Pre-eclampsia and related disorders

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Disclaimers

- I serve as an expert witness
- I serve as Director at Large of the LGBT Caucus of the AAPA
- I have no other conflicts of interest to disclose
- I certify that this material is based on current standards of care

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Objectives

- By the conclusion of this lecture, the attendee will be able to:
  - Discuss the epidemiology, pathophysiology, signs, symptoms, physical exam findings, diagnostic studies, management and sequelae of:
    - Pre-eclampsia
    - Pre-eclampsia with severe features
    - Hemolysis, elevated liver function tests, and low platelets (HELLP) syndrome
    - Eclampsia

Case

- A 38 yo gravida 1, para 0 with no past medical history at 37 weeks and 3 days gestational age presents complaining of a severe headache for 8 hours as well as decreased fetal movement for the past four hours. The patient also notes severely painful contractions and dark red vaginal bleeding with clots for the past two hours. She denies: blurred vision, scotomata or epigastric or RUQ pain.
- Her physician asked her to go straight to Labor and Delivery.

Introduction, epidemiology, and sequelae

Hypertensive disorders of pregnancy: why they matter[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Among the most common medical complications of pregnancy
- Affects up to 10% of all pregnancies
- Responsible for up to 16% of all maternal deaths
- Incidence has increased over 25% in the past 20 years

Why hypertensive disorders of pregnancy matter[2]

[2]Centers for Disease Control and Prevention. Pregnancy mortality surveillance system. Reviewed March 23, 2023. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm Accessed July 2, 2023.

Maternal mortality rates have increased in the U.S. over the past four years

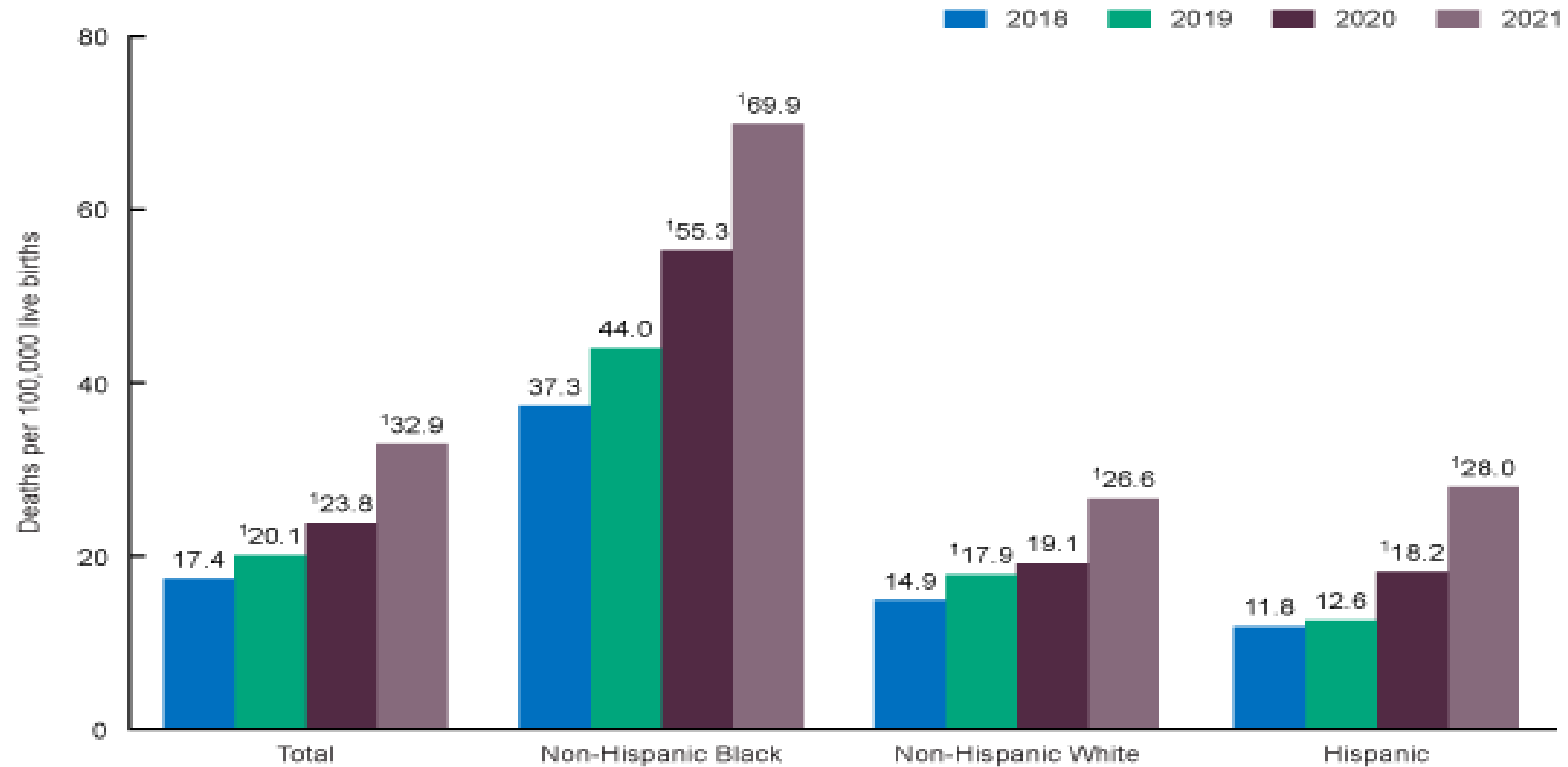
17.4/100,000 live births in 2018 to 23.8/100,000 in 2020

Hypertensive disorders ranks **sixth** among direct causes of maternal deaths

Most common cause of maternal death is cardiovascular disease

U.S. maternal mortality rates by race and Hispanic origin, 2018-2021[3]

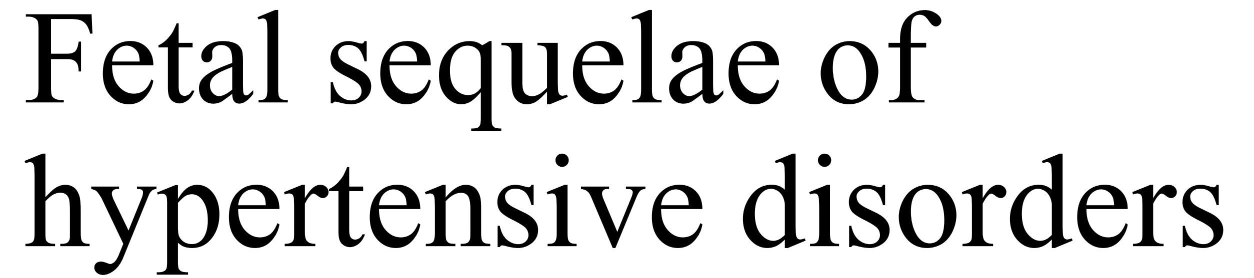
[3]Hoyert DL. Maternal mortality rates in the United States, 2021. NCHS Health E-Stats. 2023. Last reviewed March 21, 2023. https://www.cdc.gov/nchs/data/hestat/maternal-mortality/2021/maternal-mortality-rates-2021.htm#:~:text=In%202021%2C%201%2C205%20women%20died,20.1%20in%202019%20(Table). Accessed July 2, 2023.



Long-term maternal sequelae of hypertensive disorders of pregnancy[4]

[4]Chourdakis E, Oikonomou N, Fouzas S, Hahalis G, Karatza AA. Pre-eclampsia emerging as a risk factor of cardiovascular disease in women. *High Blood Press Cardiovasc Prev.* 2021;28(2):103-114.

- Patients with a history of pre-eclampsia have twice the risk of cardiovascular disease in later years than patients who were normotensive
- Patients with a history of pre-eclampsia who delivered at <34 weeks gestational age have an eight to ninefold risk of cardiovascular disease
    - Not due to the pre-eclampsia, but rather due to common risk factors between cardiovascular disease and pre-eclampsia
        - These patients may benefit from yearly H&P, lipids, glucose and BMI



Fetal sequelae of hypertensive disorders

- Prematurity
- Intrauterine growth restriction (IUGR)
  - Fetal weight at or <10%ile (by estimated fetal weight) at current gestational age based on ultrasonographic measurement of:
    - Head circumference
    - Biparietal diameter
    - Abdominal circumference
    - Femur length

Fetal sequelae of hypertensive disorders, cont'd (2)

- Associated with an increased relative risk of death (RR 2.77)
- All of the sequelae listed below are due to prematurity:
    - Intraventricular hemorrhage (RR, 1.19)
    - Respiratory distress syndrome (RR, 1.27)
    - Necrotizing enterocolitis (RR, 1.27)

Pre-eclampsia and related disorders

Pre-eclampsia[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Occurs at or after 20 weeks GA
- Blood pressure of 140/90 mm Hg or higher on 2 separate occasions at least 4 hours apart after 20 weeks gestation in patients who were previously normotensive, **with at least one of the following:**
  - New onset proteinuria
  - Thrombocytopenia
  - Elevated transaminases
  - Renal insufficiency
  - Pulmonary edema
  - Cerebral symptoms

Risk factors for pre-eclampsia[5]

[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222. Gestational hypertension and pre-eclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- Chronic hypertension
- Diabetes mellitus (pregestational or gestational)
- History of thrombophilia
- Multifetal gestation
- Nulliparity
- Prior history of pre-eclampsia

Risk factors for pre-eclampsia, cont’d (2)[5]

5American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222. Gestational hypertension and pre-eclampsia. Washington, D.C.: ACOG, 2020.

- Advanced maternal age (>35 yo)
- History of antiphospholipid antibody syndrome
- History of conception via in vitro fertilization
- History of obstructive sleep apnea
- Prepregnancy obesity
- Renal disease
- Systemic lupus erythematosus

Pathophysiology of pre-eclampsia[6]

[6]Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. *BMJ* 2019;366:12381.

- We may subdivide this disorder in those that present before 34 weeks EGA and those that occur after 34 weeks EGA
- **Early-onset pre-eclampsia** tends to be associated with placental abnormality
    - Cytotrophoblasts normally migrate into the spiral arteries; this increases blood flow, but in these patients the cytotrophoblasts invade the spiral arteries, narrowing them and leading to placental ischemia, hypoxia, and pre-eclampsia
- There is also an association between placenta accreta spectrum and retained placenta with pre-eclampsia

Pathophysiology of pre-eclampsia, cont'd (2)[6]

[6]Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. *BMJ* 2019;366:12381.

- **Late-onset pre-eclampsia** tends to be associated with obesity and primiparity
- Other factors include:
  - In vitro fertilization
  - Donor oocyte
  - Autologous frozen embryo transfers
  - Maternal immune response to paternally derived antigens

Laboratory results that define pre-eclampsia[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Proteinuria
  - May be defined as any of the following:
    - 300 mg proteinuria or higher in 24 hour urine collection
    - Protein/creatinine ratio of 0.3 or higher
    - Creatinine >1 mg/dL
    - Urine dipstick of 1+ protein or higher
      - Use this method only if no other method is available
- Thrombocytopenia
  - Platelet count <100,000/mcl
- Transaminase abnormalities
  - Elevated transaminases with or without RUQ or epigastric pain

Signs and symptoms of pre-eclampsia[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Central nervous system
  - Headache
  - Blurred vision
  - Scotomata
- Pulmonary edema

Pre-eclampsia with severe features[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Systolic BP of ≥160 mm Hg **and/or** diastolic BP of ≥110 mm Hg on 2 separate occasions 4 hours apart while at rest **with at least one of the following:**
  - New onset proteinuria
  - Thrombocytopenia
  - Elevated transaminases
  - Persistent severe RUQ or epigastric tenderness
  - Renal insufficiency
  - Pulmonary edema
  - Cerebral symptoms
    - Persistent headache or visual changes

Hemolysis, elevated liver function tests, and low platelets (HELLP) syndrome[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

Associated with pre-eclampsia, but up to 20% of all patients do not have a history of HTN or of pre-eclampsia at diagnosis

However, 20% of patients with pre-eclampsia will develop HELLP	All patients with HELLP should be presumed to have pre-eclampsia

Symptoms and signs of HELLP syndrome[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Epigastric or RUQ pain
- Headache
- Visual changes
- Nausea and vomiting
- **However, the syndrome is defined by presence of thrombocytopenia, hemolysis, and elevated transaminases**

Lab data to obtain in suspected HELLP syndrome[1]

[1]Salzer EAJ. “Hypertensive disorders of pregnancy.” In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Peripheral smear for schistocytes
- Decreased serum haptoglobin
- LFTs
  - Elevated indirect bilirubin
  - Elevated transaminases
  - Elevated LDH
- CBC
  - Decreased platelets

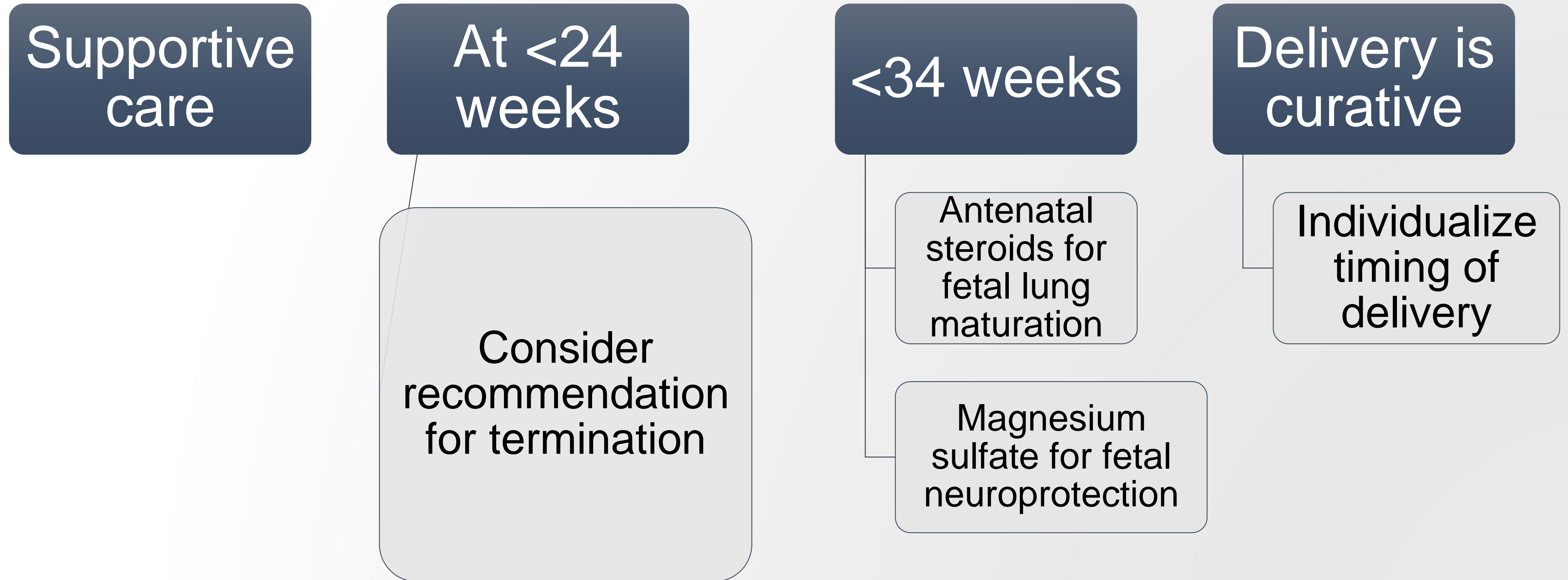
Lab results that define HELLP syndrome[1]

[1]Salzer EAJ. “Hypertensive disorders of pregnancy.” In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Elevated transaminases ≥70 IU/L
- Elevated LDH ≥600 IU/L
- Platelets ≤100 x 10^6/L

Management of HELLP syndrome[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.



Eclampsia[5]

[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- New onset tonic-clonic, focal, or multifocal seizures in a pre-eclamptic patient
- Often preceded by severe frontal or occipital headache, visual changes, photophobia, and altered mental status
  - Headaches are due to cerebral edema and hypertensive encephalopathy
- Up to 25% of patients do not present with hypertension or proteinuria prior to onset of eclampsia
- Manage with magnesium sulfate 6 gm IV over 15-20 minutes
- Maternal mortality rate is as high as 7%
- Perinatal mortality is as high as almost 12%

Intrapartum management of the patient with pre-eclampsia or a related disorder

"The only two questions to answer in obstetrics are when to deliver, and how to deliver."

-Irwin Merkatz, M.D.

Chairman emeritus, Department of Obstetrics and Gynecology

Albert Einstein College of Medicine and Montefiore Medical Center

Bronx, NY

The treatment of pre-eclampsia and related disorders is

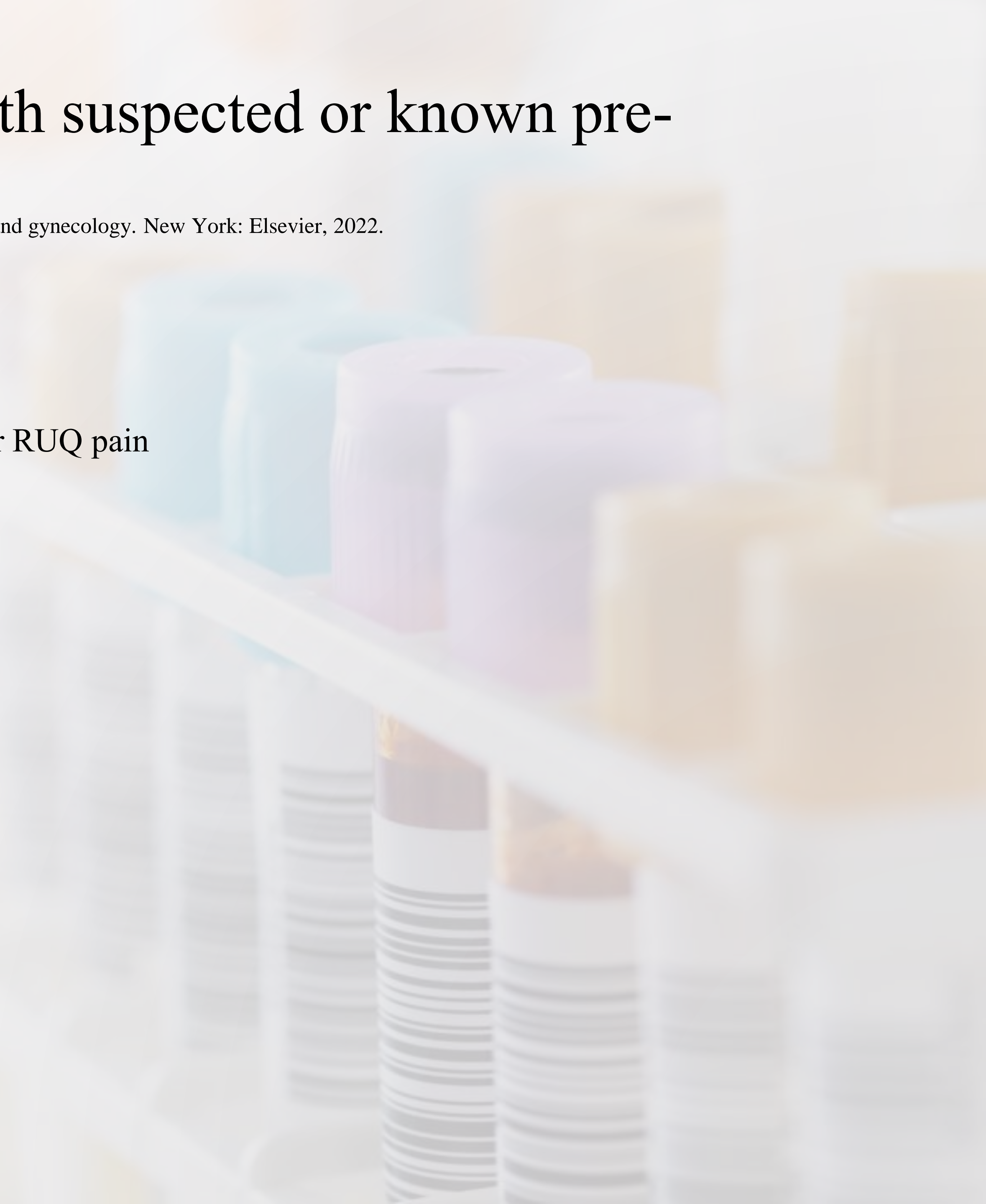
DELIVERY

But other things may have to be done to manage the disease before delivery!

- Manage hypertension
- Possible induction of labor
- Prophylaxis to reduce risk of eclampsia

Evaluation of the antepartum patient with suspected or known pre-eclampsia and related disorders[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.



- History
    - Inquire about
        - Headache, blurred vision, scotomata, dyspnea, epigastric or RUQ pain
        - Vaginal bleeding, painful contractions, fetal movement
- Laboratory data
    - CBC
    - Transaminases
    - BUN/creatinine
    - 24 hour urine or elevated protein/creatinine ratio
    - Coagulation profile
    - Liver function tests
    - Lactate dehydrogenase

Evaluation of the antepartum patient with pre-eclampsia and related disorders, cont'd (2)[1]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

- Fetal surveillance
  - External fetal heart monitoring
  - Ultrasound
    - Measurement of estimated fetal weight (normal: >10%ile for gestational age)
    - Amniotic fluid index (normal: 5-25 cm)
    - Biophysical profile (normal: 8-10/10)
      - Evaluates fetus via real time sonography for: fetal breathing movements, amniotic fluid index, gross fetal movements, fetal tone, and nonstress test

Management of hypertension in patients with pre-eclampsia[7]

[7]American College of Obstetricians and Gynecologists. Practice advisory. Clinical guidance for the integration of the findings of the Chronic Hypertension and Pregnancy (CHAP) Study. Washington, D.C.: ACOG, 2022.

- ACOG now recommends institution of treatment of chronic hypertension in pregnancy with a blood pressure of 140/90 mm Hg rather than at SBP of 160 mm Hg or DBP of 110 mm Hg, based on the results of the CHAP Study that demonstrated a reduced risk of:
    - Pre-eclampsia with severe features
    - Induction at <35 weeks gestational age
    - Abruptio placentae
    - Fetal or neonatal death

When to deliver with pre-eclampsia and related disorders: **maternal** indications[1,5]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.
[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- Any of the following:
  - Uncontrolled severe range BPs not responsive to medication
  - Persistent headache with no response to medication
  - Right upper quadrant or epigastric pain with no response to pain medication
  - Visual or motor deficit
  - Cerebrovascular accident
  - Myocardial infarction
  - Liver and/or renal disturbances
  - Pulmonary edema
  - Seizure
  - Suspected abruptio placentae

When to deliver with pre-eclampsia and related disorders: **fetal** indications[1,5]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.
[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- Any of the following:
  - Abnormal electronic fetal testing
  - Fetal death
  - Previable fetus
  - Fetus not expected to survive
  - Persistent reversed end-diastolic flow in umbilical artery

Magnesium sulfate[5]

[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

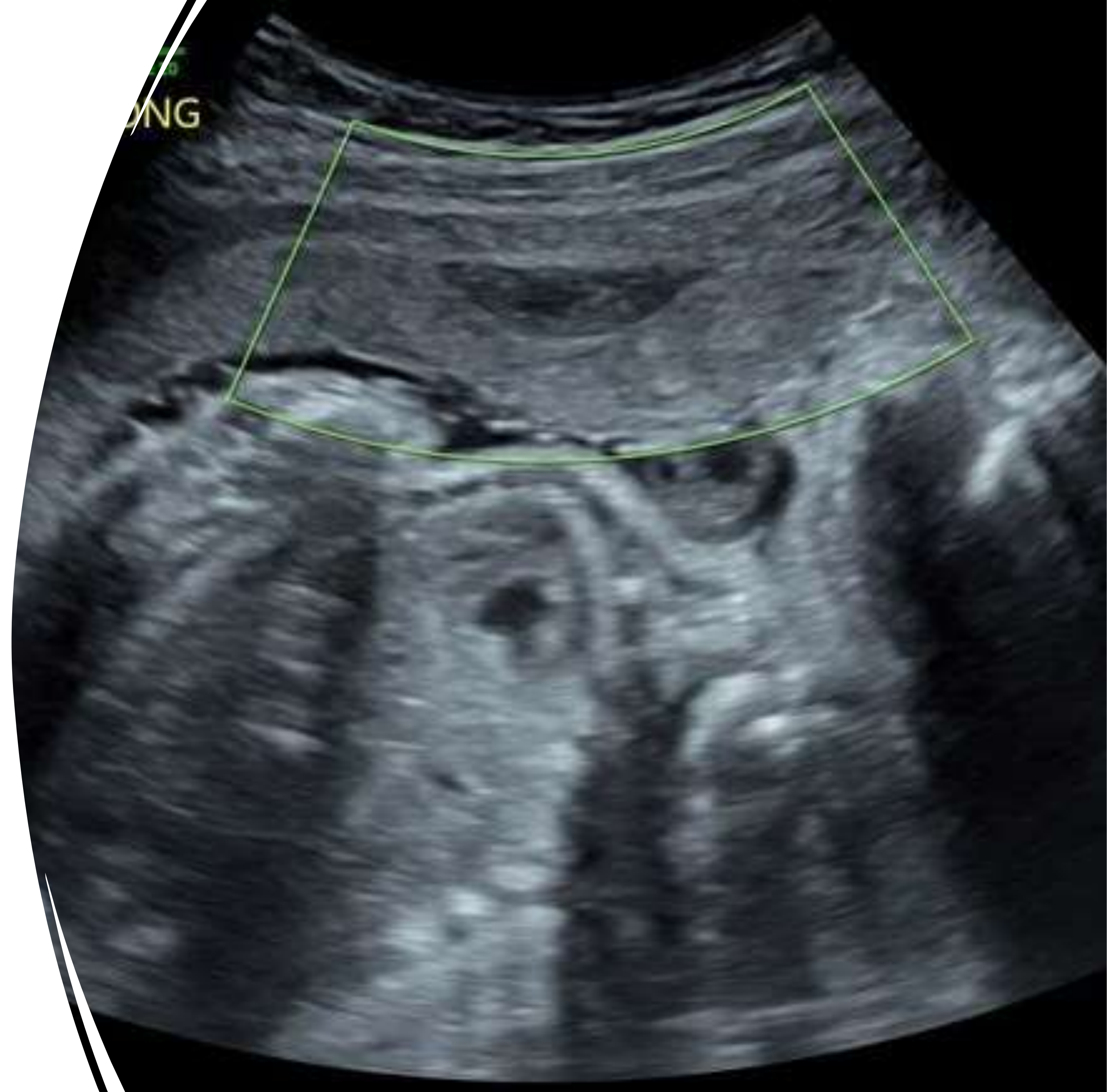
- Used to reduce the risk of eclampsia
- Mechanism of action: decreased cerebral edema
- Will not lower blood pressure
- Loading dose: 4 gm IV x 1 dose; then 1-2 gm IV infusion/hr
- Continue until the patient is 24 hrs postpartum
- Pre-eclampsia with severe features who are **not** treated with magnesium sulfate have a rate of seizure 400% higher than those with pre-eclampsia without severe features

Case: initial evaluation

- BP upon presentation to Labor & Delivery: 180/118 mm Hg
- HR: 120/min
- Fetal heart rate 170/min with abnormal pattern noted
- Contractions every 1-2 minutes
- Pelvic exam: speculum exam reveals some dark red blood and clots in the vaginal vault
- Cervical exam: 1 cm dilated, 50% effaced, presenting part -4 station

Retroplacental hematoma seen in abruptio placentae

Retroplacental hematoma



Management of pre-eclampsia with severe range blood pressures: manage hypertension[1,5]

[1,5]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.
[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- Treat for systolic BP of 160 mm Hg or higher and/or diastolic BP of 110 mm Hg or higher (severe range BPs) if persistent for 15 minutes or longer to avoid sequelae of severe hypertension
- Reassess BP every 10 minutes
- Administer labetalol 20 mg IVP, then 40 mg, then 80 mg every 10 minutes if the patient continues to have severe range pressures
    - Maximum dose: 220 mg over 24 hours
    - Never use labetalol in asthmatic patients

Management of pre-eclampsia with severe range blood pressures: manage hypertension, cont'd (2)[1,5]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.
[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- If the patient continues to have severe range pressures after maximal doses of labetalol, administer hydralazine 10 mg IVP, then repeat as needed in 10 and 20 minutes, respectively
- If the patient continues to have severe range pressures, consult:
  - Intensivist
  - Maternal fetal medicine specialist
  - Anesthesia team

Case: repeat BP and lab data

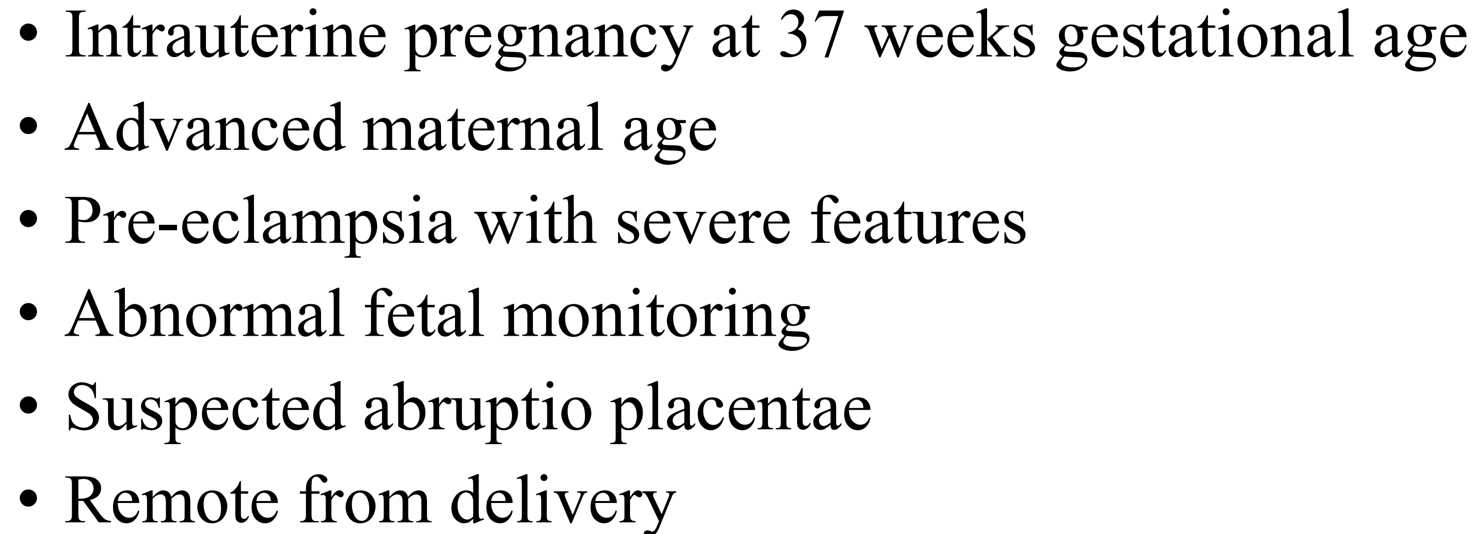
- Repeat BP: 173/112 mm Hg
- Lab data:
  - Protein/creatinine ratio: 0.81
  - Creatinine=1.2 mg/dL
  - AST/ALT 98/122 U/L
  - Platelets 61,000/mcl

Management of pre-eclampsia with indication for magnesium and delivery[1,5]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.
[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- Magnesium sulfate 4 gm IV bolus followed by IV infusion of 1-2 gm/hr
- Manage BP as needed
- Expeditious delivery (spontaneous NSVD, induction of labor, or Caesarean section, depending on the patient)
- Continue magnesium sulfate infusion for 24 hours postpartum
- Manage blood pressure during postpartum hospitalization (and possibly beyond) with PO nifedipine or labetalol (in non-asthmatic patients)

Case: assessment



- Intrauterine pregnancy at 37 weeks gestational age
- Advanced maternal age
- Pre-eclampsia with severe features
- Abnormal fetal monitoring
- Suspected abruptio placentae
- Remote from delivery

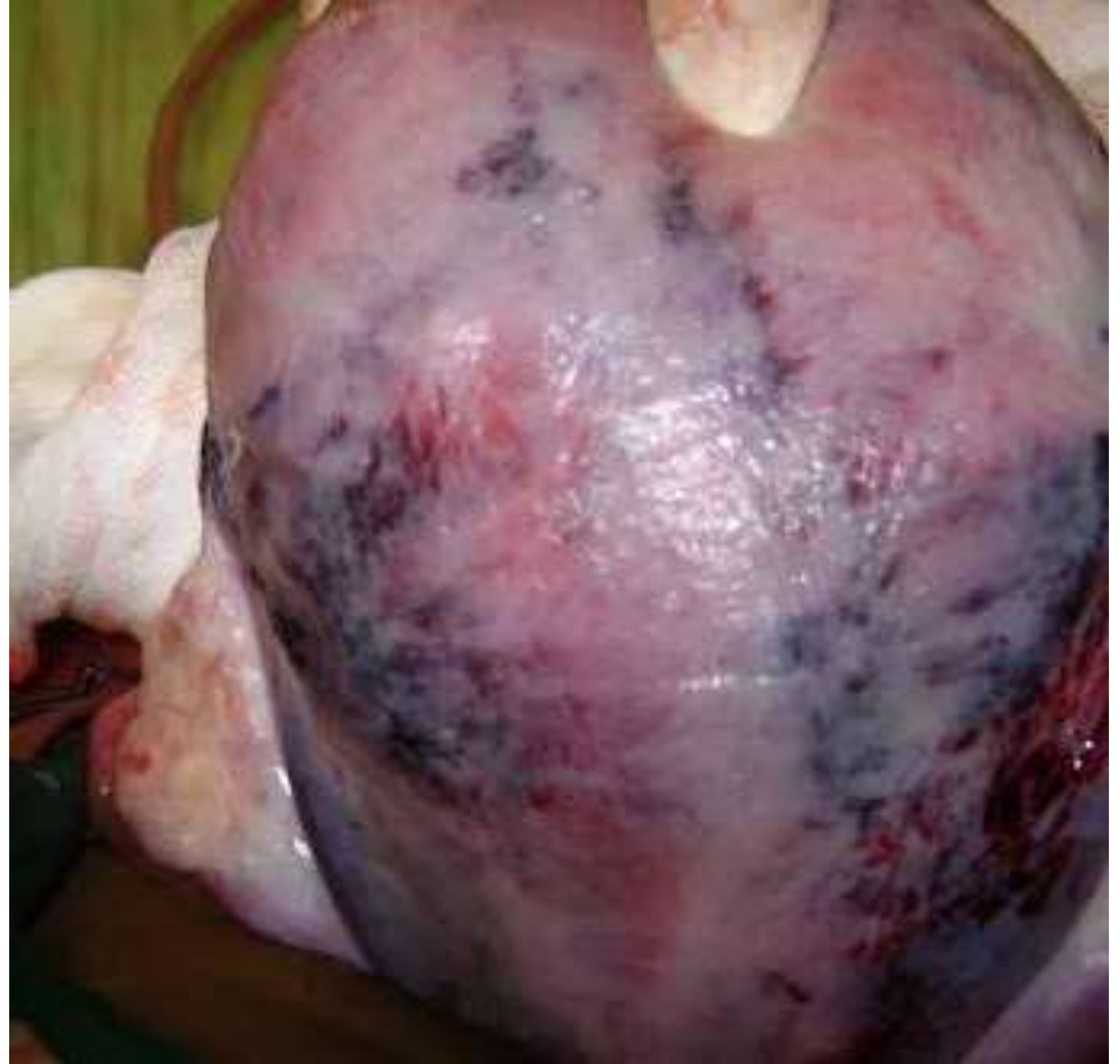
Case: plan

- Admit
- Labetalol 20 mg IVP now; repeat as needed
- Stabilize with labetalol and/or hydralazine
- Magnesium sulfate 4 gm IV loading dose followed by 1-2 gm IV infusion per hr
- Keep NPO
- To OR for stat C/S when the patient is stabilized
  - C/S indicated because the patient is remote from delivery with abnormal fetal heart rate pattern AND with suspected abruptio placentae

Case: findings at Caesarean section

- Live male fetus
- 70% placental abruption
- Birth weight: 2500 gm (3%ile)
- Couvelaire uterus
- Estimated blood loss: 1200 cc

Couvelaire uterus seen in abruptio placentae



Case: postpartum course

- Magnesium sulfate continued x 24 hours postpartum
- The patient developed oliguria (urine output: 20-30 cc/hr), followed by significant diuresis (200-250 cc/hr)
- Blood pressures ranged from 150-155/88-97 mm Hg
  - Nifedipine XL 30 mg PO daily begun with BPs of 133-138/83-87 mm Hg

Case: postpartum course, cont’d (2)

- The patient denied headache, visual changes or epigastric or right upper quadrant pain
- Discharged home on postoperative day #4 on nifedipine XL 30 mg PO daily, oxycodone/acetaminophen, docusate
- Follow-up in office within 1 week of discharge for blood pressure and wound check

Management of patients with hypertensive disorders of pregnancy at time of discharge from postpartum unit[1,5]

[1]Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.
[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- Rx for antihypertensive, if indicated
- Follow up within 1 week in obstetrician's office for blood pressure check
  - Maternal Early Warning System (MEWS) standard

Prevention of pre-eclampsia[5]

[5]American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.

- Aspirin 80-100 mg PO daily to begin between 12-28 weeks gestational age is indicated in patients with prior history of at least one of the following:
  - Pre-eclampsia
  - Multi-fetal gestation
  - Renal disease
  - Autoimmune disease
  - Diabetes mellitus (type 1 or type 2)
  - Chronic hypertension
  - Black patients (due to sequelae of allostatic load, not biological differences)

References

- American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #222: gestational hypertension and preeclampsia. Washington, D.C.: ACOG, 2020. Reaffirmed 2023.
- American College of Obstetricians and Gynecologists. Practice advisory. Clinical guidance for the integration of the findings of the Chronic Hypertension and Pregnancy (CHAP) Study. Washington, D.C.: ACOG, 2022.
- Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. *BMJ* 2019;366:12381.
- Centers for Disease Control and Prevention. Pregnancy mortality surveillance system. Reviewed March 23, 2023. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm Accessed July 2, 2023.
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- Salzer EAJ. "Hypertensive disorders of pregnancy." In: Watkins E, ed. Physician assistant clinics: obstetrics and gynecology. New York: Elsevier, 2022.

Feel free to e-mail me with questions at esalzer@pace.edu