DIAGNOSING PREECLAMPSIA & HELLP

FLAME LECTURE: 104

BURNS/SISTO 10.10.23

LEARNING OBJECTIVES

- Classify the types of hypertension in pregnancy
- Describe the pathophysiology of preeclampsia
- List the risk factors for preeclampsia
- Recognize the signs and symptoms to diagnose preeclampsia
- See also:
  - FLAME 27 – Chronic HTN in Pregnancy
  - FLAME 105 – Management of Preeclampsia
  - FLAME 106 - Eclampsia

DEFINITIONS

Chronic Hypertension	Gestational Hypertension	Preeclampsia w/o severe features	Preeclampsia w/ severe features	Eclampsia
Spectrum →				
Starts < 20 wks	Starts > 20 wks	Usually > 20 wks	Starts > 20 wks	Starts > 20 wks
BP > 140/90	**BP > 140/90*** w/ no proteinuria and no severe features	**BP > 140/90*** + proteinuria *Proteinuria defined as:* - 24-hr urine collection w/ ≥300 mg protein - P:C >0.3 - 1+ protein on urine dipstick (if other methods not avail)	**BP > 160/105*** + proteinuria OR one of the following signs of *end-organ damage*: - Plt <100K - Elevated LFTs 2x normal - Cr > 1.1 or 2x normal - Pulmonary edema - New cerebral or visual symptoms	PreE w/ or w/o severe features + Seizures (in absence of another neurological explanation for seizures)

*(*on two separate occasions, 4 hours apart)*

MORE DEFINITIONS!

- And this spectrum gets even more complicated…
  - Chronic hypertension w/ superimposed preeclampsia: when patient with known hypertension (started before the 20th week of pregnancy), develops proteinuria or signs of end-organ damage
  - HELLP syndrome: (Hemolysis Elevated Liver Low Platelets), often co-presents with preeclampsia but some believe it to be distinct disorder as 15-20% patients with HELLP don't have preceding HTN/pre-E

EPIDEMIOLOGY

- Occurs in 4.6% of pregnancies worldwide (3.4% of pregnancies in United States)
  - Though definition is HTN occurring after 20 weeks, majority of cases occur later in pregnancy, later in 3rd trimester (<34 weeks)[2]
  - Patients with HELLP syndrome + preeclampsia, more likely to present earlier

Maternal Complications

- Women with preeclampsia are at risk for life-threatening complications of pregnancy
  - Acute kidney injury
  - Cerebral hemorrhage
  - Hepatic failure or rupture
  - Pulmonary edema
  - Disseminated intravascular coagulation
  - Progression to eclampsia

EPIDEMIOLOGY

- In US, preeclampsia is one of the top 4 leading causes of maternal death (6.4 deaths per 10,000 preeclampsia/eclampsia cases)
- Worldwide, pre-E/eclampsia associated w/ 10-15% of direct maternal deaths[2]

Pregnancy Complications

- Pregnancies complicated by preeclampsia are at risk for:
  - Placental abruption
  - Uteroplacental insufficiency
  - Increased risk of preterm delivery
  - Increased risk of cesarean section delivery
  - Oligohydramnios

PATHOPHYSIOLOGY

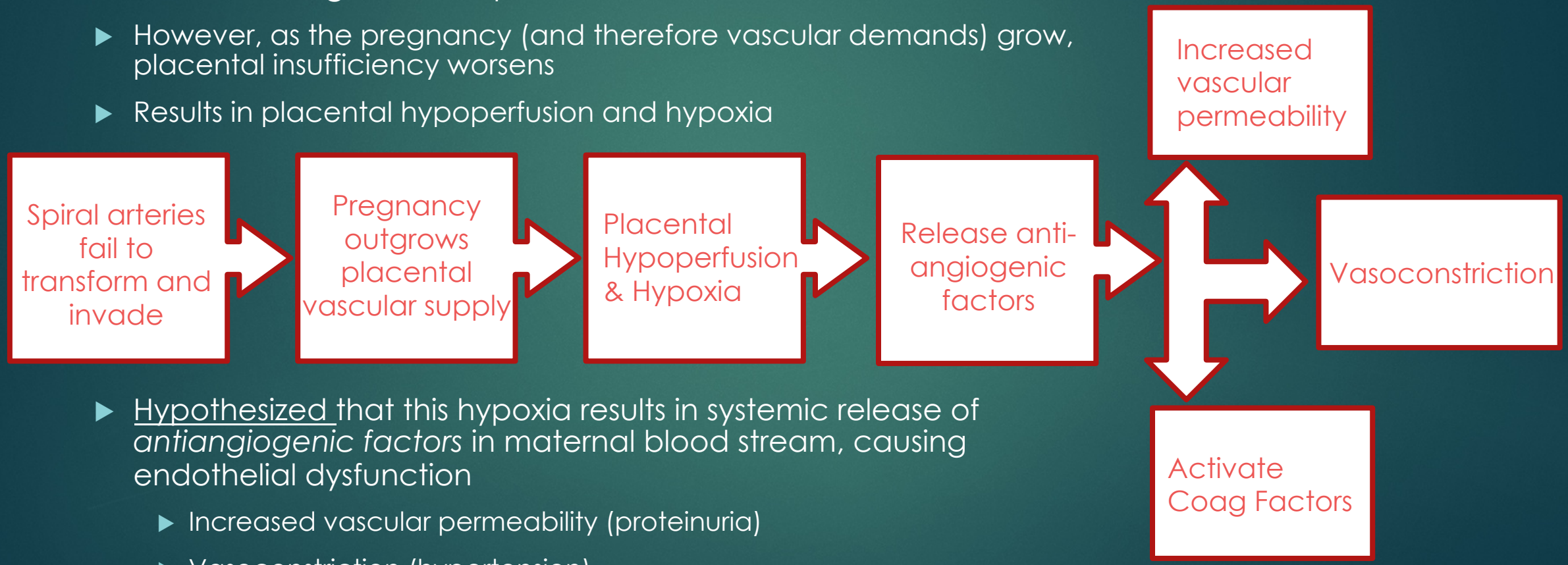
PLACENTAL ABNORMALITIES

- The pathophysiology of pre-E is still not fully solved, but we know that placenta is key:
  - Placental tissue is necessary for disease occurrence, even without fetus
  - Delivery of the placenta cures the disease
- Normally, as the placenta grows, coiled spiral arteries widen and invade myometrium to better support vascular needs of pregnancy. In pre-E:
  - Overall decreased surface area of villi (cytotrophoblasts and syncytiotrophoblasts)
  - Cytotrophoblast (CTB) invasion of the interstitial uterine compartments is shallow
  - CTBs that have invaded the uterine wall retain epithelial-like phenotypes and fail to transform to vascular-like cells
  - Spiral artery invasion is incomplete
  - Vessel abnormalities are seen (acute atherosis, fibrin deposits, increased lipid-laden macrophages)

PATHOPHYSIOLOGY

PLACENTAL ABNORMALITIES

- Placental vessels show abnormalities early in pregnancy, long before clinical signs develop
  - However, as the pregnancy (and therefore vascular demands) grow, placental insufficiency worsens
  - Results in placental hypoperfusion and hypoxia



- Hypothesized that this hypoxia results in systemic release of *antiangiogenic factors* in maternal blood stream, causing endothelial dysfunction
  - Increased vascular permeability (proteinuria)
  - Vasoconstriction (hypertension)
  - Abnormal endothelial expression of procoagulants → Clinical symptoms 2/2 endothelial dysfunction at target organs

PATHOPHYSIOLGY

IMMUNOLOGY

- It is also hypothesized that an alloimmunologic response to paternal/fetal factors contributes to development of pre-E. This is because:

PRIOR exposure to paternal and/or fetal antigens is PROTECTIVE against preeclampsia	**NEW exposure to paternal/foreign antigens is correlated w/ preeclampsia**
Decreased risk in:	*Increased risk in:*
▪ Multiple pregnancies with same partner ▪ Cohabiting with partner for >1 year prior to conception	▪ Nulliparous women or women who change partners between pregnancies ▪ Women who use barrier contraception ▪ Conceive via oocyte donation or conceive via intracytoplasmic sperm injection ▪ Couples of different ethnicities

- Evidence of increased immunologic and inflammatory responses seen in placental biopsies similar to those of transplant organ rejection samples (increased NK and dendritic cells)

RISK FACTORS

Vascular disease risk factors:

- Chronic hypertension
  - Even BPs ≥130/80 mmHg at initial prenatal visits
- Chronic renal disease
- Collagen vascular disease (SLE, antiphospholipid syndrome)
- Pre-gestational diabetes
- African American
- Advanced maternal age
- BMI ≥26

Immunologic risk factors

- History of Preeclampsia
- First pregnancy
- Family history of preeclampsia
- Multiple gestational pregnancy

Note: ***smoking*** *actually LOWERS risk for preeclampsia. It obviously has it's own host of complications with pregnancy but* ***cigarette smoking*** *is NOT a risk factor for preeclampsia*

Preeclampsia Clinical Presentation

PREECLAMPSIA WORK-UP

- H&P
  - Severe or persistent headache?
  - Blurry vision, seeing black stars?
  - RUQ or epigastric pain?
  - Nausea/vomiting?
  - Dyspnea?
  - Altered mental status?
- Labs:
  - Hemoglobin and Platelet count
  - Serum Creatinine, AST, ALT
- Other:
  - Fetal assessment (BPP or NST)
  - Fetal growth scan PRN
  - Labs PRN:
    - MAHA labs (LDH, haptoglobin, bilirubin, blood smear)
    - Coag function tests (PT, PTT, fibrinogen) in setting of severe thrombocytopenia, liver dysfunction, bleeding

PRE-ECLAMPSIA DIAGNOSIS

BLOOD PRESSURE COMPONENT

Must have 2 elevated BPs ≥ 4 hours apart

"MILD RANGE"

- ≥140 mmHg Systolic or ≥90 mmHg Diastolic

"SEVERE RANGE"

- ≥160 mmHg Systolic or ≥105 mmHg Diastolic

- New onset hypertension (>20 weeks of pregnancy)
  - Hypertension is earliest clinical sign of pre-e, typically worsens over time
- Extremely rarely, atypical preeclampsia can present earlier than 20 weeks, or you can have patient with chronic hypertension with superimposed preeclampsia
  - Existing hypertension + new onset proteinuria/symptoms

PRE-ECLAMPSIA DIAGNOSIS

PROTEINURIA COMPONENT

Proteinuria is defined as any of following:

- **≥ 0.3 g (300mg)** protein in 24 hr urine sample
- **protein:creatinine ratio >0.3** in one time urine sample
- **1+ protein** on urine dipstick (if the other modalities are unavailable)

- Proteinuria is a common, but not essential finding
- Previously, "mild preeclampsia" threshold was >300mg/24hr while >5g/24hr was diagnostic for severe preeclampsia
  - However, ACOG reports POOR correlation between proteinuria and disease severity, thus we no longer use proteinuria for diagnosis of severe features
- Proteinuria typically worsens overtime as a result of renal damage (decreased integrity of glomerular filtration barrier and tubular damage)
  - Likely due to vasoconstriction and hypoperfusion of renal vasculature

PRE-ECLAMPSIA DIAGNOSIS

END-ORGAN DAMAGE

- As with proteinuria, end-organ damage is due to vasoconstriction and oxidative stress

System	Pathology	Symptom
Vascular	Endothelial damage results in capillary leakage; proteinuria causes loss of albumin	▪Edema, particularly fast onset and in face, legs and lungs
Pulmonary	Inc. SVR and afterload cause pulmonary vasocongestion, worsened by hypervolemia from renal dysfunction, decreased serum albumin, and capillary damage.	▪Pulmonary edema
Renal	Decreased GFR/increased plasma Cr, due to renal vasoconstriction and decreased VEGF	▪Oliguria/Acute kidney injury ▪Hyperuricemia
Hematologic	Endothelial injury ➔ coagulation cascade and thrombi formation in microvasculature = platelet consumption ➔ thrombocytopenia May also have microangiopathic hemolysis	▪Thrombocytopenia ▪DIC ▪Hemolytic anemia
Hepatic	Hepatic hypoperfusion leads to ischemia and hemorrhage. Endothelial dysfunction can cause HELLP syndrome. Thrombi in portal system cause swelling/necrosis of liver capsule	▪RUQ pain (from liver capsule swelling) ▪Elevated AST, ALT
Neurological	Cerebral artery vasospasm and retinal artery spasm. Cerebral edema	▪Headache ▪Blurry vision ▪Hemorrhagic stroke ▪Seizures (= eclampsia)

PRE-ECLAMPSIA DIAGNOSIS

TRICKY IN PATIENTS WITH CHRONIC HTN

- Women with chronic HTN may already have baseline proteinuria
  - Thus, while you cannot make a diagnosis using proteinuria, you can compare their current proteinuria to their baseline (hopefully collected earlier in pregnancy) to look for acute rises
- Women with chronic HTN will have a steady elevation in both their systolic and diastolic BPs from 20 weeks until delivery
  - Thus, practitioners need to have a high index of suspicion for superimposed pre-eclampsia before titrating up home blood pressure meds
- Likely new neurologic symptoms or abnormal Cr/LFTs may be the most specific indicators, however, blood pressures that have dramatically increased over baseline or are not responding adequately to IV anti-hypertensives are also clues

DIAGNOSTIC REVIEW[1]

- New onset hypertension + proteinuria AND/OR end-organ damage in previously normotensive woman

Blood Pressure		Proteinuria		End Organ Dysfunction
Systolic BP ≥140 mmHg AND/OR Diastolic BP ≥ 90 mmHg	+	≥300mg/24hr urine AND/OR Protein:creatinine ≥0.3	OR	Platelets <100k/μL AND/OR Serum Cr >1.1 mg/dL (or 2x baseline) AND/OR Elevated LFTs (2x normal) AND/OR Cerebral/visual Sx AND/OR Pulmonary Edema

HELLP SYNDROME

- Hemolysis, Elevated Liver, Low Platelets
- Most often occurs in conjunction with preeclampsia, but ⅕ of patients with HELLP don't have preceding diagnosis of preeclampsia
- Labs show schistocytes on blood smear, elevated LDH and indirect bilirubin, decreased hemoglobin
- Risk of developing DIC

Distinguishing syndromes with ↑ LFTS:	
HELLP	↑ LDH, Bilirubin + hemolysis, ↓ Plt
AFLP*	↑ Ammonia, ↓ Glucose, ↓ Fibrinogen
ICP**	↑ Bile acids, (symptoms: itching palms and soles)

*AFLP: Acute Fatty Liver of Pregnancy
*ICP: Intrahepatic Cholestasis of Pregnancy

Abnormal placentation causes systemic inflammation from oxidative stress → Activates coag cascade resulting in platelet consumption and microangiopathic hemolytic anemia → Thrombi formation in portal system causes swelling and necrosis of liver capsule → RUQ or epigastric pain plus elevated liver enzymes

REFERENCES & RESOURCES

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