HTN in Pregnancy: DDx

Advanced, Clinical Subspecialties

Hypertensive disorders are one of the leading causes of maternal mortality worldwide. Blood pressure typically falls early in pregnancy and reaches nadir between 16-20 weeks gestational age. Later in pregnancy, the blood pressure will return to baseline. There are multiple categories of elevated blood pressure in pregnancy; management varies depending on the classification.

- **Chronic hypertension:** occurs in 0.9-1.5%of pregnant women
    - SBP≥140mmHg or DBP ≥90mmHg existing before pregnancy or diagnosed before 20-weeks gestation
    - patient is diagnosed with hypertension during pregnancy but persists ≥12 weeks after delivery
    - As with hypertension in non-pregnant population, can be primary or secondary hypertension attributable to other causes
- **Gestational Hypertension**
    - New onset SBP ≥140mmHg or DBP ≥90mmHg on at least 2 occurrences 4 hours apart after 20 weeks of gestation in previously normotensive female
    - No proteinuria or severe features of pre-eclampsia
    - 10-25% will develop signs/symptoms of pre-eclampsia later in pregnancy
    - Typically resolve within 12 weeks after delivery (otherwise considered chronic, as above)
- **Pre-eclampsia/Eclampsia/HELLP syndrome**
    - **Pre-eclampsia:**
        - New onset SBP≥140mmHg or DBP ≥ 90mmHg on at least 2 occasions 4 hours apart after 20-weeks gestation (i.e. patient was normotensive prior to pregnancy) OR SBP ≥160mmHg or DBP≥110mmHg
        - AND
        - Proteinuria ≥300mg per 24hour urine collection, OR protein:creatinine ratio ≥0.3

- OR

- If no proteinuria, new-onset hypertension with new onset of one or more of the following (severe features):

    - Thrombocytopenia (platelet count <100,000)

    - Renal insufficiency (Cr >1.1 or doubling from baseline in absence of other disease)

    - Impaired liver function (LFTs 2x upper limit of normal)

    - Pulmonary edema

    - Cerebral or visual symptoms (new onset headache not responsive to Tylenol)

    - Pre-eclampsia CAN develop post-partum

    - **Risk factors for pre-eclampsia:**

        - High risk factors: prior pregnancy with pre-e, multifetal gestation, renal disease, autoimmune disease (SLE, antiphospholipid antibody syndrome), diabetes, chronic hypertension)

        - Moderate risk factors: nulliparas/first pregnancy, advanced maternal age, BMI >30, family history

    - Patients are started on ASA 81mg/day for pre-eclampsia prophylaxis

- **Pre-eclampsia with severe features**

    - SBP ≥160mmHg or DBP≥110mmHg on 2 occasions at least 4 hours apart

    - Thrombocytopenia (plt <100,000)

    - Impaired liver function (LFTs 2x upper limit of normal)

    - Pulmonary edema

    - Cerebral or visual symptoms (new onset headache not responsive to Tylenol)

- **Eclampsia:**

- Seizures occurring in patient with pre-eclampsia without alternate cause for seizure (no other neurologic conditions, drug use, etc.)

- **HELLP Syndrome:**

    - Hypertension + elevated liver enzymes + low platelets

    - Potentially subtype of pre-eclampsia; patients do not have to have hypertension (~15% lack hypertension or proteinuria), though majority do

    - Main presenting symptom is often RUQ pain and malaise, may have nausea/vomiting

    - Associated with higher rates of morbidity/mortality

    - Typically occurs in 3rd trimester, but can occur postpartum

- **Pre-eclampsia superimposed on chronic hypertension**

    - In patient with chronic hypertension as above, new sudden increase in blood pressure in patient on previously stable anti-hypertensive regimen or elevated BP resistant to treatment OR new development of proteinuria or increase in proteinuria (if present before/early in pregnancy)

    - Can be with severe features as well

Sources

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020 Jun;135(6):e237-e260.

Pathogenesis

- **Normal trophoblastic cell invasion into spiral arteries, which occurs in the first 18 weeks of pregnancy, is incomplete or may not occur; decidual arteries are constricted with high resistance**
- Oxidative stress via increased sub-endothelial LDL accumulation which recruits monocytes that cause increased lipid peroxidation
- Free radical and lipid peroxidases cause membrane damage, subsequent edema/proteinuria, inhibition of NO production, increased endothelin-1, increased thromboxane, and decreased prostacyclin

- Acute atherosis via decreased prostacyclin, increased thromboxane, and endothelin-1 upsets the usual balance between these substances that leads to thrombosis and vasoconstriction of vessels in the placenta and systemically
- Prostacyclin – decreases vasoconstriction, platelet aggregation, uterine activity, increases uteroplacental blood flow
- NO – vasodilator, anti-aggregatory
- Thromboxane – increases vasoconstriction, platelet aggregation, uterine activity, decreases uteroplacental blood flow
- Endothelin-1 – potent vasoconstrictor and platelet activator
- Plasma volume loss, hypoalbuminemia, and vasoconstriction lead to systemic hypovolemia and decreases in placental perfusion with a decrease in transplacental gas exchange
- Antiangiogenic proteins lead to systemic endothelial damage especially in the kidney, liver and brain with associated oliguria, hypoalbuminemia, and eclamptic seizures

Management

Normally, invasive monitoring is not required and central venous lines may increase risk without known benefit. However, in certain cases of severe preeclampsia and HELLP an invasive pressure line and central venous catheter may be beneficial. These clinical situations might include (1) management of labile hypertension, (2) need for frequent blood gas/laboratory studies (severe pulmonary edema), (3) need for rapid central acting vasoactive medications, or (4) estimation of intravascular volume status (oliguria). [81] The use of judicious administration of fluids to sustain or augment intravascular volume before initiation of neuraxial blockade may be necessary.

Magnesium

Magnesium sulfate is used for seizure prophylaxis in preeclamptic women. Although a magnesium sulfate infusion reduces seizure rates in women with preeclampsia with severe features, new guidelines do not recommend administering magnesium sulfate to preeclamptic women without severe features. [76] Magnesium reduces CNS irritability by decreasing activity at the neuromuscular junction. Consequently, it can potentiate the action of both depolarizing and nondepolarizing muscle relaxants. Magnesium sulfate also provides uterine and smooth muscle relaxation. Based on the new guidelines magnesium sulfate should be continued intrapartum, including during cesarean delivery and until 24 hours postpartum. Magnesium toxicity is important to consider in preeclamptic women with worsening renal function and oliguria, as it is renally excreted. Women are monitored for magnesium toxicity with evaluation of deep tendon reflexes, respiratory depression, and neurologic compromise. The infusion usually is administered by loading 4 to 6 g over 20 to 30 minutes with a continued magnesium sulfate infusion of 1 g/h until 12 to 24 hours after delivery. The therapeutic range for seizure prophylaxis is between 6 to 8 mg/dL. Loss of deep tendon reflexes occurs at 10 mg/dL with prolonged PQ intervals and widening QRS complex on the electrocardiogram (ECG). Respiratory arrest occurs at 15 to 20 mg/dL, and asystole occurs when the level exceeds 20 to 25

mg/dL. If toxicity occurs, IV calcium chloride (500 mg) or calcium gluconate (1 g) should be administered.

Antihypertensives

During the intrapartum management of preeclampsia, women often have additional elevations in arterial blood pressure from pain. Arterial blood pressure management may require antihypertensives. Current guidelines recommend treating systolic blood pressure greater than 160 mm Hg for prevention of intracerebral hemorrhage. [76] Initial therapy normally includes IV labetalol and hydralazine; however, without IV access oral nifedipine can be considered. [82] In refractory severe hypertension, nitroglycerin and sodium nitroprusside may be used in the acute situation with appropriate invasive monitoring. Evaluation of maternal arterial blood pressure and FHR are important as drug-induced decreases in maternal perfusion pressure can result in uteroplacental insufficiency and fetal bradycardia.

Neuraxial Analgesia Considerations

The ACOG considers neuraxial analgesia the preferred analgesic method for labor in preeclamptic patients, but careful titration of the local anesthetic is needed to prevent the reduction in uteroplacental perfusion pressure. [76] Although a routine platelet count is not necessary in otherwise healthy laboring women, for women with preeclampsia, a thorough evaluation of the patient's current hematologic status should be performed. The anesthesia provider should verify hemoglobin and platelet levels prior to placement of any neuraxial block given the potential for thrombocytopenia in severe preeclampsia and HELLP. A specific platelet count predictive of neuraxial anesthetic complications has not been determined, but a stable platelet count of 75 to 80 $\times 10^9$ /L has been suggested as a reasonable minimum platelet level for neuraxial techniques, assuming no additional contraindications to neuraxial anesthesia exist. Regardless, the risk-benefit ratio of neuraxial block placement should be frankly discussed with the patient given the risks of epidural hematoma compared to other anesthetic and analgesic alternatives. Care should be taken before epidural catheter removal, as platelet levels often decrease further after delivery. Bleeding time has not been demonstrated to be of clinical value. If hypotension occurs following initiation of neuraxial analgesia, prompt but judicious titration of phenylephrine or ephedrine should be administered, understanding that the patient with preeclampsia may have hypersensitivity to catecholamines.

Given the potential for placental insufficiency with preeclampsia, the anesthesia provider must be prepared for urgent delivery. Exaggerated upper airway edema is frequent in preeclamptics and increases the risk of difficult intubation if an emergent general anesthetic is required. Endotracheal intubation may produce further hypertension during laryngoscopy and a small amount of nitroglycerin (2 μg/kg) or esmolol (1.5 mg/kg) can be beneficial when administered with propofol for induction. [84] If there is concern for a difficult airway, appropriate alternatives such as video laryngoscopy at the outset should be considered. Postpartum uterine atony is more common with magnesium sulfate infusion and accentuated if an inhaled anesthetic is administered. Pitocin and prostaglandins are safe for uterine atony, but methylergonovine (methergine) is relatively contraindicated because it can precipitate hypertensive crisis.

Multiple changes are seen in the coagulation system during pregnancy. The greatest change occurs at term. Overall, pregnancy is a hypercoagulable state. However, the traditional measures of coagulation (PT, aPTT, INR) either do not change or decrease slightly during pregnancy. Platelet counts often decrease secondary to dilutional (increase in plasma volume) and consumptive (from the uteroplacental unit) effects. Rarely does this drop result in clinical significance.

Please see table below for individual factor changes.

Hemostatic Changes in Pregnancy	
Hemostatic Parameter	Change at Term Pregnancy (% change)
Factors II and V	No change
Fibrinogen	Increases more than 100%
Factor VII	Up to 1,000% increase
Factors VIII, IX, X, XII and vWF	Increase more than 100%
Factor XI	Variable
Factor XIII	Up to 50% decrease
Protein C	No change
Protein S	Up to 50% decrease
D-dimer	Up to 400% increase
Platelet count	Up to 20% decrease

II. Hemorrhage in Pregnant Women

Hemorrhage in pregnant women remains a significant cause of maternal fatality. Placenta previa, abruptio placentae, and uterine rupture are the major causes of bleeding and uncontrolled hemorrhage during the third trimester and labor. Postpartum hemorrhage occurs in 3% to 5% of all vaginal deliveries and is typically due to uterine atony, retained placenta, placenta accreta, or lacerations involving the cervix or vagina. Common problems identified with hemorrhages leading to significant morbidity and mortality risks in obstetrics include (1) poor quantification of blood loss, (2) unrecognized associated risk factors for hemorrhage, (3) delayed initiation of treatment, and (4) inadequate readiness and resources including inadequate transfusion of appropriate blood products in a massive hemorrhage situation. [85]

Placenta Previa

Placenta previa results from an abnormal uterine implantation of the placenta in front of the presenting fetus. The incidence is approximately 1 in 200 pregnancies. Risk factors include advanced age, multiparity, assisted reproductive techniques, prior hysterotomy, and prior placenta previa. Historically, the classic presentation of placenta previa is painless vaginal bleeding that typically occurs preterm in the third trimester. However, most previas are now

diagnosed antenatally by ultrasonography. A trial of labor is acceptable if the placenta edge is further than 2 cm from the internal os. If the placenta is within 1 cm, the patient should undergo cesarean delivery. For placentas that lie between 1 cm and 2 cm from the cervical os, the optimal management remains uncertain and delivery management is currently individualized. [86] Neuraxial anesthesia is an appropriate choice if there is no active bleeding or hypovolemia. The use of two large-bore IV lines with fluid warmers and availability of invasive monitoring is suggested with cesarean delivery for rapid infusion of fluids or blood products given the increased risk of placenta accreta with known previa. [87]

Massive Hemorrhage

For emergency situations with active hemorrhage, general anesthesia may be required. *Ketamine* (1 to 1.5 mg/kg) or *etomidate* (0.3 mg/kg) IV are useful drugs for induction of anesthesia. If a massive hemorrhage occurs, activation of a massive transfusion protocol with aggressive use of fresh frozen plasma, platelets, and fibrinogen in addition to packed red blood cells may be needed for transfusion in ratios similar to those used for a trauma resuscitation, as a dilutional coagulopathy can quickly result in such a situation. [88] In these cases of uncontrolled rapid hemorrhage, there is often insufficient time to wait for the return of laboratory studies before transfusion of appropriate blood products. Although numerous randomized controlled trials conclude that the use of tranexamic acid significantly decreases postpartum blood loss, [89] these studies do not adequately address questions on safety and efficacy of empiric tranexamic acid use at the time of hemorrhage recognition. An ongoing multicenter randomized controlled trial enrolling 20,000 patients with postpartum hemorrhage (the WOMAN trial) is currently investigating the use of tranexamic acid on a composite end point of maternal death or hysterectomy. [90] Neonates delivered from pregnant women in hemorrhagic shock are likely to be acidotic and hypovolemic and may need resuscitation. If hemorrhage is not controlled with standard pharmacologic measures, the obstetric team can consider (1) uterine artery ligation, (2) B-Lynch sutures, (3) an intrauterine balloon, (4) use of arterial embolization by interventional radiology if the patient is stable for transport, or (5) hysterectomy.

Abruptio Placentae

Abruptio placentae is separation of the placenta from the uterine wall after 20 weeks of gestation but before delivery. The incidence is approximately 0.4 to 1 in 100 pregnancies. Risk factors include advanced age, hypertension, trauma, smoking, cocaine use, chorioamnionitis, premature rupture of membranes, placenta previa, and history of prior abruption. Placental abruption is associated with 10% to 20% of all perinatal deaths, and although maternal death is rare, maternal mortality rate is increased sevenfold. [91] When the separation involves only the placental margin, the escaping blood can appear as vaginal bleeding often associated with uterine tenderness. Alternatively, large volumes of blood loss (>2 L) can remain entirely concealed in the uterus. Chronic bleeding and clotting between the uterus and placenta can cause maternal disseminated intravascular coagulopathy (DIC). Ultrasound is specific if abruption is noted but has poor sensitivity, and a normal examination does not exclude abruption. Definitive treatment of abruptio placentae is to deliver the pregnancy. The anesthetic plan is based on both the delivery urgency and the abruption severity. If there are no signs of maternal hypovolemia, active bleeding, clotting abnormalities, or fetal distress, epidural analgesia can be used for labor and vaginal delivery. However, severe hemorrhage necessitates emergency cesarean delivery and the

use of a general anesthetic similar to that described for placenta previa. It is predictable that neonates born under these circumstances will be acidotic and hypovolemic.

III. Uterotonic agents: Symptoms

Uterotonic agents increase the frequency and tonicity of uterine contractions. They are used to induce labor and to treat postpartum hemorrhage and uterine atony. Their side effects are related to their mechanism of action.

Oxytocin analogues:

Oxyctocin is the endogenous posterior pituitary hormone that stimulates cervical dilation and uterine contractions during labor. Its synthetic, IV analogue, Pitocin, is often used to induce labor through IV titration. Side effects include hypotension at high doses due to systemic vascular smooth muscle relaxation and subsequent reflex tachycardia.

Ergot alkaloids:

Ergot alkaloids are part of a family of chemicals originally derived from fungi. Methylergonovine (Methergine) causes intense uterine contraction and is used postpartum for atony and/or PPH. It causes non-specific smooth muscle contraction and therefore its side effects are hypertension, coronary vasospasm, and bronchospasm. Usually given in a single IM dose (to avoid severe and profound hypertension if given as an IV bolus) but can also be used as a diluted IV infusion. Methylergonovine is contraindicated in hypertensive patients.

Prostaglandins:

Carboprost (Hemabate) is a synthetically derived analogue of Prostaglandin F2 that causes uterine contractions and used to treat uterine atony and PPH. Side effects include increased cardiac output, increased pulmonary vascular resistance, bronchospasm and nausea. Carboprost is contraindicated in patients with asthma. The Prostaglandin E1 analogue, misoprostol (Cytotec) and Prostaglandin E2 (Dinoprostone) may cause nausea, hypotension and fever. These latter two do not have the bronchospasm associated with carboprost. Prostaglandins are administered via intramuscular injection.

Sources

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Uterine tone and anesthetics

Advanced, Obstetric Anesthesia, Pharmacology

All volatile halogenated agents cause dose-related relaxation of the uterus which may lead to increased blood loss during cesarean section. From induction to delivery of the infant 1.0 MAC is given to avoid maternal awareness. After delivery, volatile anesthetics are decreased to 0.5 – 0.75 MAC and oxytocin is given concurrently to decrease the uterine relaxation and thus blood loss. Less than 0.75 MAC interfere with oxytocin's effects and at elevated doses lead to uterine atony. Nitrous oxide, opioids, and ketamine at less than 2 mg/kg have minimal if any effect.

Pre-term labor: treatment

Definition : presence of uterine contractions of sufficient frequency and intensity that causes progressive effacement and dilation of the cervix prior to term gestation (between 20 and 37 wk). The earlier it occurs, the less the odds of survival of the fetus

What exactly causes it? Nobody really knows, but there are certain things that can predispose pts to it

Risk Factors:

- decidual hemorrhage
- abruption
- mechanical factors such as uterine overdistension from multiple gestation or polyhydramnios),
- cervical incompetence/short cervix
- trauma
- cone biopsy
- uterine distortion: fibroids, müllerian duct abnormalities
- cervical inflammation/infection
- maternal inflammation/fever : UTI
- nonwhite race,
- extremes of maternal age (<17 y or >35 y),
- low socioeconomic status
- low prepregnancy weight.
- hormonal changes (eg, mediated by maternal or fetal stress)

- uteroplacental insufficiency
- HTN
- IDDM
- IVDU
- Tobacco/ETOH

How to assess pt?

- check integrity of cervix w/ serial digital exams
- transvaginal US of cervix
- Labs: GC/CL, RPR, APTT, whiff test for BV, lupus anticoagulant
- Hysterosalpingogram(preconceptual)

Management

1. **TOCOLYSIS**

- **MgSO4**
- check CBC, follow urine output in mom,
- watch Mom for toxicity: respiratory depression or even cardiac arrest, flushing, nausea, headache, drowsiness, and blurred vision
- watch BABY for toxicity: it CROSSES PLACENTA, respiratory and motor depression of neonate
- dc magnesium sulfate therapy after 48 hours in most patients unless the gestational age is less than 28 weeks when a gain of an additional 3-4 days may significantly reduce neonatal morbidity and mortality
- **INDOMETHACIN**
- first-line tocolytic for the pregnant patient in early preterm labor (<30 wk) or preterm labor associated with polyhydramnios.
- PG inhibitor
- cross placenta and can impair fetal renal function,oligohydramnios
- can cause fetal ductus arteriosus to close after 32weeks, so it is not usually given after that
- if fetal anuria persistm increases odds of fetal DEMISE
- **NIFEDIPINE**
- ccb, inhibits uterine contraction
- SFx: maternal tachycardia, palpitations, flushing, headaches, dizziness, and nausea
- **Beta agonists are rarely used because of adverse maternal and fetal effects: tachycardia, pulmonary edema,palpitations, hyperglycemia**
- **Tocolytics : side effects**
- **What are tocolytics?** Rx which stop labor contractions
- **Why are they used?** Mainly to buy time to allow fetal lung maturity, stabilize mom/fetus
- **Does this requiring monitoring?** It depends; for certain drugs, yes especially for BP and HR in mom

CONTRAINDICATIONS to using TOCOs

1. fetal death/distress/demise
2. IUGR
3. fetus older than 37 wks
4. chorioamnionitis
5. cervical dilation of 4 cm
6. MOM has : PIH, eclampsia, active bleeding, cardiac dz

The RX

- MgSO4: blocks neuromuscular transmission and prevents release of ACH
- Muscle weakness
- Respiratory depression
- Low bp, tachycardia
- BETA agonists: MOA relax smooth muscle
- RITODRINE: inc HR, hyperglycemia, inc BP, pulmonary edema
- TERBUTALINE: inc HR, hyperglycemia, inc BP, pulmonary edema, fetal tachycardia and hypoglycemia
- NIFEDIPINE: constipation, HA, hypotension, lightheadedness
- INDOMETHACIN: PG inhibitor–> inh renin–>inhibit aldosterone–> hyperNatremia, hyperKalemia, edema, HTN, in more severe cases: renal failure/nephritis