



UTAH SOCIETY OF HEALTH–SYSTEM PHARMACISTS

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Baby On Board! Management of the Critically Ill Obstetric Patient

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Disclosure

Relevant Financial Conflicts of Interest

The presenter, Azelia Brown, has no financial conflicts of interest to disclose. The project mentors, Cole Sloan and Thomas Peterson, have no financial conflicts of interest to disclose.

Off-Label Uses of Medications

There will be no off-label uses of medications discussed



Pharmacist Learning Objectives

At the conclusion of this program, *pharmacists* should be able to successfully:

- Evaluate the different stages of pregnancy and contraindicated medications
- Compare and contrast the clinical presentations of common obstetric emergencies
- Prepare appropriate medication regimens for the management of ante- and post-partum complications
- Choose an appropriate sedation and vasopressor regimen for obstetric patients requiring these interventions



Technician Learning Objectives

At the conclusion of this program, *technicians* should be able to successfully:

- Recognize the potential consequences of inappropriate medication use during pregnancy
- Review common pregnancy complications that may require pharmacological intervention
- Identify medications that are contraindicated in pregnant patients and medications associated with the treatment of obstetric emergencies
- Distinguish between high priority medications and normal medication regimens used in the management of obstetric patients



Background

12.7 to 43.5 deaths per
100,000 live births



26 % of all maternal deaths attributed to preeclampsia



Pregnancy related cardiomyopathy mortality has a mortality between 5-32%



Amniotic fluid embolization has a mortality rate of up to 37%



Postpartum hemorrhage is the leading cause of maternal death and occurs in about 18% of all pregnancies



Leading Causes of Maternal Death

- Cardiovascular disease/Cardiomyopathy
- Amniotic fluid embolism
- Hypertensive disorders
- Thrombosis/Hemorrhage
- Infection/sepsis

Peripartum Cardiomyopathy



Patient Case

PP is a 33 year old, 32 week pregnant African American female who presents to the ED with worsening shortness of breath, persistent cough, palpitations and chest pain. On examination she had jugular distention and her extremities were cold and clammy. While in the ED, she had increasing labored breathing and was transferred to the CVICU.

Vitals: HR 94 BP: 120/72 SpO2: 91%

EKG: Sinus rhythm with 1st degree AV block

Echo: LVEF 25%

Peripartum Cardiomyopathy (PPCM)

- Last month of pregnancy to up to 5 months after delivery
- Findings are consistent with heart failure
- Risk factors include:
 - African American descent
 - Pre-eclampsia/ gestational hypertension
 - Increased maternal age
 - Multiparous pregnancies
 - Multiple pregnancies



Clinical Presentation

- Shortness of breath
- Chest pain
- Jugular venous distention
- Peripheral edema
- Fatigue
- Arrhythmias
- Acute myocardial infarction
- Thromboembolism



Proposed Etiologies

- Viral myocarditis
- Abnormal immune response
- Abnormal hemodynamic response
- Apoptosis and inflammation
- Prolactin
- Malnutrition
- Prolonged use of tocolytic agents



Treatment

Compensated Heart Failure

- Goal: Increase inotropy and decrease preload and afterload
- Managed similarly to heart failure:
 - Diuretics*
 - Nitrates
 - Digoxin
 - Hydralazine
 - Beta blockers*



Treatment

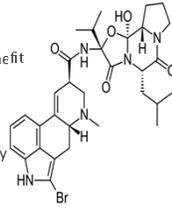
Decompensated Heart Failure

- Manage ABC's (Airway, Breathing, Circulation)
- Pharmacotherapy

Class	Agent/Dosage	Indication
Inotropes	Milrinone 0.125-0.5 mcg/kg/min Dobutamine 2.5-10 mcg/kg/min	<ul style="list-style-type: none"> • Improves cardiac output • Facilitates diuresis • Maintains end organ function • Improves hemodynamic/clinical stability
Vasodilators	Nitroglycerin 5-10 mcg/min Nitroprusside 0.1-5 mcg/kg/min*	<ul style="list-style-type: none"> • Maintain perfusion
Anticoagulation	Heparin IV or Low molecular weight heparin	<ul style="list-style-type: none"> • Prevention of left ventricular thrombus when LVEF is <35%
Loop Diuretics*	Furosemide 20-40 mg IV Q12-24H if GFR >60 Furosemide 20-80 mg IV Q12-24H if GFR <60	<ul style="list-style-type: none"> • Reduces preload

Bromocriptine in PPCM

- o Hilfiker-Keliner, et al. conducted a study to determine the benefit of bromocriptine in PPCM
 - o Improved LVEF recovery
 - o Decreased morbidity and mortality
- o It is proposed that prolactin leads to cardiac cell dysfunction by causing damage to the endothelium
- o Bromocriptine inhibits the secretion of prolactin



Hilfiker-Keliner, et al. Eur Heart J. 2017;38(35):2671-9

Bromocriptine in PPCM

Not so fast...

- o Patients from the Investigation in Pregnancy Associate Cardiomyopathy (IPAC) study served as placebo group
- o Significant difference in patient demographics between studies
- o Post hoc analysis
 - o No difference in LVEF recovery, morbidity or mortality



Hilfiker-Keliner, et al. Eur Heart J. 2017;38(35):2671-9
McNamara, et al. J Am Coll Cardiol. 2015;66(8): 905-914

Other Interventions

Mechanical Cardiovascular Support

- o Left Ventricular Assist Devices (LVADs)
- o Intra-aortic Balloon Pump
- o Extracorporeal Membrane Oxygenation (ECMO)
- o Defibrillators

Surgical Interventions

- o Heart Transplant
- o Cardiac revascularization



Patient Case

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Vitals: HR 94 BP: 120/72 SpO2: 91%

EKG: Sinus rhythm with 1st degree AV block

Echo: LVEF 25%

Question 1

The team wants to initiate vasodilator therapy for PP. Which regimen would you recommend?

- Nitroglycerin 0.4 mg tabs Q5min PRN
- Nitroprusside 10 mcg/kg/min
- Nitroglycerin 5 mcg/min
- Nitroprusside 5 mcg/kg/min

Question 1

The team wants to initiate vasodilator therapy for PP. Which regimen would be most appropriate?

- Nitroglycerin 0.4 mg tabs Q5 min PRN
- Nitroprusside IV 10 mcg/kg/min
- Nitroglycerin IV 5 mcg/min**
- Nitroprusside IV 5 mcg/kg/min

Question 2

Dr. Khan just read an article about the benefits of bromocriptine use in patients with PPCM. She asks you for assistance selecting the appropriate dosing regimen. What do you recommend?

- A. 7.5 mg po daily
- B. 5 mg for 2 weeks followed by 2.5 mg for 6 weeks
- C. Initiate once patient is more stable
- D. Do not recommend

Question 2

Dr. Khan just read an article about the benefits of bromocriptine use in patients with PPCM. She asks you for assistance selecting the appropriate dosing regimen. What do you recommend?

- A. 7.5 mg po daily
- B. 5 mg for 2 weeks followed by 2.5 mg for 6 weeks
- C. Initiate once patient is more stable
- D. Do not recommend**

Hypertension Disorders



Patient Case

PP is now in the ICU and her nurse notes that she has been hypertensive since her transfer from the ED. Her blood pressure ranged from 155-178/90-110. Proteinuria was detected on urinalysis and a 24-hour urine sample revealed excretion of 458 mg of protein.



Preeclampsia/Eclampsia

- Abnormal vascular response to placentation
- Occurs \geq 20 weeks of gestation
- New onset hypertension associated with proteinuria or other complications
- Eclampsia is when the disease progresses to the convulsive phase
- Usually symptoms improve with delivery of fetus*



Risk Factors

- First-time pregnancy
- Previous pregnancy associated with preeclampsia/Family history
- Multifetal pregnancy
- Chronic hypertension
- Renal disease
- History of thrombocytopenia
- Diabetes Mellitus
- Lupus Erythematosus
- Obesity
- Maternal age \geq 40



Preeclampsia Diagnostic Criteria

SBP \geq 140 mm Hg or DBP \geq 90 mm Hg repeatedly at least 4 hours apart
SBP \geq 160 mm Hg or DBP \geq 110 mm Hg repeatedly within minutes

+

Proteinuria (24 urine collection \geq 300 mg, 1+ on dipstick or protein/creatinine ratio greater \geq 0.3)

OR

Thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms

Severe Preeclampsia

- Best treated by prompt delivery of the fetus

Treatment Goals:

- Prevent peripartum cardiomyopathy or myocardial ischemia
- Prevent renal failure
- Prevent stroke (ischemic or hemorrhagic)



Pharmacological Management

Anti-seizure Prevention

- Magnesium sulfate
- Recommended when progressed to severe preeclampsia
- Not routinely recommended if blood pressure $<$ 160/110

Hypertension Management

- Goal SBP 140-160, DBP 90-100
- Hydralazine (IV)
- Labetalol (IV or PO)
- Nifedipine (PO)



Eclampsia

- Hallmark feature: Grand mal seizures
- May be preceded by:
 - Headaches
 - Blurred vision
 - Photophobia
 - Altered mental status
 - Right upper quadrant/epigastric pain
- Can progress to eclampsia even after delivery
 - Anesthetics used in C-section can lower seizure threshold



Seizure Management

Magnesium sulfate

- Loading dose 4-6 g, followed by continuous infusion of 1-2 g/hour
- Infusion should continue at least 24 hours after last seizure
- Infusions should be continued intraoperatively despite interaction with anesthetics
- Delivery of fetus once patient is stable
- Not be used to prolong gestation/expectant management



Question 3

PP is now in the ICU and her nurse notes that she has been hypertensive since her transfer from the ED. Her blood pressure ranged from 155-178/90-110. Proteinuria was detected on urinalysis and a 24-hour urine sample revealed excretion of 458 mg of protein. What is her likely diagnosis?

- Postpartum cardiomyopathy
- Sepsis
- Pre-eclampsia
- Eclampsia

Question 3

PP is now in the ICU and her nurse notes that she has been hypertensive since her transfer from the ED. Her blood pressure ranged from 155-178/90-110. Proteinuria was detected on urinalysis and a 24-hour urine sample revealed excretion of 458 mg of protein. What is her likely diagnosis?

- A. Postpartum cardiomyopathy
- B. Sepsis
- C. Pre-eclampsia**
- D. Eclampsia

Question 4

PP is now in the ICU and her nurse notes that she has been hypertensive since her transfer from the ED. Her blood pressure ranged from 155-178/90-110. Proteinuria was detected on urinalysis and a 24-hour urine sample revealed excretion of 458 mg of protein. She was diagnosed with severe preeclampsia and the team wanted to start treatment. What is your advice?

- A. Magnesium sulfate IV 2 g x 1 dose
- B. Methyldopa 250 mg TID to manage hypertension until she is full term
- C. Hydralazine 10 mg IV for hypertension management
- D. Patient is not a candidate for pharmacological treatment

Question 4

PP is now in the ICU and her nurse notes that she has been hypertensive since her transfer from the ED. Her blood pressure ranged from 155-178/90-110. Proteinuria was detected on urinalysis and a 24-hour urine sample revealed excretion of 458 mg of protein. She was diagnosed with severe preeclampsia and the team wanted to start treatment. What is your advice?

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Amniotic Fluid Embolization



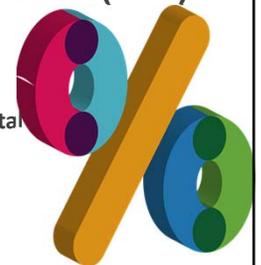
Patient Case

Twenty minutes after emergency C-section, PP has increasing anxiety and tells her husband and the nurse that she feels like something bad is going to happen. Within 10 minutes her mental status becomes altered and her blood pressure is 79/42, heart rate 115 bpm and her oxygen saturation has dropped to 81%. As the nurse calls for rapid response, she notes that the patient is bleeding from her IV site and her gown is becoming soaked with blood.

Amniotic Fluid Embolization (AFE)

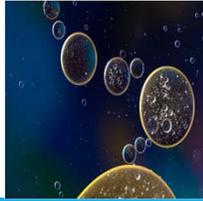
○ Maternal mortality rate 13-26%

○ In AFE that occurs antepartum, fetal mortality rate is greater than 10%



Amniotic Fluid Embolization (AFE)

- o Amniotic fluid or fetal tissue enters the maternal pulmonary circulation
- o The mother's immune system mounts a response
- o Reaction can range from mild organ dysfunction to cardiovascular collapse, coagulopathy and even death



Risk Factors/ Causes

Maternal Factors	Fetal Factors
<ul style="list-style-type: none"> • Multiple pregnancy • Older maternal age • Abdominal trauma • Cesarean section • Placenta previa • Labor induction • Eclampsia 	<ul style="list-style-type: none"> • Death of fetus • Male fetus • Fetal distress

Clinical Presentation

- o Dyspnea/cough
- o Encephalopathy/altered mental status
- o Rapid decrease in oxygen saturation or end tidal carbon dioxide
- o Hypotension
- o Cardiac arrest
- o Cyanosis
- o Coagulopathy/severe hemorrhage



Pharmacological Treatment

Right Ventricular Failure

Class	Agents/Dosages	Indication
Inotropes	Dobutamine 2.5-5 mcg/kg/min Milrinone 0.25-0.75 mcg/kg/min	<ul style="list-style-type: none"> • Improve right ventricular output • Decrease pulmonary vascular resistance
Pulmonary Vasodilators	Sildenafil 20 mg TID PO or per feeding tube Inhaled nitric oxide 5-40 ppm Inhaled prostacyclin 10-50 ng/kg/min Intravenous prostacyclin 1-2 ng/kg/min	<ul style="list-style-type: none"> • Decrease pulmonary vascular resistance
Vasopressors	Norepinephrine 0.05-3.3 mcg/kg/min Epinephrine 0.01-2 mcg/kg/min Phenylephrine 0.1-10 mcg/kg/min Dopamine 0.5-20 mcg/kg/min	<ul style="list-style-type: none"> • For management of hypotensive shock

Pharmacological Treatment

Disseminated Intravascular Coagulation and Embolism

- o Commonly presents as hematuria, vaginal bleeding, gastrointestinal hemorrhage, venipuncture or surgical sites.
- o AFE can also be associated with hypercoagulability. Choose an agent that is:
 - Not teratogenic /does not cross placenta
 - Is not secreted in breast milk/not orally bioavailable
 - Ex: Heparinization

Patient Case

Twenty minutes after emergency C-section, PP has increasing anxiety and tells her husband and the nurse that she feels like something bad is going to happen. Within 10 minutes her mental status becomes altered and her blood pressure is 79/42, heart rate 115 beat and her oxygen saturation has dropped to 81%. As the nurse calls for rapid response, she notes that the patient is bleeding from her IV site and her gown is becoming soaked with blood.

Question 5

After PP was intubated and adequately transfused, she still had persistent hypotension. Dr. Khan wanted to initiate vasopressor therapy and wanted your input regarding the drug of choice with the most clinical evidence. Which agent do you recommend?

- A. Norepinephrine
- B. Epinephrine
- C. Vasopressin
- D. Phenylephrine
- E. No drug of choice

Question 5

After PP was intubated and adequately transfused, she still had persistent hypotension. Dr. Khan wanted to initiate vasopressor therapy and wanted your input regarding the drug of choice with the most clinical evidence. Which agent do you recommend?

- A. Norepinephrine
- B. Epinephrine
- C. Vasopressin
- D. Phenylephrine
- E. **No drug of choice**

Postpartum Hemorrhage



Postpartum Hemorrhage

- Definition: blood loss ≥ 500 mL and ≥ 1000 mL vaginal and cesarean delivery, respectively
- Blood loss ≥ 1000 mL results in hemodynamic instability
- **Possible causes (4T's)**
 - Tone – Atonic uterus
 - Trauma – Hematomas, lacerations, uterine inversion or uterine rupture
 - Tissue – Invasive placenta (accreta, percreta or increta) or blood clots
 - Thrombin – Thrombin abnormalities/coagulopathies



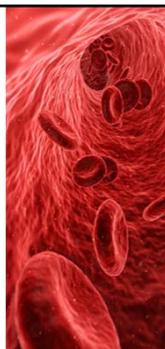
Outcomes and Risk Factors

○ Potential Outcomes:

- Hemorrhagic Shock
- Myocardial Ischemia
- Coagulopathy
- Death

○ Risk factors:

- Multiple deliveries
- Fetus > 8 pounds and 13 ounces
- History of postpartum hemorrhage
- Prolonged third stage of labor



Clinical Presentation

- Tachycardia
- Hypotension
- Shortness of breath
- Nausea
- Decreased urine output
- Chest pain



Pharmacological Treatment

Class	Agents/Dosages	Indication
Oxytocic Agents	Oxytocin 20-40 IU in 1 L of normal saline (1 st 500 mL in 10 mins then 250 mL/hr) Methylergonovine 0.2 mg IM every 2-4 hours until uterine atony is resolved	<ul style="list-style-type: none"> Stimulates myometrial contraction Decreases uterine blood flow
Prostaglandin Analogues	Carboprost 250 mcg IM or directly injected into myometrium. Repeat every 15 mins for a maximum of 2 grams Misoprostol 600-1000 mcg orally or rectally or 800 mcg sublingually as a single dose	<ul style="list-style-type: none"> Causes vasoconstriction Improves uterine contractility by increasing the number of oxytocin receptors (carboprost)
Antifibrinolytic Agent	Tranexamic acid (TXA) 1 gram administered over 30 mins within 3 hours of hemorrhage, may be repeated after 30 mins*	<ul style="list-style-type: none"> Prevents plasmin from breaking down fibrinogen and fibrin

The WOMAN trial

- Measured the effect of early TXA administration on mortality, hysterectomy and other morbidities
- Randomized, double-blinded, placebo controlled international study with over 20,000 participants.
- Results showed a reduction in death due to bleeding when TXA was administered within 3 hours of hemorrhage



WOMAN Trial Collaborators. Lancet. 2017;389(10084):2105-16

Question 6

Dr. Khan asks for your advice regarding the appropriate regimen to manage PP's post partum hemorrhage. She states that she plans on continuing IV oxytocin and may consider TXA if the bleeding continues. You are aware that PP's bleeding started a little over an hour ago and the IV oxytocin regimen will last approximately 2 hours. What do you tell her regarding TXA therapy?

- "I agree with your plan. Continuing oxytocin will be sufficient."
- "We should probably try carboprost before we do TXA"
- "I recommend starting TXA since its benefit is shown within the first 3 hours of hemorrhage"
- "Let's start with misoprostol instead since it's first line for post partum hemorrhage"

Question 6

Dr. Khan asks for your advice regarding the appropriate regimen to manage PP's post partum hemorrhage. She states that she plans on continuing IV oxytocin and may consider TXA if the bleeding continues. You are aware that PP's bleeding started a little over an hour ago and the IV oxytocin regimen will last approximately 2 hours. What do you tell her regarding TXA therapy?

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- "I recommend starting TXA since its benefit is shown within the first 3 hours of hemorrhage"**
- "Let's start with misoprostol instead since it's first line for post partum hemorrhage"

Question 7

You are working in central pharmacy and your coworker asks for help with the inventory. There are a lot of errors with the latest delivery that he needs to document before the end of the shift. You were just about to deliver TXA to the labor and delivery floor for a patient who is having postpartum bleeding. What do you do?

- Help with the inventory first if narcotics are involved
- Put the TXA in a safe place so that you can deliver it after you help sort out the inventory
- Deliver the TXA as soon as possible and then help with inventory afterwards

Question 7

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General ICU Medications



General ICU Medications

Sedatives and Analgesia

Class/Agent	Concerns
Propofol	<ul style="list-style-type: none"> - Safety of extended infusions (>24 hours) is uncertain - Propofol infusion syndrome in pediatrics - Should be reserved for short term use, ex. cesarean deliveries
Dexmedetomidine	<ul style="list-style-type: none"> - Can induce uterine contractions - Limited data
Benzodiazepines	<ul style="list-style-type: none"> - Cross the placenta - Can cause withdrawal, respiratory depression and floppy infant syndrome in the fetus
Opioids	<ul style="list-style-type: none"> - Crosses the placenta - Extended infusions, high doses or use with other respiratory depressants can lead to fetal respiratory depression or withdrawal

General ICU Medications

Neuromuscular Blocking Agents (NMBA)

- o Several factors affect the amount of agent that crosses the placenta
- o Prolonged paralysis and fetal respiratory depression can occur with atypical plasma pseudocholinesterase levels and succinylcholine
- o Prolonged neuromuscular blockage with vecuronium
- o Non-depolarizing NMBAs associated with prolonged neuromuscular blockade in the setting of hypermagnesemia



General ICU Medications

Antibiotics

Class Agent	Concerns
Aminoglycosides	<ul style="list-style-type: none"> • Fetal nephrotoxicity and ototoxicity when doses are higher than conventional dosing
Antifungals	<ul style="list-style-type: none"> • Caspofungin toxic to the embryo • Fluconazole use in the first trimester can lead to fetal abnormalities at doses >400 mg/day • Voriconazole found to be teratogenic in animal studies
Collistin	<ul style="list-style-type: none"> • Malformations and embryotoxicity
Fluoroquinolones	<ul style="list-style-type: none"> • May impact cartilage development
Sulfamethoxazole	<ul style="list-style-type: none"> • Use in 3rd trimester may lead to fetal brain dysfunction
Tetracyclines	<ul style="list-style-type: none"> • Tooth and bone discoloration
Trimethoprim	<ul style="list-style-type: none"> • Cleft lip/palate, heart and neural tube defects

Question 8

PP is had significant pain in her hips, back and knees prior to delivery. The resident is cautious about prescribing opioids due to the risk for fetal withdrawal. What do you advise?

- Opioids are contraindicated in pregnancy due to the risk of fetal withdrawal
- Opioids are contraindicated because they cross the placenta
- There are no concerns with using opioid in pregnancy
- PP can be prescribed morphine 2 mg IV Q6H PRN for pain

Question 8

PP is had significant pain in her hips, back and knees prior to delivery. The resident is cautious about prescribing opioids due to the risk for fetal withdrawal. What do you advise?

- Opioids are contraindicated in pregnancy due to the risk of fetal withdrawal
- Opioids are contraindicated because they cross the placenta
- There are no concerns with using opioid in pregnancy
- PP can be prescribed morphine 2 mg IV Q6H PRN for pain**

Question 9

You are verifying orders in central pharmacy when you receive an order for fluconazole 150 mg once daily for one dose for a yeast infection in a woman who is in her 1st trimester of pregnancy. What do you do?

- A. Call the prescriber and recommend switching to caspofungin because fluconazole can be embryotoxic
- B. Call the prescriber and recommend switching to voriconazole because fluconazole is associated with fetal malformations
- C. Call the prescriber and recommend increasing the dose to 400 mg BID because pregnant patients have increased clearance
- D. Verify the order after reviewing pertinent laboratory and culture results

Question 9

You are verifying orders in central pharmacy when you receive an order for fluconazole 150 mg x 1 dose for vaginal candidiasis in a woman who is in her 1st trimester of pregnancy. What action do you take?

- A. Call the prescriber and recommend switching to caspofungin because fluconazole can be embryotoxic
- B. Call the prescriber and recommend switching to voriconazole because fluconazole is associated with fetal malformations
- C. Call the prescriber and recommend increasing the dose to 400 mg BID because pregnant patients have increased clearance
- D. Verify the order after reviewing pertinent laboratory and culture results**

Question 10

You are completing a medication history and your patient who is 4 months pregnant states that sometimes she takes oxycodone 15 mg (that was prescribed for her husband) a 4-5 times per day for severe shoulder pain. Which of the following are potential risks to the fetus from oxycodone use?

- A. Fetal tooth and bone discoloration
- B. Cleft lip and palate
- C. Fetal withdrawal
- D. Impaired cartilage development

Question 10

You are completing a medication history and your patient who is 4 months pregnant states that sometimes she takes oxycodone 15 mg (that was prescribed for her husband) a 4-5 times per day for severe shoulder pain. Which of the following are potential risks to the fetus from oxycodone use?

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HELLP Syndrome

- **H**emolysis
- **E**levated **L**iver Enzymes
- **L**ow **P**latelets
- Usually occurs in patients with severe preeclampsia
- Symptoms include:
 - General malaise/viral-like symptoms
 - Right upper quadrant pain
 - Hepatic hemorrhage/rupture
 - Excessive weight gain
 - Generalized edema



Diagnosis

- Two diagnostic criteria:
 - Tennessee Classification System
 - Platelets $< 100 \times 10^9/L$
 - AST ≥ 70 U/L
 - LDH ≥ 600 U/L
 - Serum bilirubin ≥ 1.2 mg/100 mL
 - Mississippi Triple Class
 - Class 1: LDH > 600 U/L, AST ≥ 70 , Platelets $< 50 \times 10^9/L$
 - Class 2: LDH > 600 U/L, AST ≥ 70 , Platelets $50-100 \times 10^9/L$
 - Class 3: LDH > 600 U/L, AST ≥ 40 , Platelets $> 100 \times 10^9/L$



Treatment

- If it occurs antepartum, symptoms usually resolve with delivery
- If symptoms of preeclampsia, treat hypertension and seizure prevention
- Corticosteroids:
 - Helps recover the mother's platelet count
 - Helps with fetal lung development if gestational age < 34 weeks

