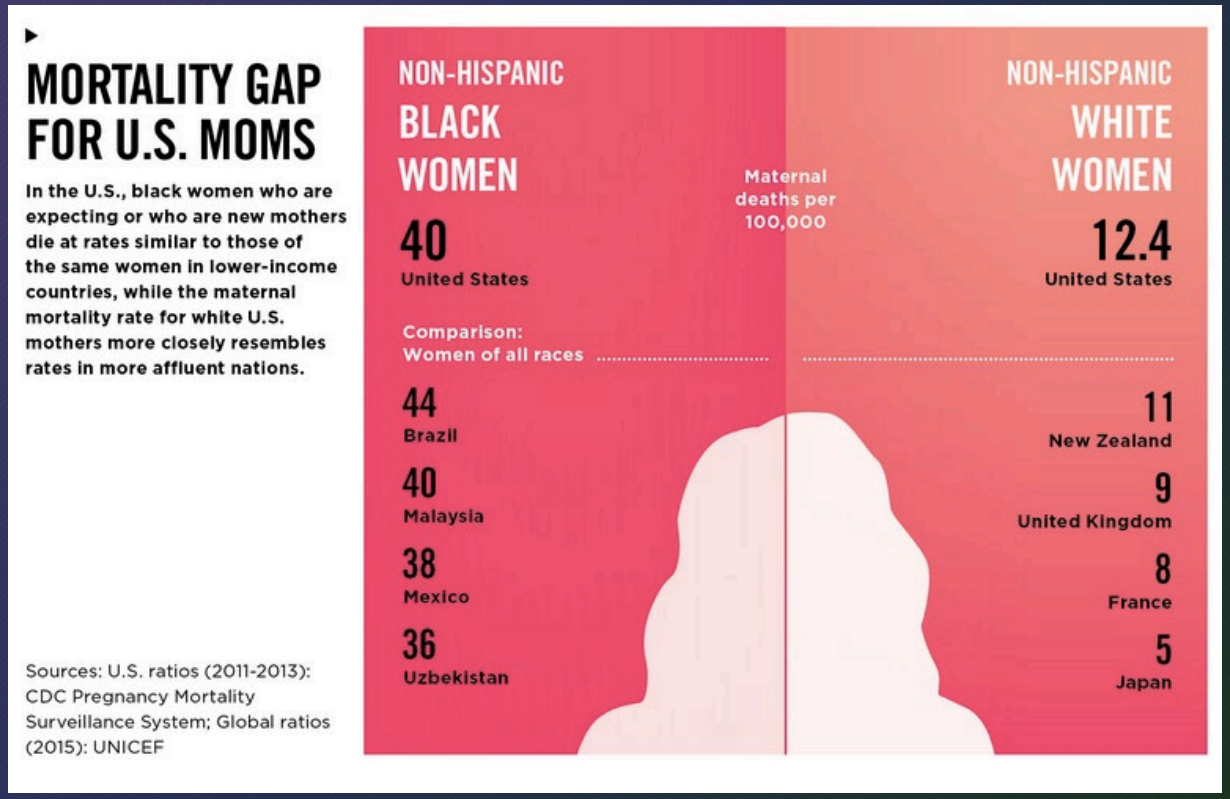


Data: Centers for Disease Control and Prevention Pregnancy-Related Mortality Surveillance data from: Emily E. Petersen et al., "Vital Signs: Pregnancy-Related Deaths, United States, 2011–2015, and Strategies for Prevention, 13 States, 2013–2017," *Morbidity and Mortality Weekly Report* 68, no. 18 (May 10, 2019): 423–29.

Source: Roosa Tikkanen et al., *Maternal Mortality and Maternity Care in the United States Compared to 10 Other Developed Countries* (Commonwealth Fund, Nov. 2020). https://doi.org/10.26099/411v-9255

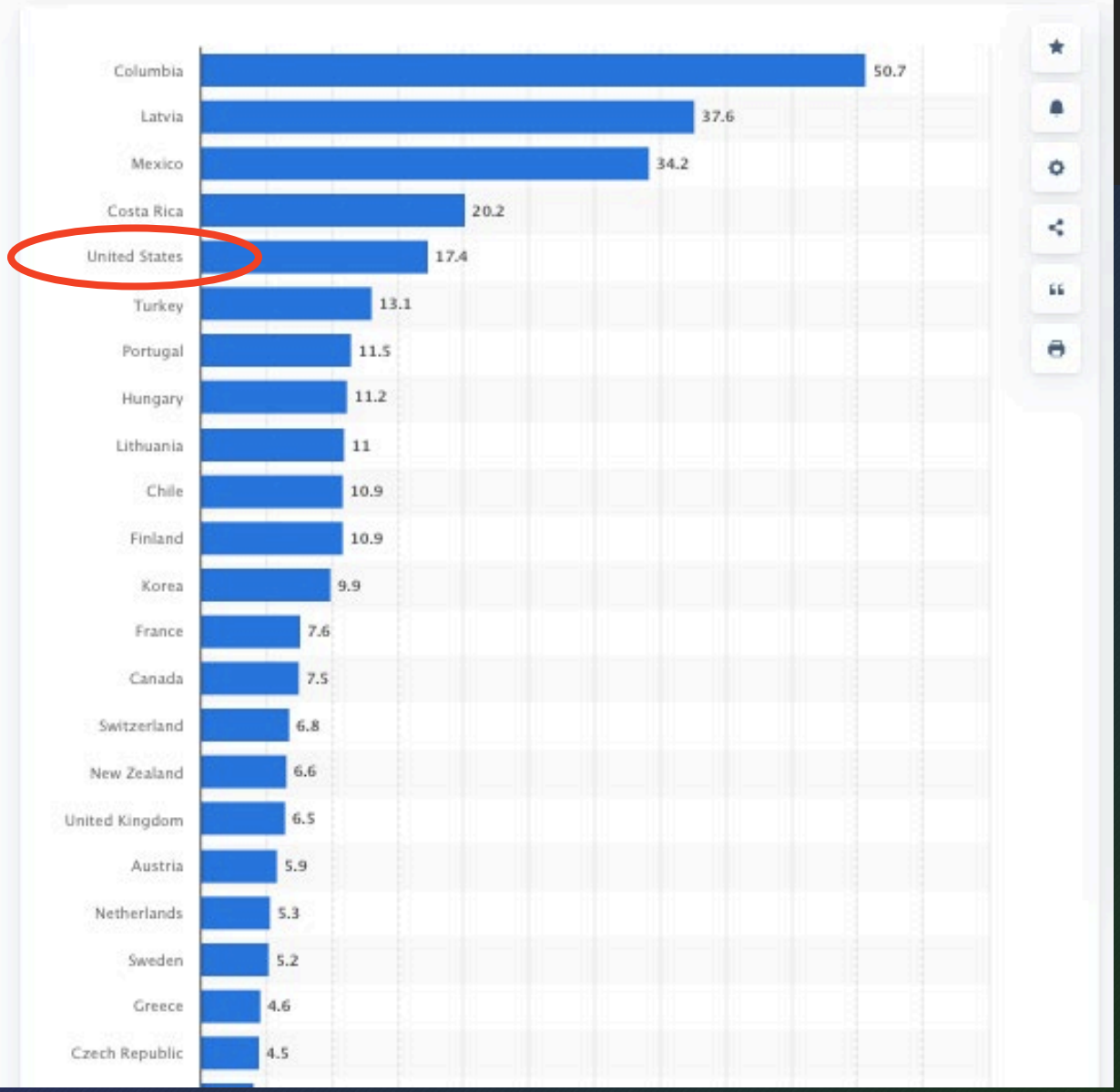
Timing of pregnancy-related deaths

The crisis:
Racial disparities in maternal mortality



Maternal mortality rates worldwide in 2019, by country

(per 100,000 live births)



Pregnancy-Related Deaths: Data from 14 U.S. Maternal Mortality Review Committees, 2008-2017

MMRIA MATERNAL MORTALITY REVIEW INFORMATION APP

- 8-9 % of all maternal deaths related to suicide, overdose, homicide, substance use disorder, mental health conditions.
- 67% occur after 6-wks PP.

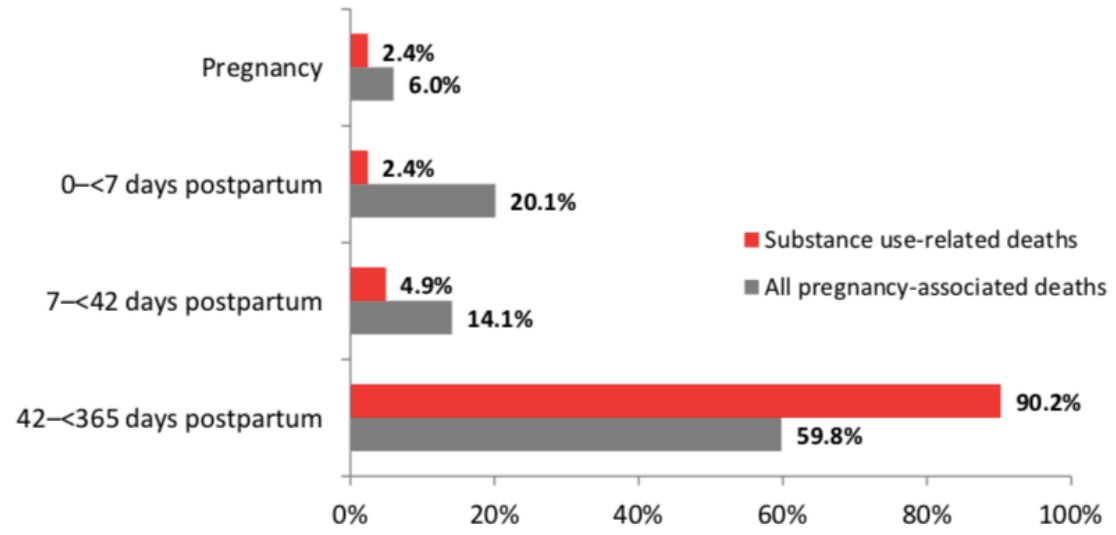
Table 3. Leading underlying causes of pregnancy-related deaths, overall and by race-ethnicity, data from 14 maternal mortality review committees, 2008-2017.*

	Total		non-Hispanic Black		non-Hispanic White	
	N	%	n	%	n	%
Cardiovascular Conditions†	58	13.8	22	13.9	27	13.4
Hemorrhage	55	13.1	17	10.8	27	13.4
Infection	48	11.4	16	10.1	25	12.4
Embolism‡	40	9.5	16	10.1	16	8.0
Cardiomyopathy	39	9.3	22	13.9	16	8.0
Mental Health Conditions§	37	8.8	--	--	30	14.9
Preeclampsia and Eclampsia	35	8.3	18	11.4	13	6.5

*Specific cause of death was missing or listed as "Unknown" for a total of 34 (7.5%) pregnancy-related deaths. Numbers are not presented when cell size is <5. Deaths among women not classified as non-Hispanic Black or non-Hispanic White are included in the total number of deaths.

Timing of Substance-use related maternal deaths

Figure 2: Timing of substance use-related vs. all pregnancy-associated deaths —Massachusetts, 2005–2014.



Maternal Mortality and Morbidity Review in Massachusetts
A Bulletin for Health Care Professionals

Substance Use among Pregnancy-Associated Deaths — Massachusetts, 2005–2014

Massachusetts Department of Public Health SPRING 2018

The Problem: Rising Cesarean rates

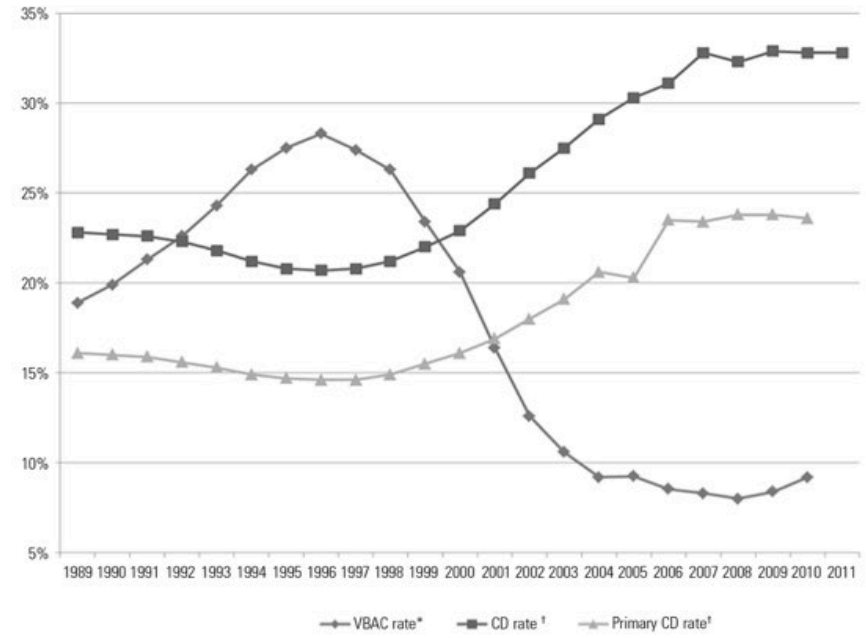


Fig. 1. U.S. delivery rates, 1989–2011. Data from National Vital Statistics. Abbreviations: CD, cesarean delivery; VBAC, vaginal birth after cesarean delivery . *Percent of women who have a vaginal birth after prior cesarean delivery. †Rate based on total number of deliveries. (Data from Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Mathews TJ. Births: final data for 2011. Natl Vital Stat Rep 2013;62(2):1–90.) ⇦

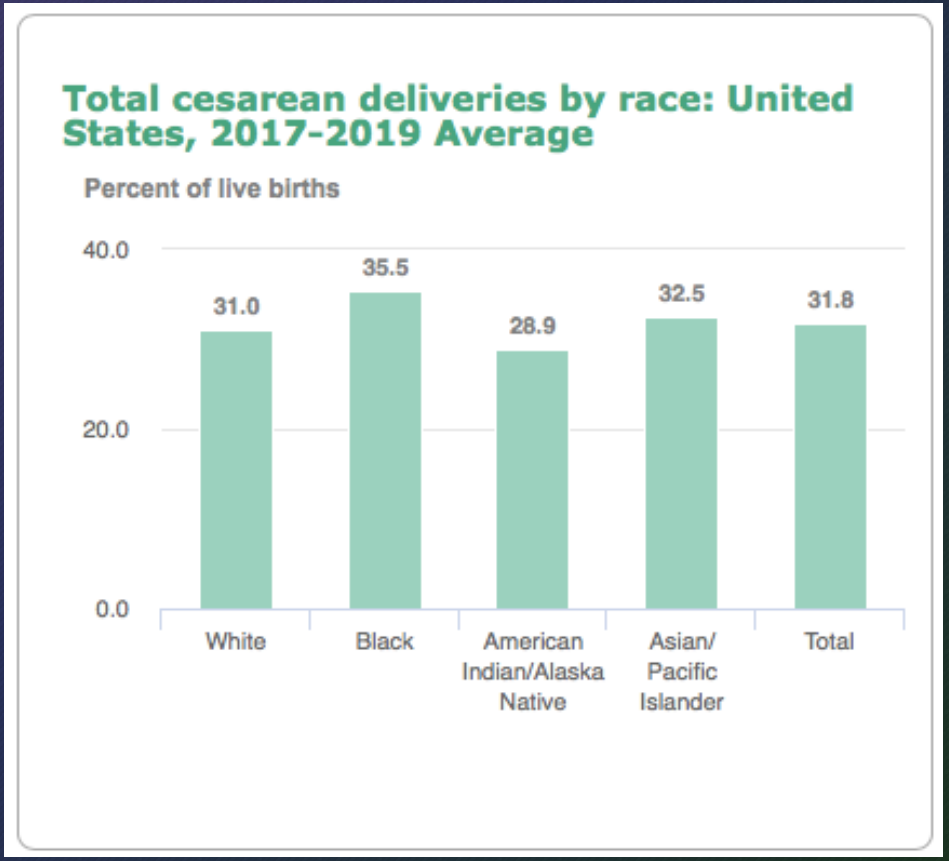
Cesarean rate

Primary Cesarean rate

Vaginal birth after CS rate

C-section rates differ by race/ethnicity

HEALTHY MOMS. STRONG BABIES. | MARCH OF DIMES | PERISTATS



Hot topic: Doulas

Perceptions and experiences of labour companionship: a qualitative evidence synthesis

Meghan A Bohren [1], Blair O Berger, Heather Munthe-Kaas, Özge Tunçalp

A doula is a trained companion who is not a healthcare professional and who supports another individual through a significant health-related experience

- Emotional support: using praise and reassurance to help women feel in control and confident, and providing a continuous physical presence.
- Informational support: providing information about childbirth, bridging communication gaps between health workers and women, and facilitating non-pharmacological pain relief.
- Practical support: including encouraging women to move around, providing massage, and holding her hand.
- Advocates: spoke up in support of the woman

Cochrane Database Syst Rev 2019 Mar 18

Continuous labor support: Cochrane review

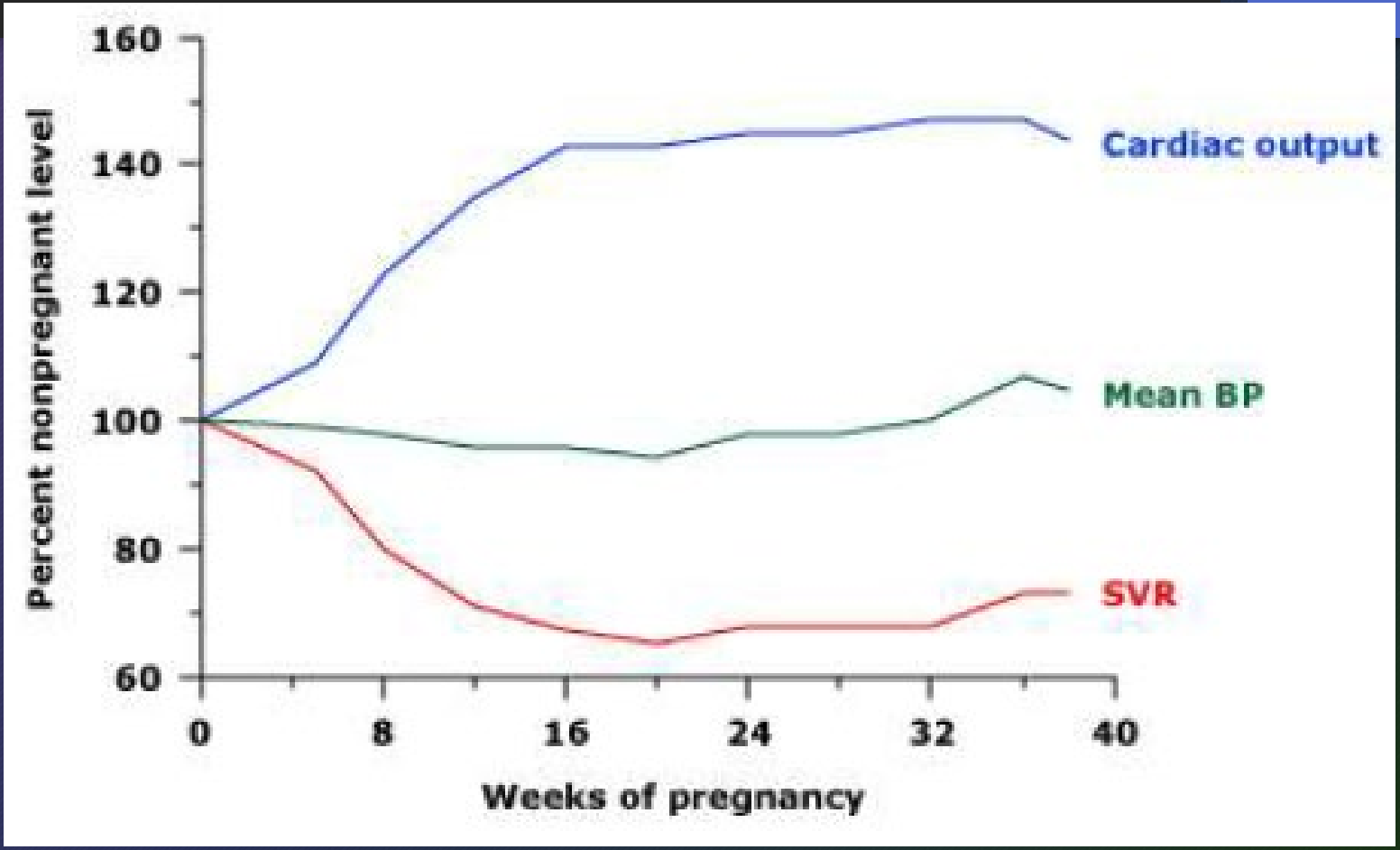
- 15,858 women across 26 studies
  - 13 high income countries, 13 middle income countries
  - Labor support by doula, medical team,or friend/family
- “Continuous labor support appears to offer impressive benefits and no harms to women and newborns, especially when provided by someone in a doula role.”
- Statistically significant INCREASE
  - Vaginal birth
  - Shorter labor
- Statistically significant DECREASE
  - Cesarean birth
  - Operative vaginal deliver
  - Use of regional anesthesia
  - Negative birth experience
  - Low 5 minute Apgar score

Brittanyriddick.com

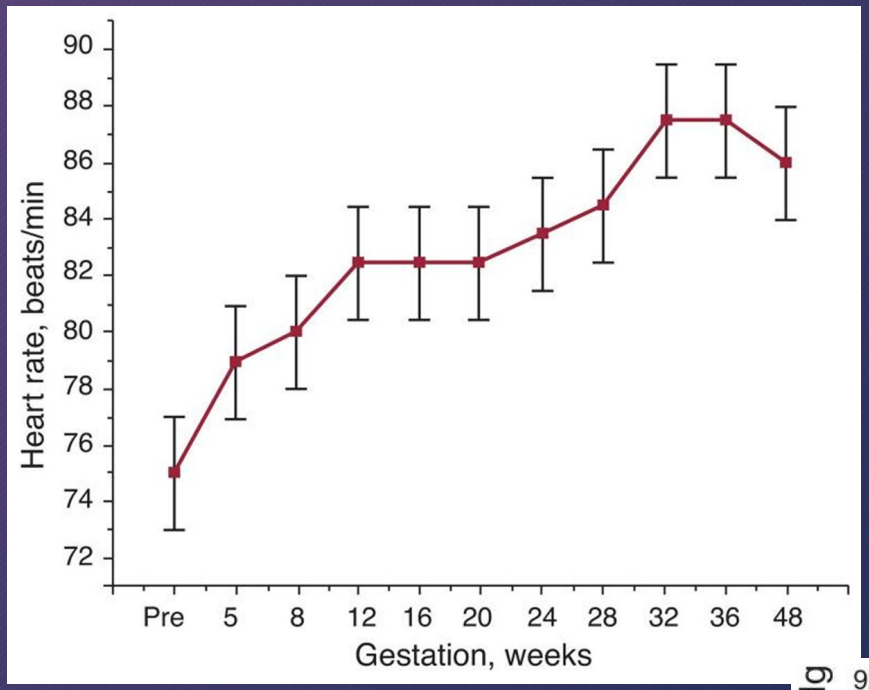
Obstetric Physiology and Pathology

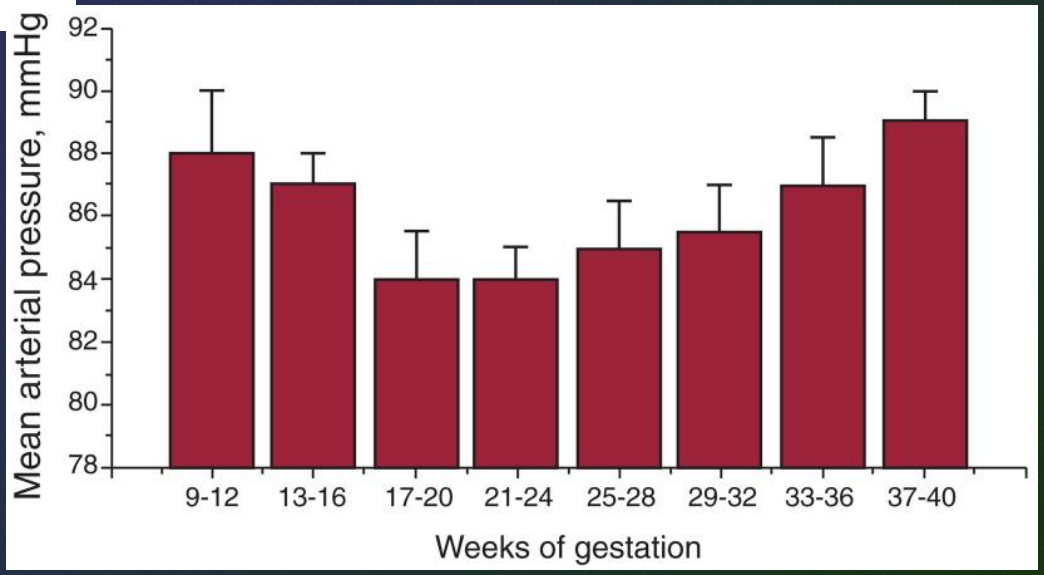
Cardiovascular changes & hypertensive disorders of pregnancy

Physiology: CV changes



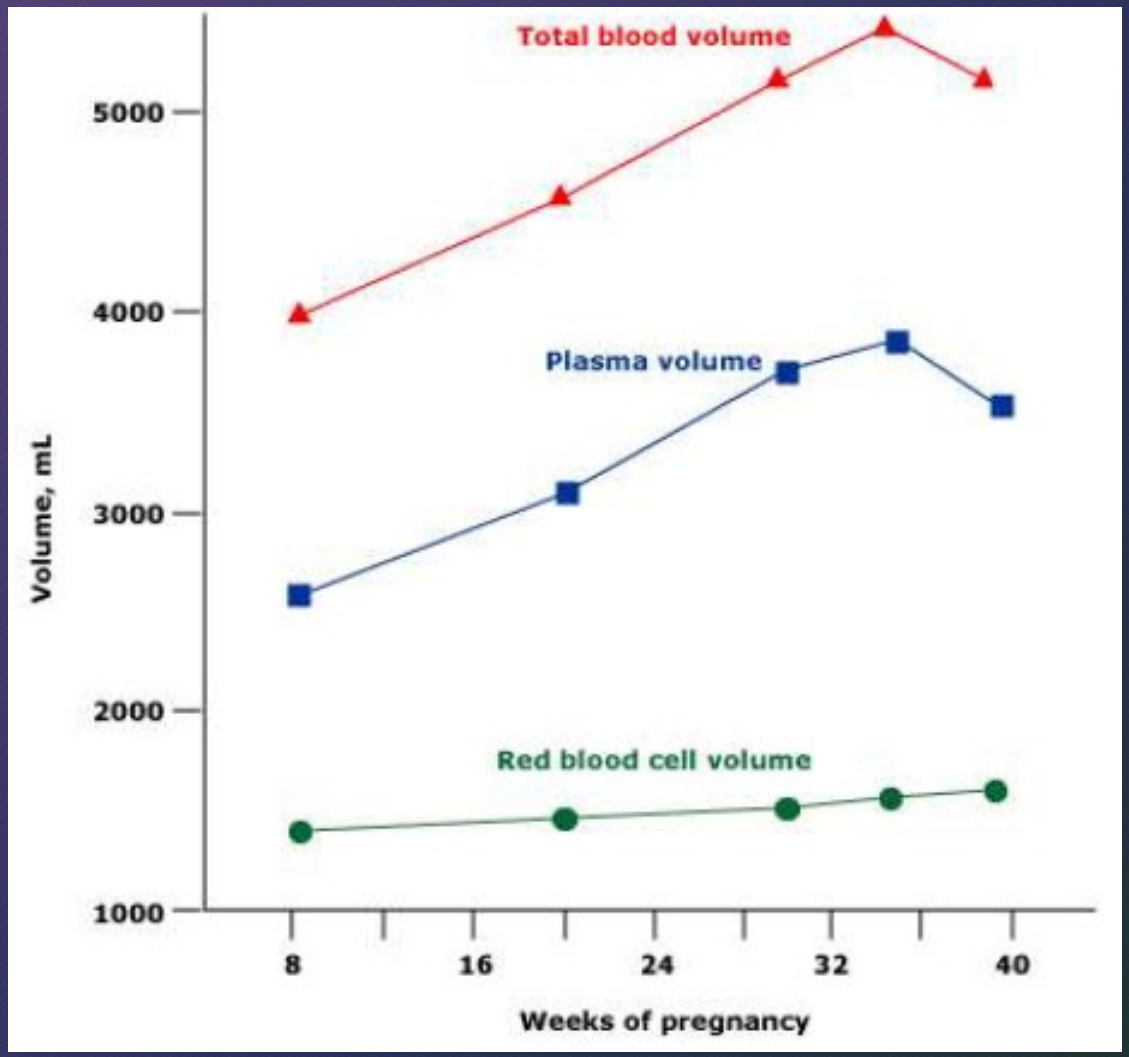
From Meah VL, Cockcroft JR, Backx K, Shave R, Stöhr EJ, Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses, Heart. 2016;102(7):518.





From: Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. Br Heart J. 1992;68:540–3
Moutquin JM, Rainville C, Giroux L, Raynauld P, Amyot G, Bilodeau R, et al.
A prospective study of blood pressure in pregnancy: prediction of preeclampsia.
Am J Obstet Gynecol. 1985;151:191–6

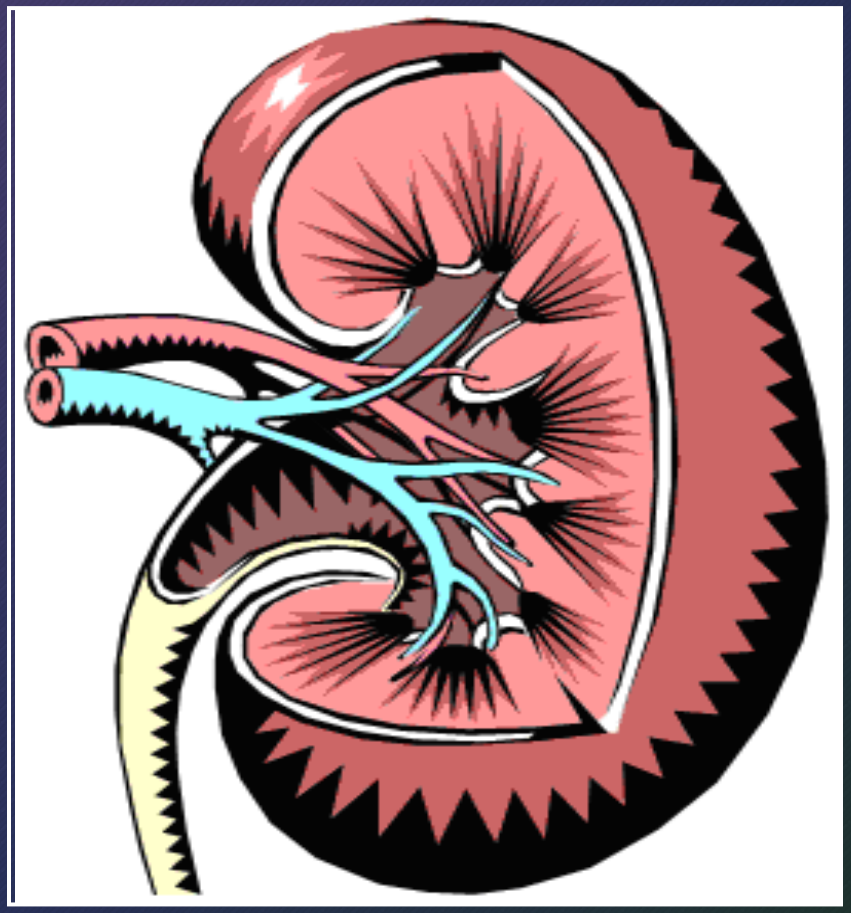
Circulating Volume



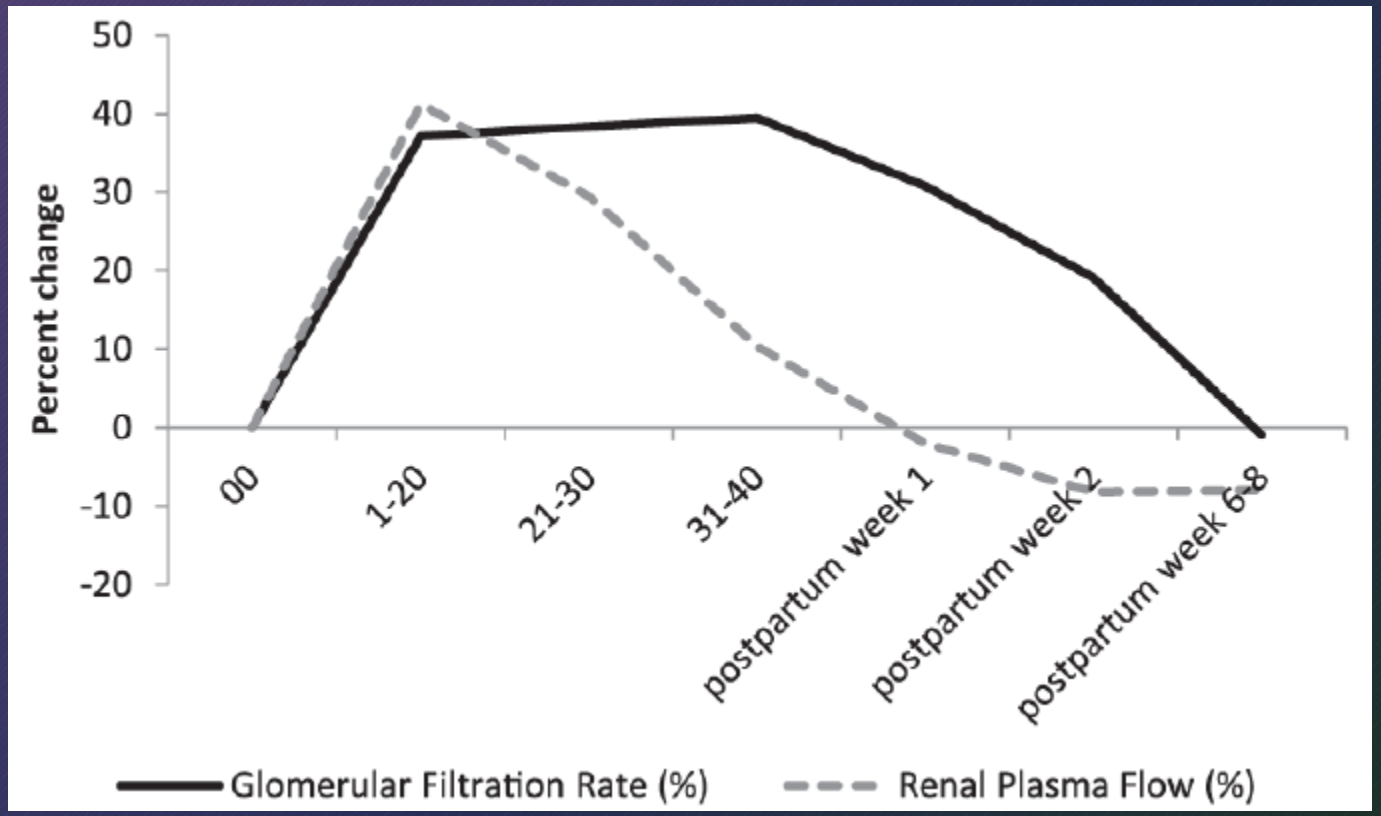
Plasma volume increases
1200 - 1600 mL
~40% above baseline

Data from: Shnider SM, Levinson G. Anesthesia for Obstetrics, 3rd ed, Williams & Wilkins, Baltimore 1993. p.8.

Renal



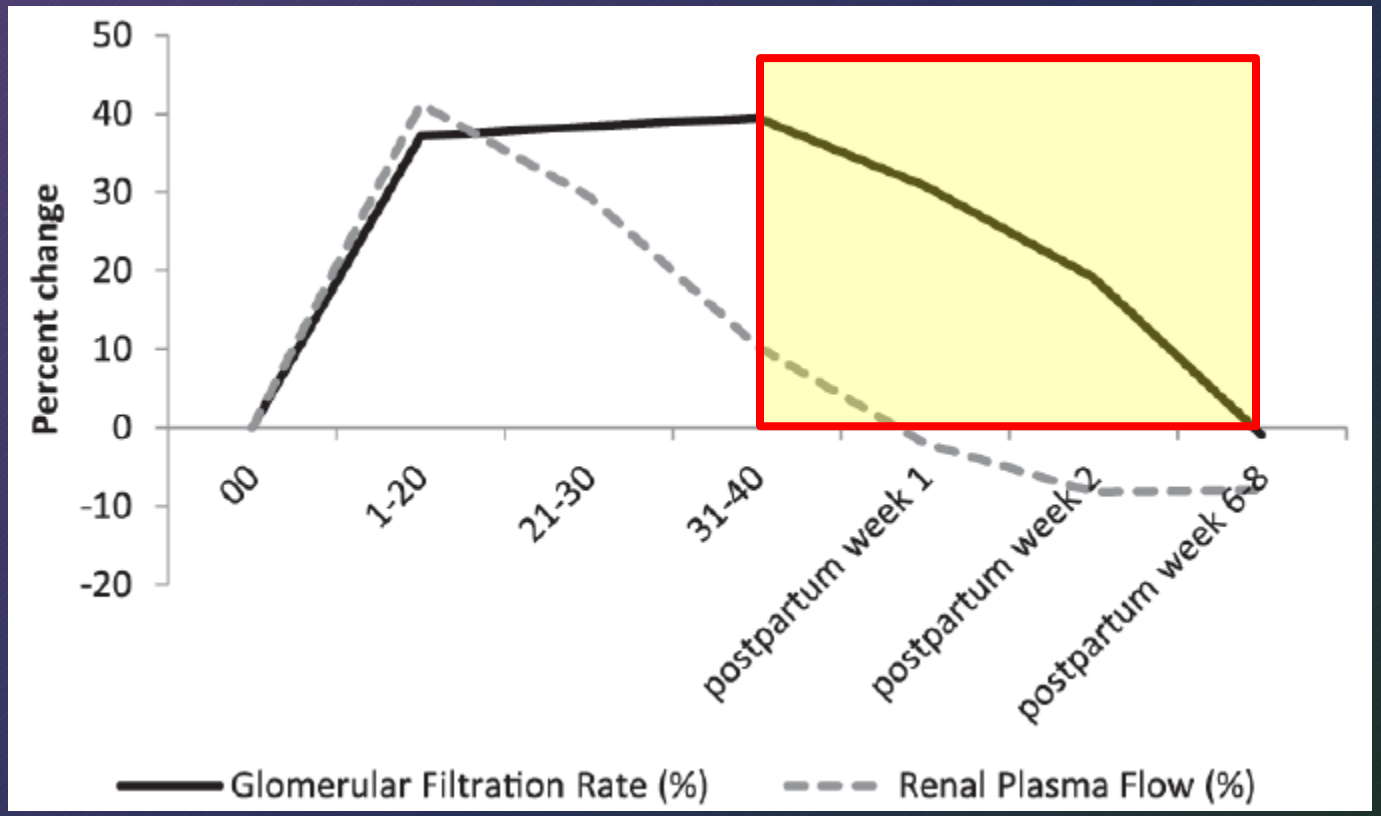
Renal



30-50% increase in renal clearance due to increases in renal blood flow and glomerular filtration rate.

From: Cheung KL, Lafayette RA, Renal Physiology of Pregnancy, Adv Chronic Kidney Dis. 2013 May ; 20(3): 209–214

Renal



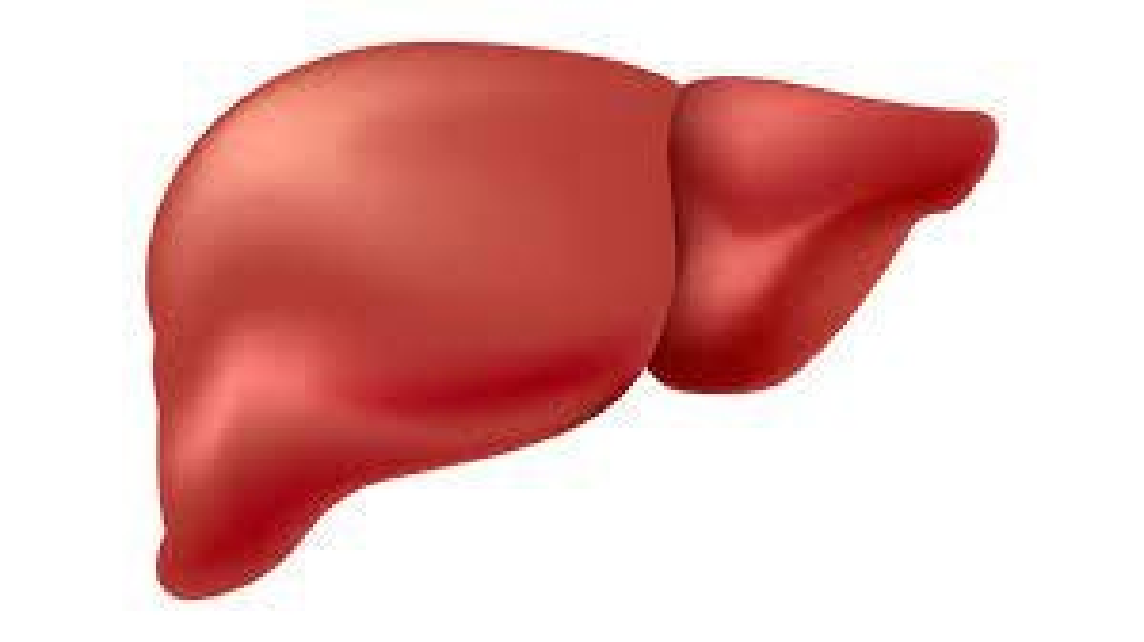
30-50% increase in renal clearance due to increases in renal blood flow and glomerular filtration rate.

From: Cheung KL, Lafayette RA, Renal Physiology of Pregnancy, Adv Chronic Kidney Dis. 2013 May ; 20(3): 209–214

Volume Changes Post-Partum

- Postpartum diuresis
  - Hct difference PP w SVD: +5.2% on day 3
  - Hct difference PP w C-sec: -5.8 % on day 5
- Most of the volume loss in following SVD is due to diuresis
  - Diuresis normally occurs b/w days 2-5 PP
  - Allows for loss of excess ECF accumulated in pregnancy
  - Average ~6lb weight loss

Hepatic



Hepatic

Pregnancy-induced changes in hepatic enzymes

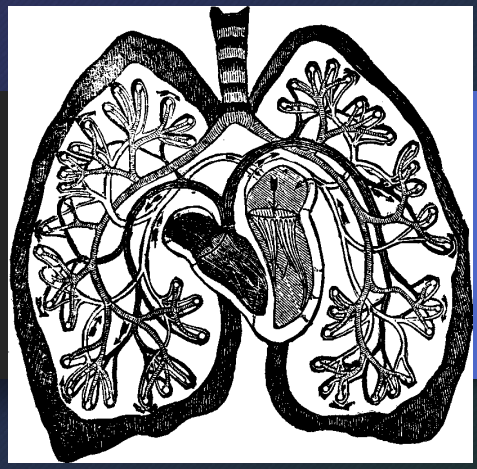
Enzyme (references)	Pregnancy-induced change	Potential substrates in obstetrics
CYP3A4[19,20,77,78]	Increased	Glyburide, nifedipine, and indinavir
CYP2D6[77,79]	Increased	Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, and citalopram
CYP2C9[18,80]	Increased	Glyburide, NSAIDs, phenytoin, and fluoxetine
CYP2C19[18,80]	Decreased	Glyburide, citalopram, diazepam, omeprazole, pantoprazole, and propranolol
CYP1A2[17,23,77,81]	Decreased	Theophylline, clozapine, olanzapine, ondansetron, and cyclobenzaprine
UGT1A4[82–84]	Increased	Lamotrigine
UGT1A1/9[25]	Increased	Acetaminophen
NAT2[17,24,85]	Decreased	Caffeine

From: Feghali et al. Pharmacokinetics of drugs in pregnancy, *Semin Perinatol*. 2015 November; 39(7): 512–519.

Take home point for small molecule meds

From Voinescu PE et al. Neurology 2018;91:e1228-e1236
Pennell et al. Neurology 2007;70(22 Pt 2):2130–6.

Physiology: Dyspnea



- Common symptom in pregnancy
  - Up to 70% of women experience this sensation in a normal pregnancy
- The obstetric patient presenting with an acute onset of shortness of breath deserves a careful evaluation
- Cardiovascular diseases as a cause of dyspnea complicate 1–4% of pregnancies.
  - Peripartum cardiomyopathy is an uncommon but life threatening complication of pregnancy
  - Women with underlying valvular disease may poorly tolerate plasma volume expansion

Soubra, S, Gunupalli, K. Critical illness in pregnancy: an overview. Critical Care Medicine. Volume 33, (10) Supplement. S248-55. October 2005

Preeclampsia

1. Preeclampsia diagnosis (updated by ACOG, 2013)
2. Preeclampsia management
3. Preeclampsia prevention (low-dose aspirin)
4. Postnatal counseling

Classic presentation

- C.M., a 32 year old prima gravida
- Initiated prenatal care: 16 weeks GA
  - BP 106/70 mmHg, no proteinuria
  - Weight 102 pounds
- Pregnancy proceed unremarkably
- At 36 weeks:
  - Edema of the hands and face
  - BP 160/115 mmHg
  - Urine contained 6g of albumin in a 24 hour sample
  - 30 pound weight gain, 11 in last 4 weeks

Admitted to Boston Lying In Hospital in 1862

TABLE E-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.

Preeclampsia Diagnosis

Hypertensive disorders of pregnancy

- Chronic Hypertension
- Preeclampsia
- Superimposed Preeclampsia
- Gestational Hypertension
- Eclampsia
- HELLP Syndrome

ACOG, November 2013

Differential diagnosis: It's complicated…

Chronic Hypertension

- Hypertension prior to pregnancy
- Hypertension prior to 20 wks GA
- Hypertension first seen after 20 weeks but persisting >12 weeks PP
- Medication optimization

Superimposed preeclampsia

- New proteinuria in chronic hypertensive after 20 weeks
- Sudden increase in protein, pressures, other findings in patients with nephrotic syndrome and hypertension prior to 20 weeks

Gestational Hypertension

- Not preeclampsia
- BP≥140/90
- May be associated with adverse outcomes
- 10% of eclamptics seize without proteinuria

HELLP syndrome

- RUQ pain (80%)
- Hemolysis, elevated LFTs, low platelets

Epidemiology

Overall:

4.6% of pregnancies worldwide

3.4% in US (1.5-2x increase in first pregnancy)

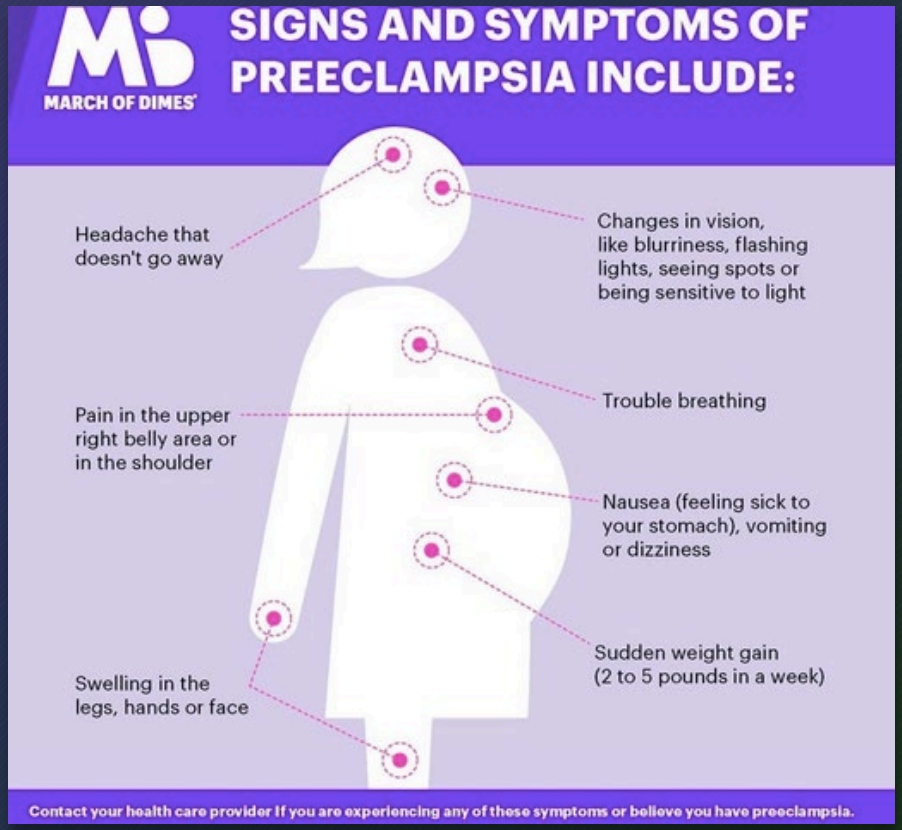
By gestational age:

< 34 weeks: 0.3%

≥ 34 weeks: 2.7%

Up to 23 days postpartum

*Comprehensive evaluation for other sources should be undertaken for late occurrence



Differential diagnosis

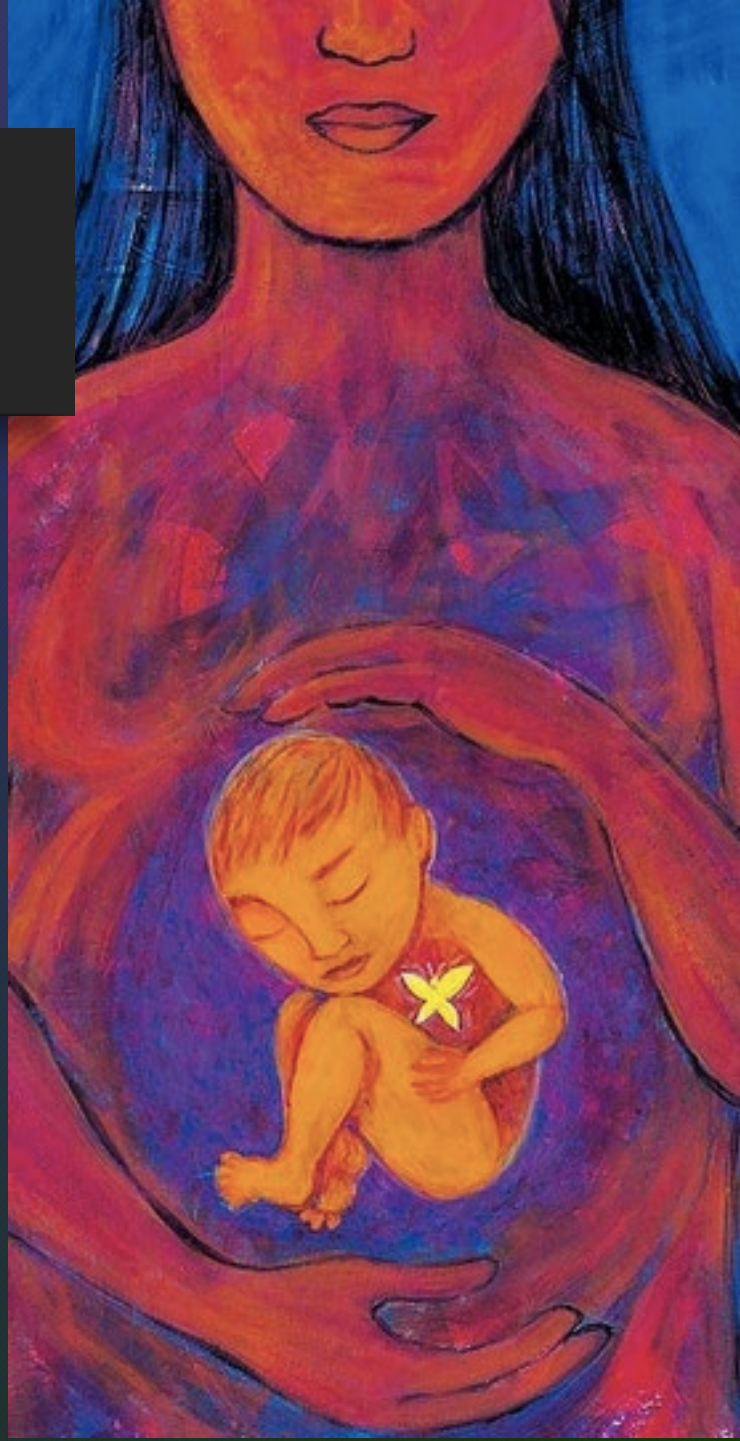
- Preexisting hypertension vs. preeclampsia
- Chronic hypertension vs. superimposed preeclampsia
- Exacerbation of preexisting renal disease
- Antiphospholipid syndrome
- Acute fatty liver of pregnancy (AFLP)
- TTP (thrombotic thrombocytopenic purpura) or HUS (hemolytic uremic syndrome)
- SLE exacerbation
- Pheochromocytoma
- Mirror syndrome (assoc w/ fetal hydrops)

Preeclampsia Risk Factors

- Prior preeclampsia (RR 8.4)
- Chronic hypertension (RR 5.1)
- Pregestational diabetes (RR 3.7)
- Multifetal gestation (RR 2.9)
- Family history preeclampsia (RR 2.9)
- Autoimmune disease (SLE, RR 1.8; APS, RR 2.8)
- BMI >30 (RR 2.8)
- First pregnancy (RR 2.1)
- Chronic kidney disease (RR 1.8)

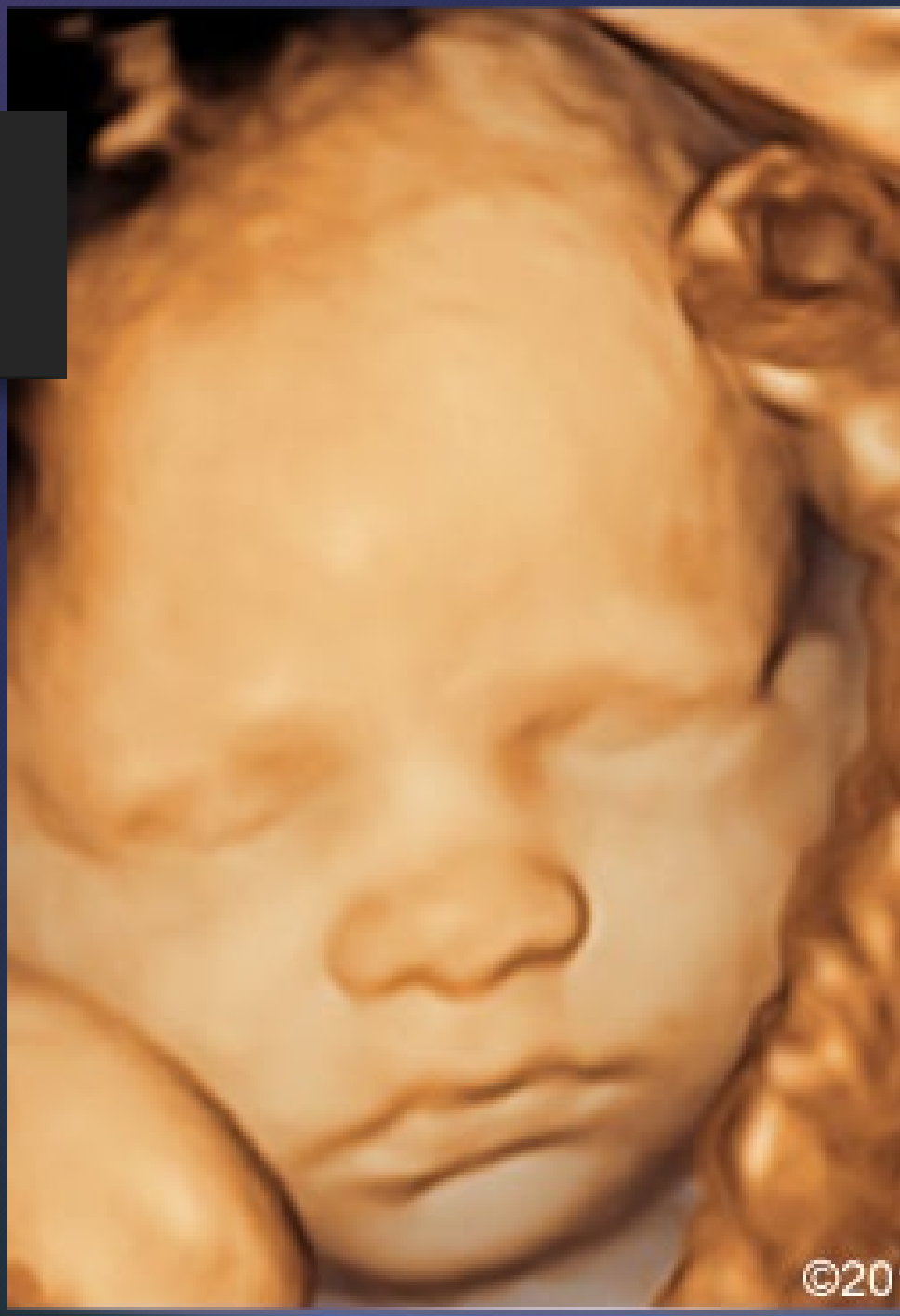
Short Term Maternal Complications

- Liver rupture/ hemorrhage
- Acute pancreatitis
- Posterior reversible leukoencephalopathy syndrome (PRES)
- Cortical blindness (usually transient) or retinal pathology (can be permanent)
- Stroke (most are hemorrhagic):
- 36% of strokes during pregnancy are due to preeclampsia/ eclampsia



Fetal/Neonatal Complications

- Growth restriction
- Preterm delivery
- Fetal demise
- Long-term health consequences



Management: Gestational Age Dependent

If preeclampsia with severe features, deliver if ≥ 34 weeks gestation

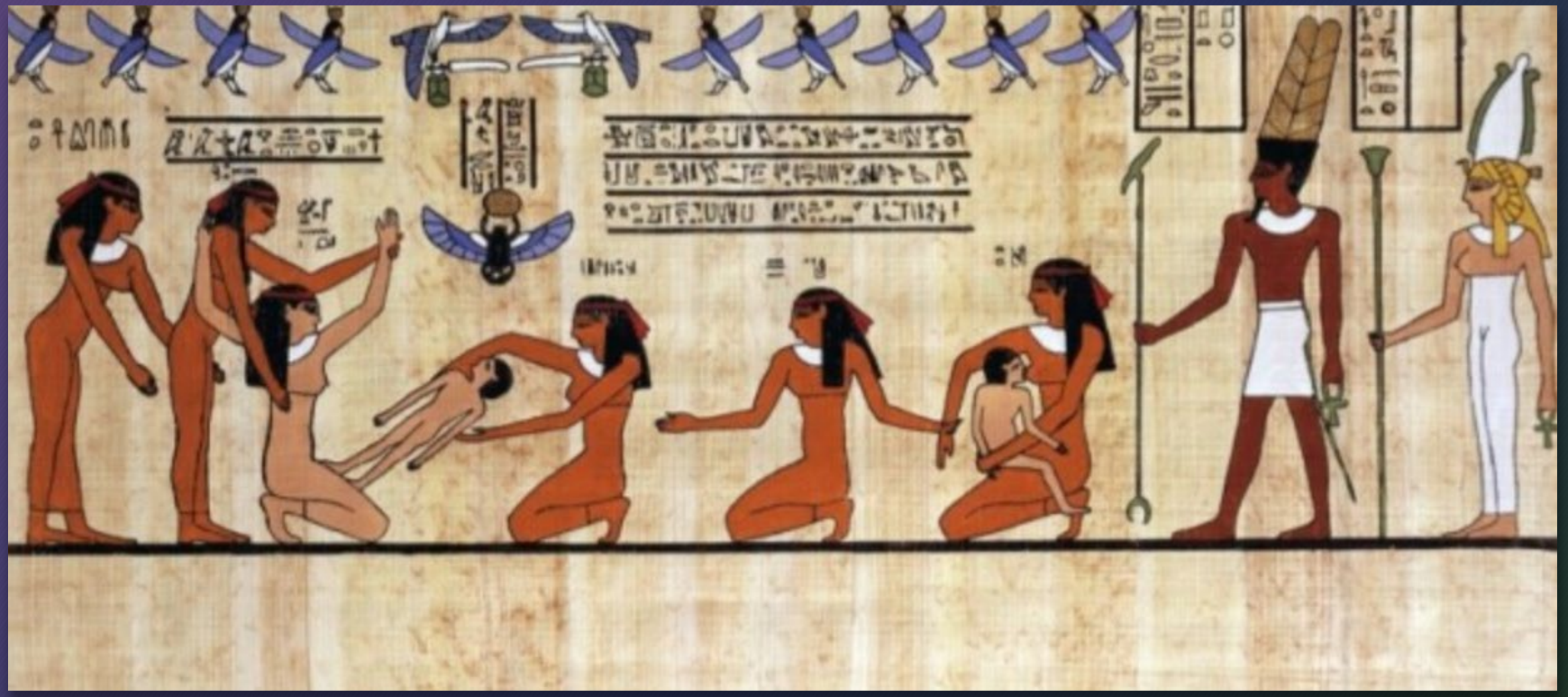
- Delivery minimizes maternal and fetal complications
- Also deliver if previable gestational age or if maternal or fetal status not stable

If < 34 weeks and stable, expectant management

- Administer antenatal corticosteroids
- Blood pressure control and maternal/fetal surveillance
- Delivery at 34 weeks if severe features
- Delivery at 37 weeks without severe features
  - HYPITAT trial: women induced had 30% decrease in maternal morbidity/ mortality, decreased c-section rate (14 vs 19%), no difference in neonatal outcome

Why do pregnant women develop preeclampsia?

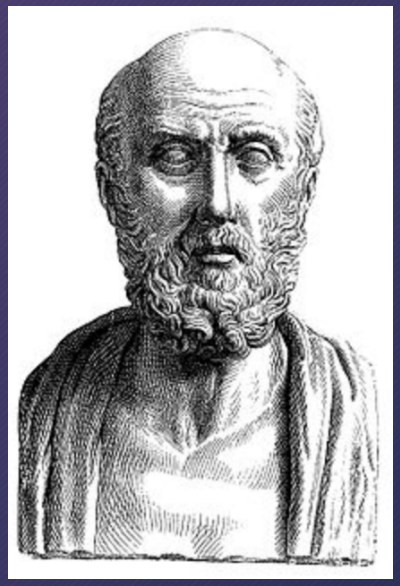
- We still lack the ability to predict which women will develop preeclampsia
- Preventative and therapeutic options are limited
- Delivery remains the primary intervention



3000 Years of eclampsia

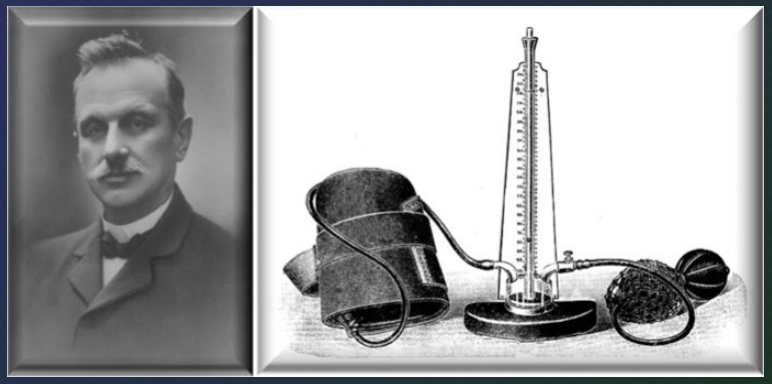
Eclampsia: the development of generalized tonic clonic seizures in a pregnant patient without history of a seizure disorder

Eclampsia



Hippocrates (400 BCE)

Bossier du Sauvages
(1710-1795)
First to use the Greek term "eclampsia"



Scipione Riva-Rocci's sphygmomanometer: 1896

PREECLAMPSIA
foundation

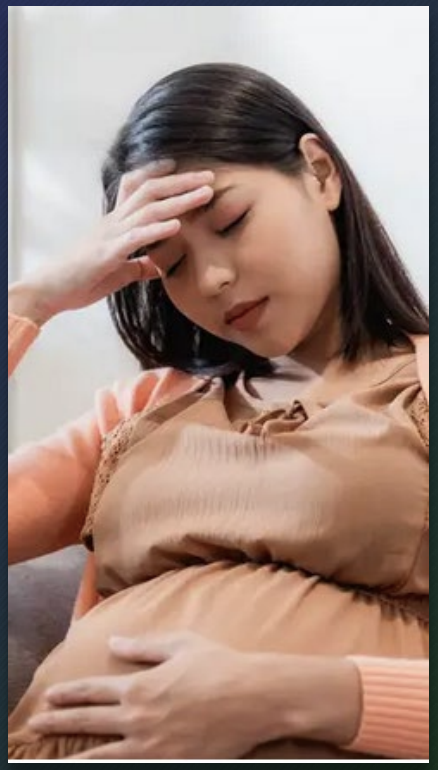
Eclampsia

Incidence

- Ranges from 1/2000-3448 pregnancies

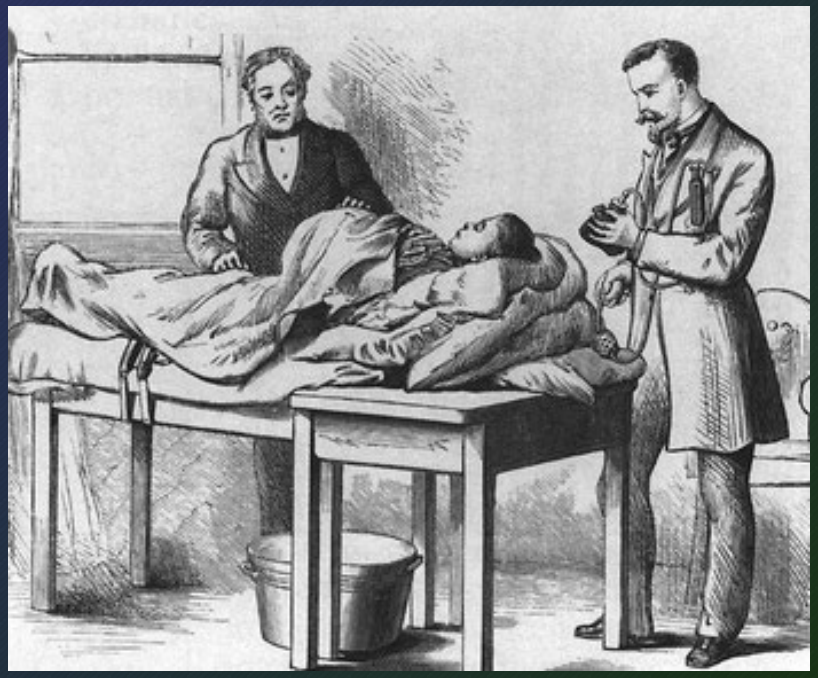
Symptoms

- May occur before or after convulsions
- Persistent occipital or frontal headache
- Blurred vision
- Photophobia
- Epigastric or RUQ pain
- Altered mental status



Seizure prophylaxis: Magnesium

- Intramuscular magnesium was introduced in the 1900s
- Intravenous injection in the 1920s
- 1990s brought RCTs demonstrating superiority over other methods.
- Magnesium sulfate IV:
  - 6 g load, 2 g IV (or 4/1)
  - or 5 g / buttock IM
- NNT = 60 (prevention of eclampsia in preeclampsia with severe features)

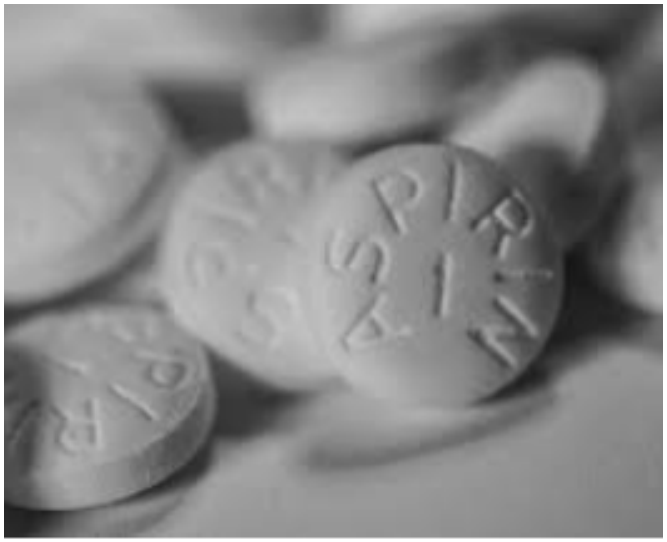


Preeclampsia:Postpartum course

- Acute features generally resolve postpartum
- Some symptoms resolve within hours (headache), others take weeks or months (proteinuria, hypertension)
- Mobilization of 3rd spaced fluid: within 48 hrs of delivery
- Hypertension can worsen 1-2 weeks postpartum, usually normalizes by 4 weeks

Preeclampsia: prevention

- Low-dose aspirin (60-150 mg/day; by 16 weeks) decreases preeclampsia by 10-20% in women at moderate to high risk
- Excellent safety profile
- 2019 Cochrane meta-analysis
  - 74 trials, >40,000 women; RR 0.82



Preeclampsia: Postnatal counseling

History of preeclampsia is associated with increased lifelong risks

Condition	Lifetime RR
Hypertension	3.7
Ischemic heart disease	2.2
Stroke	1.8
VTE	1.8

Absolute risk by age 50-59: 18% with preeclampsia hx vs 8% without.

- Gradation in risk by severity and GA at delivery
  - Mild disease: RR 2.0
  - Moderate preeclampsia: RR 3.0
  - Severe preeclampsia: RR 5.3
- Lifestyle interventions may decrease risk by 4-13 %

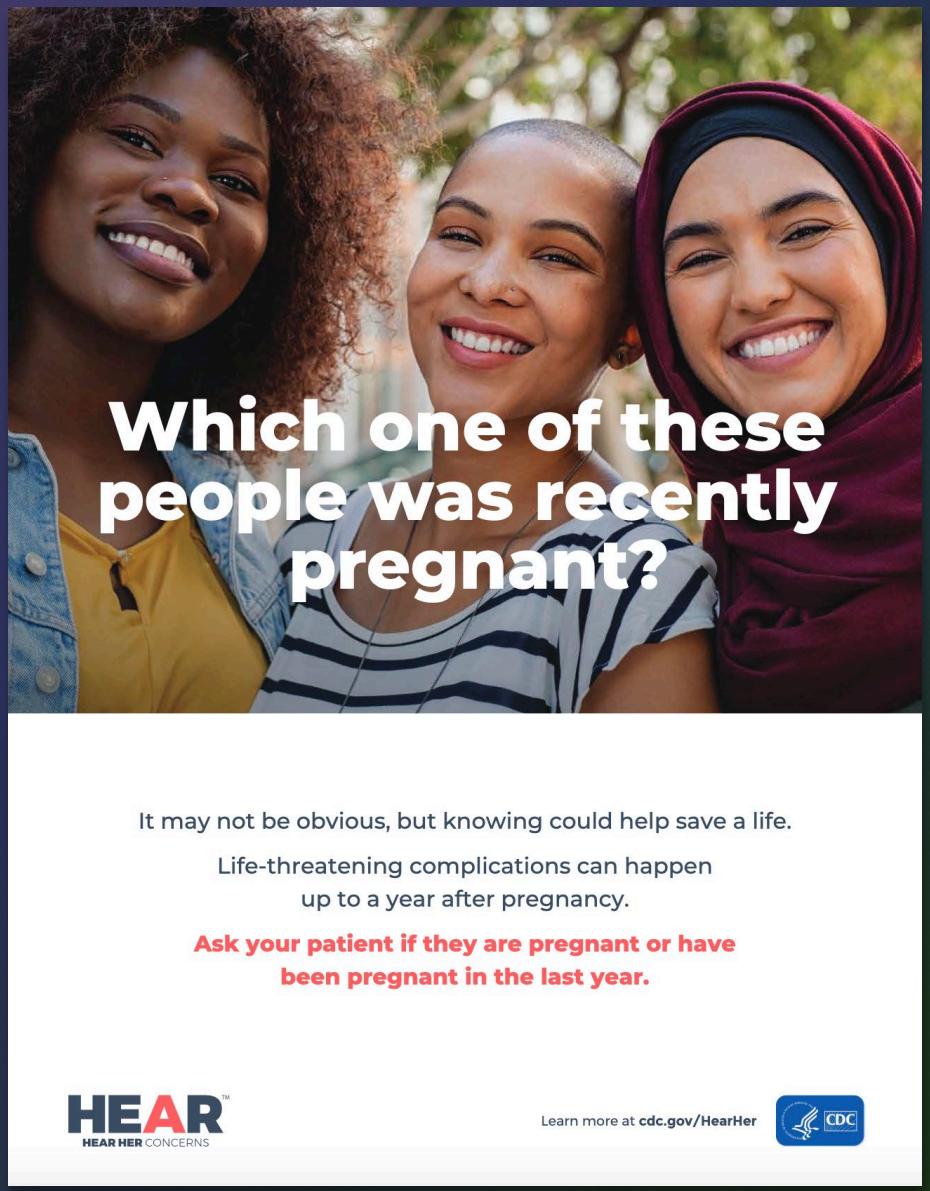
Schwartz Am J Med 2010

HEAR HER Campaign

EXPLORE TOPICS

Resources for non-Ob health care providers

- Pregnancy complications: 1/3 maternal deaths occur within the year postpartum
- Always ask if your patient is pregnant or was pregnant in the last year
- Recognize urgent maternal warning signs



Pregnant now or within the last year?

Get medical care right away if you experience any of the following symptoms:

Headache that won't go away or gets worse over time

Dizziness or fainting

Changes in your vision

Fever of 100.4˚F or higher

Extreme swelling of your hands or face

Thoughts of harming yourself or your baby

Trouble breathing

Chest pain or fast beating heart

Severe nausea and throwing up

Severe belly pain that doesn't go away

Baby's movement stopping or slowing during pregnancy

Severe swelling, redness or pain of your leg or arm

Vaginal bleeding or fluid leaking *during* pregnancy

Heavy vaginal bleeding or discharge *after* pregnancy

Overwhelming tiredness

These could be signs of very serious complications. If you can't reach a healthcare provider, go to the emergency room. Be sure to tell them you are pregnant or were pregnant within the last year.

Learn more at www.cdc.gov/HearHer/AIAN

HEAR™ HEAR HER CONCERNS

OMH CDC

This list of urgent maternal warning signs was developed by the Council on Patient Safety in Women's Health Care.

Diabetes in Pregnancy

Gestational Diabetes

- First documentation in 1824, of hyperglycemia and stillbirth of a macrosomic infant at 22 weeks
- *"Of pregnancy and progeny:" 1980*

- Carbohydrate intolerance of variable severity with onset or first recognition during pregnancy
- May not depend on treatment with insulin
- Complicates 7% of pregnancies

Two Step Process

- Screen with 50 gm load, test one hour
  - Abnormal ≥ 140 mg/dl (130 in some sites)
- 100 gm 3 hr OGTT performed fasting
  - 2 values ≥ fasting 95 mg/dl, 1 hr 180, 2 hr 155, 3 hr 140 (Carpenter-Coustan) Or fasting 105 mg/dl, 1 hr 190, 2 hr 165, 3 145 (NDDG)

Diagnosis of Gestational DM

- Usually screen 24-28 weeks gestation
- Two step endorsed by ACOG (6-7% of patients)
- One step endorsed by ADA and IADPSG (15-20% of patients)
- NIH consensus recommend two step continue
  - Vandorsten et al, NIH Concens State Sci 2013;29(1):1

ACOG=American College of Obstetrics and Gynecology
ADA= American Diabetes Association
IADPSG= International Association Diabetes and Pregnancy Groups

White's Classification

- **Type A1**: Diet modification is sufficient
- **Type A2:** Additional rx with insulin or oral hypoglycemics
- Type B: onset at age 20+ and duration of <10 years
- Type C: onset at age 10-19 or duration of 10–19 years
- Type D: onset age <10 or duration greater than 20 years
- Type E: overt diabetes mellitus with calcified pelvic vessels
- Type F: diabetic nephropathy
- Type R: proliferative retinopathy
- Type RF: retinopathy and nephropathy
- Type H: ischemic heart disease
- Type T: prior kidney transplant

Principles of Treatment

- Daily self monitoring
  - Fasting and 1 or 2 hour postprandial
- Individual medical nutrition therapy (70%)
  - Restrict diet to 35-40% CHO
- Insulin is the therapy most tested to reduce fetal morbidity
  - Fasting<90 1 Hr PP <140
- Fetal surveillance due to increased risk of stillbirth when poorly controlled sugars

Postnatal counseling- Diabetes

- 50% risk of Type 2 diabetes in women with gestational diabetes
- Encourage 75 g testing at 6 weeks postpartum

Schwartz Am J Med 2010

Mitigating obstetric risk

Optimize maternal conditions prior to pregnancy

Screen postpartum for T2DM in patients with GDM

Early GDM screen in patients with risk factors (HbA1c <5.7)

LDASA to prevent preeclampsia

MFM consultation for medications rather than abrupt discontinuation

Breastfeeding

Breastfeeding: Medicine and Culture

Risk of harm

Risks and benefits to birthing person- infant dyad

Breastfeeding: Medicine and Culture

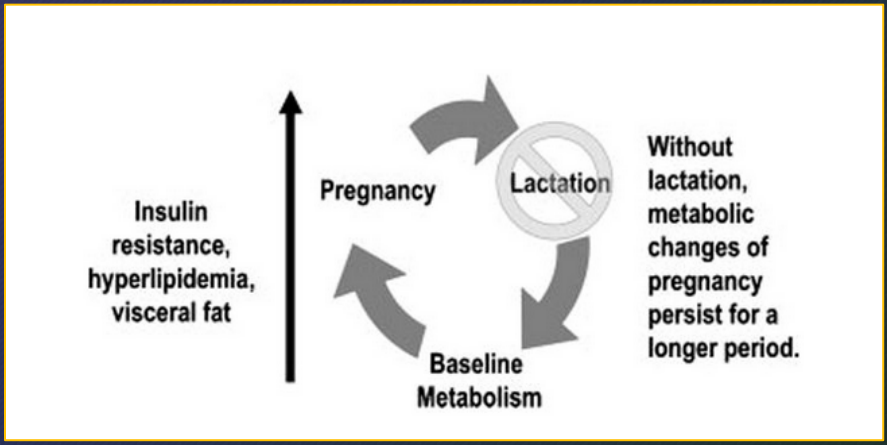
- How to move the needle?
  - Better understanding of benefits of breastfeeding to mothers/lactating persons
  - Better understanding of risk of medication exposure in breastmilk to newborns and babies

Breastfeeding: Medicine and Culture

- Breastfeeding is not the right choice for every individual
- Complex relationships between mood and breastfeeding
- Breast surgeries may reduce/eliminate supply
- Despite best efforts, sometimes breastfeeding is not successful

Importance of Lactation

- For maternal metabolism, pregnancy ends with weaning, not birth.
- Pregnancy is a time of increases in visceral fat, insulin production, insulin resistance, and circulating lipid levels
- In the absence of lactation, these changes persist for longer duration



Stuebe A, Am J Perinatol. 2009 Jan; 26(1): 81–88

Maternal metabolic health

- Protective effect of breastfeeding appears to persist after weaning
  - CARDIA cohort study
    - Individuals with history of GDM, breastfeeding for >9 mos associated with markedly lower risk of metabolic syndrome than 0-1 months (OR 0.14 (0.04-0.55)
    - Adjusted for baseline demographics, BMI, metabolic syndrome components, physical activity
  - German cohort study suggested lower progression from GDM to type 2 diabetes among those breastfeeding for >3 months compared to < 3 months. (Adj HR 0.54 (0.34-0.85)

Gunderson 2010, Zeigler 2012

Breastfeeding: Protection from T2DM

- 2233 women in California (Kaiser)
- 56% BF for >1 month
- BF>1 mo had similar rates of T2DM as nulliparas
  - (OR 1.01 95%CI 0.56-1.81)
- No BF more likely to develop T2DM than nulliparas
  - (OR 1.93 95%CI 1.14-3.27)
- No BF more likely to develop T2DM than BF 1-3 months
  - (OR 1.52 95% CI 1.11-2.1)

Risk of type 2 diabetes increases when term pregnancy is followed by <1 month of BF, independent of physical activity and BMI later in life

Schwartz Am J Med 2010

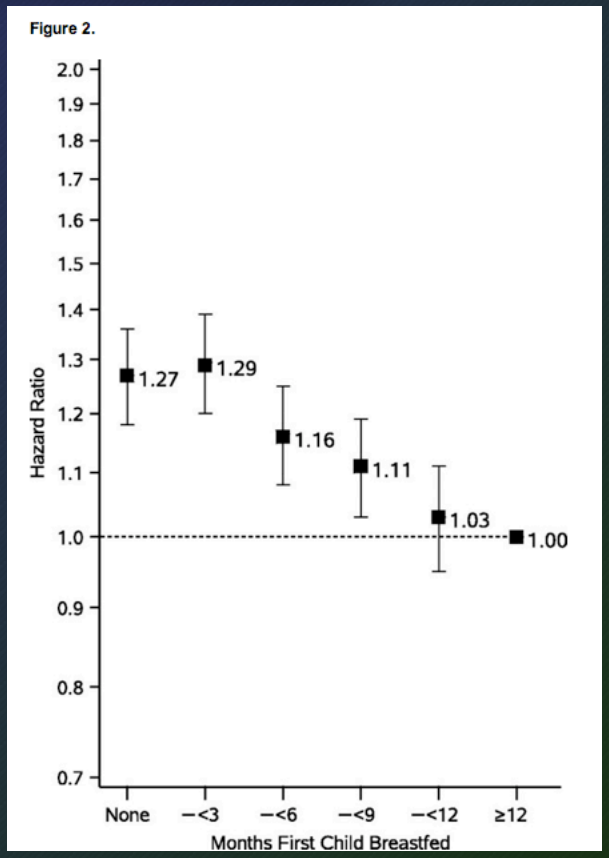
Type 2 Diabetes

- **Longer lifetime lactation is associated with lower incidence of type 2 diabetes**
- Nurses Health Study cohorts: lifetime duration of lactation was associated with reduced likelihood of incident type 2 diabetes in the 15 years since a woman's last birth
  - HR per year lifetime lactation NHS 0.85 (95% CI 0.73-0.99)
  - In NHS II 0.86 (95% CI 0.79-0.93)
- Longer lactation also associated with reduced DM risk in Women's Health Initiative, Reproductive Risk factors for Incontinence Study at Kaiser, the Shanghai Women's Health Study, and EPICPotsdam Study

Jager 2014, Schwarz 2010, Stuebe 2005, Villegas 2008, Schwarz 2009

Breastfeeding: Reduced risk heart disease

- 89,326 women from the Nurses Health Study
- BF for lifetime total 2 years +
  - 23% lower risk of CVD (95%CI 6-38), p=0.02) controlled for age, parity, stillbirth history, early-adult adiposity, parental history, and lifestyle factors.
- Observational cohort of 55,636 parous women in US Nurses' Health Study II
- **Never or curtailed lactation was associated with an increased risk of incident HTN compared with >6 months of exclusive (HR 1.29) or >12 months of total lactation per child (1.22)**



Stuebe Ob/Gyn 2009
Stuebe Am J Epi 2011

Caveats and confounders

- Pre-pregnancy obesity is associated with reduced BF initiation and duration
- Obesity associated with delayed lactogenesis
- Perinatal depression and anxiety disorders may mediate associations between lactation and metabolic disease
- Maternal metabolic health may affect lactation performance

Stuebe 2015

Additional benefits to mother and baby

- Reduced risks of breast and ovarian cancer
- Reduced newborn infections
- Reduced asthma, type 1 diabetes, obesity, SIDS in children

How to calculate risk when medication is needed?

1. What is the benefit of the medication to disease control?
2. What is the risk of harm if medication is not administered?
3. Is there a risk of harm to newborn?
4. How to mitigate that risk?

For drugs that are not systemically absorbed, there is a standard statement indicating that maternal use is not expected to result in infant exposure

For drugs that are systemically absorbed, the risk summary must be a description of the following information or it will state that it is not available:

- Effects of drug on milk production
- Presence of drug in human milk
  - If drug not detected, it will state limits of assay
  - If drug is detected, provide drug concentration in milk and estimated infant daily dose (actual and compared to pediatric or maternal doses)
  - Effects of the drug on the breastfed child
- If data show that the drug does not affect the quantity and quality of breast milk and there is reasonable certainty that either the drug is not detectable in breast milk or will not adversely affect the breastfed child, then it will state:
  - "The use of [name of drug] is compatible with breastfeeding."

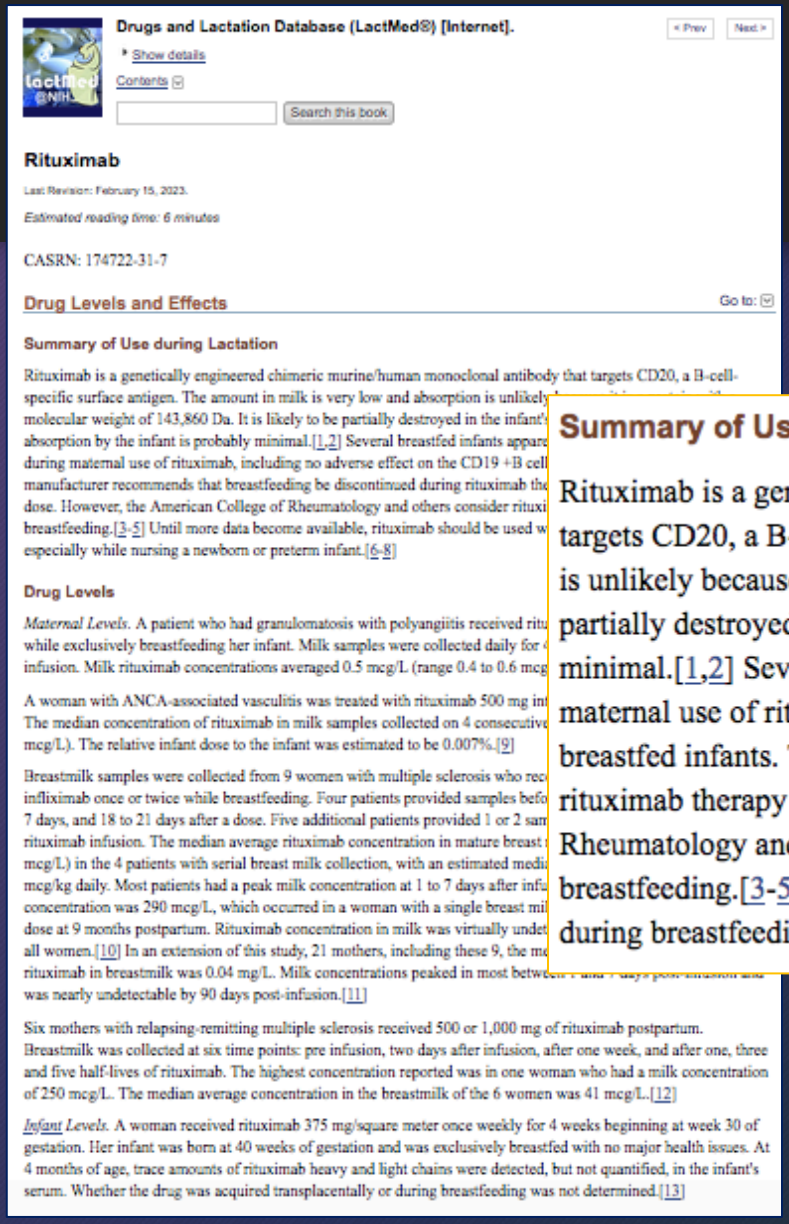
Clinical Considerations

This section must provide, when available, information on:

- Ways to minimize exposure of the breastfed infant to the drug
- Dosing adjustments during lactation

Evaluating safety of specific medications: FDA guidelines

Evaluating safety of specific medications: Lactmed



Drugs and Lactation Database (LactMed®) [Internet].

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Rituximab

Last Revision: February 15, 2023.

Estimated reading time: 6 minutes

CASRN: 174722-31-7

Drug Levels and Effects

Go to:

Summary of Use during Lactation

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody that targets CD20, a B-cell-specific surface antigen. The amount in milk is very low and absorption is unlikely because it is a protein with a molecular weight of 143,860 Da. It is likely to be partially destroyed in the infant's gastrointestinal tract and absorption by the infant is probably minimal.[1,2] Several breastfed infants apparently experienced no adverse effects during maternal use of rituximab, including no adverse effect on the CD19 +B cell count of 6 breastfed infants. The manufacturer recommends that breastfeeding be discontinued during rituximab therapy and for 6 months after the last dose. However, the American College of Rheumatology and others consider rituximab to be acceptable for use during breastfeeding.[3-5] Until more data become available, rituximab should be used with caution during breastfeeding, especially while nursing a newborn or preterm infant.[6-8]

Drug Levels

Maternal Levels. A patient who had granulomatosis with polyangiitis received rituximab while exclusively breastfeeding her infant. Milk samples were collected daily for 4 infusion. Milk rituximab concentrations averaged 0.5 mcg/L (range 0.4 to 0.6 mcg

A woman with ANCA-associated vasculitis was treated with rituximab 500 mg int The median concentration of rituximab in milk samples collected on 4 consecutive mcg/L). The relative infant dose to the infant was estimated to be 0.007%.[9]

Breastmilk samples were collected from 9 women with multiple sclerosis who rec infliximab once or twice while breastfeeding. Four patients provided samples befo 7 days, and 18 to 21 days after a dose. Five additional patients provided 1 or 2 sam rituximab infusion. The median average rituximab concentration in mature breast mcg/L) in the 4 patients with serial breast milk collection, with an estimated medi mcg/kg daily. Most patients had a peak milk concentration at 1 to 7 days after infu concentration was 290 mcg/L, which occurred in a woman with a single breast mil dose at 9 months postpartum. Rituximab concentration in milk was virtually undet all women.[10] In an extension of this study, 21 mothers, including these 9, the me rituximab in breastmilk was 0.04 mg/L. Milk concentrations peaked in most betwe was nearly undetectable by 90 days post-infusion.[11]

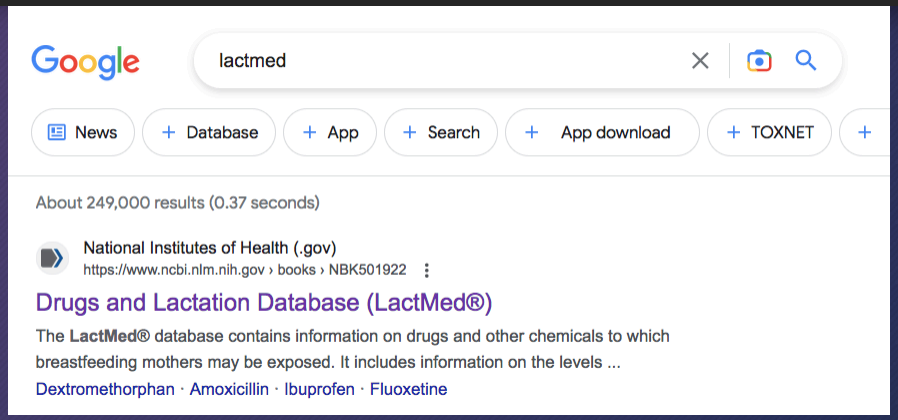
Six mothers with relapsing-remitting multiple sclerosis received 500 or 1,000 mg of rituximab postpartum. Breastmilk was collected at six time points: pre infusion, two days after infusion, after one week, and after one, three and five half-lives of rituximab. The highest concentration reported was in one woman who had a milk concentration of 250 mcg/L. The median average concentration in the breastmilk of the 6 women was 41 mcg/L.[12]

Infant Levels. A woman received rituximab 375 mg/square meter once weekly for 4 weeks beginning at week 30 of gestation. Her infant was born at 40 weeks of gestation and was exclusively breastfed with no major health issues. At 4 months of age, trace amounts of rituximab heavy and light chains were detected, but not quantified, in the infant's serum. Whether the drug was acquired transplacentally or during breastfeeding was not determined.[13]

Summary of Use during Lactation

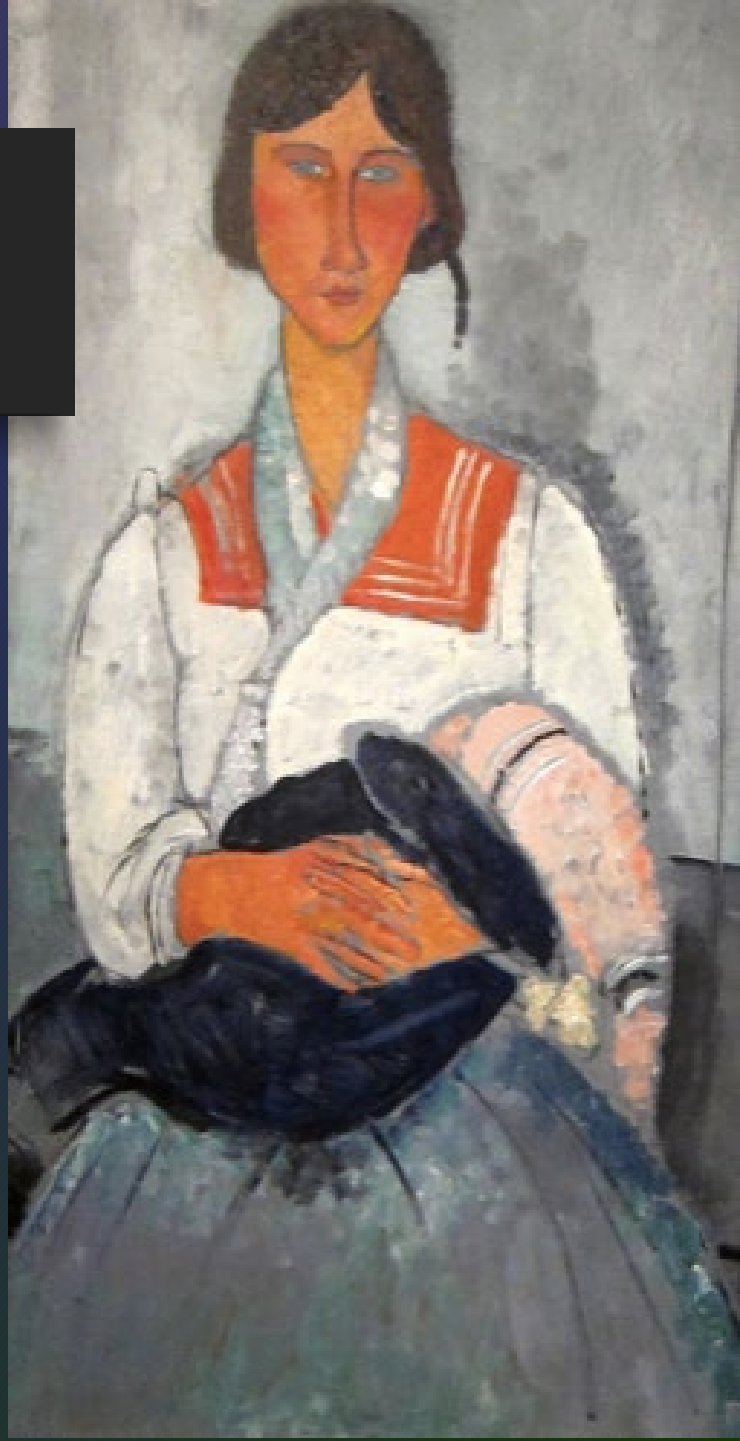
Rituximab is a genetically engineered chimeric murine/human monoclonal antibody that targets CD20, a B-cell-specific surface antigen. The amount in milk is very low and absorption is unlikely because it is a protein with a molecular weight of 143,860 Da. It is likely to be partially destroyed in the infant's gastrointestinal tract and absorption by the infant is probably minimal.[1,2] Several breastfed infants apparently experienced no adverse effects during maternal use of rituximab, including no adverse effect on the CD19 +B cell count of 6 breastfed infants. The manufacturer recommends that breastfeeding be discontinued during rituximab therapy and for 6 months after the last dose. However, the American College of Rheumatology and others consider rituximab to be acceptable for use during breastfeeding.[3-5] Until more data become available, rituximab should be used with caution during breastfeeding, especially while nursing a newborn or preterm infant.[6-8]

How to find Lactmed



Breastfeeding Summary

- Breastfeeding has significant health benefits
- Most medications are compatible with breastfeeding
- Recommendations against breastfeeding have significant health consequences and should be thoughtfully given
- In most cases, disease treatment for mothers/birthing persons can be optimized while breastfeeding continues.



Take Aways

- Maternal mortality and racial disparities in morbidity and mortality are a current crisis in the US
- Mitigating obstetric risk is feasible with optimization of maternal medical conditions and close surveillance of pregnancy complications
- Breastfeeding has important lifetime health benefits and should be supported whenever possible.

Acknowledgements- historical references

HISTORICAL PERSPECTIVE

The History of Preeclampsia and Eclampsia as Seen by a Nephrologist

2012 Benson and Pamela Harer Seminar on History Lecture

Marshall D. Lindheimer, MD, FACP,
FRCOG (London, ad eundem)
Professor [emeritus] of
Obstetrics & Gynecology and Medicine,
University of Chicago, Division of Biological Sciences*

nasmith@BWH.Harvard.edu