

Pregnancy and Hypertension

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Disclosures

- None

Overview

- Preeclampsia/Eclampsia
- Gestational hypertension
- Chronic Hypertension
- Preeclampsia super-imposed on Chronic Hypertension

Preeclampsia

- Preeclampsia is the most commonly encountered renal complication of pregnancy.
- Characterized by new onset hypertension and proteinuria, usually after 20 weeks of gestation.
- A blood pressure of $> 140/90$ is required for diagnosis.

Preeclampsia

- The U.S. National High Blood pressure education program recommends that women with a blood pressure below 140/90 mm Hg who have experienced an increase of 30 or 15 mm Hg in systolic or diastolic levels, respectively, should be managed as high risk patients.

Preeclampsia

- Affects 3-5% of pregnancies worldwide
- Most cases occur in previously healthy nulliparous women, in whom the incidence is reported to be as high as 7.5%.

Preeclampsia

- There is somewhat of a familial contributing factor as patients with first degree relatives also have a higher incidence.
- Having chronic kidney disease, hypertension, or hypercoagulable state at baseline also predisposes to a higher risk.
- African Americans have a higher incidence likely due to the higher likelihood of having underlying hypertension.

Co-existent Diseases and Preeclampsia

- Coexistent diseases that are associated with endothelial dysfunction, such as diabetes and antiphospholipid antibodies, are also known to increase the risk for preeclampsia.

So what causes preeclampsia?

Multifactorial etiologies:

- Abnormal placental vascular remodeling
- Maternal endothelial dysfunction
- Oxidative stress
- Angiogenic imbalance
- Insulin resistance
- Immunologic intolerance

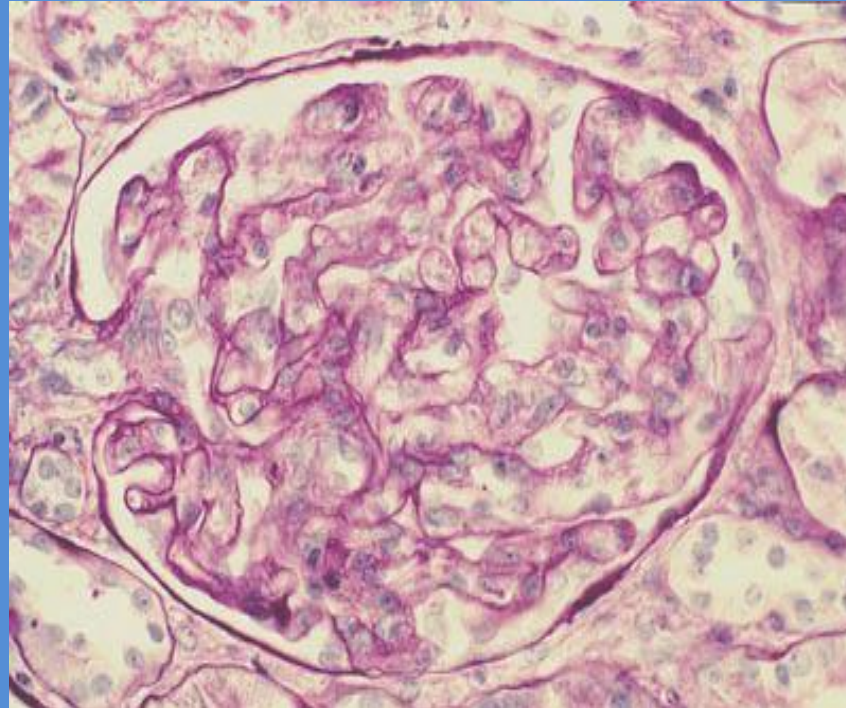
Pathophysiology

- The abnormal placentation that results from failure of trophoblast remodeling of uterine spiral arterioles is thought to lead to the release of secreted factors that enter the mother's circulation, culminating in the clinical signs and symptoms of preeclampsia.
- All of the clinical manifestations of preeclampsia can be attributed to glomerular endotheliosis, increased vascular permeability, and a systemic inflammatory response that results in end-organ damage and/or hypoperfusion.

Pathophysiology

- Endothelial dysfunction → endotheliosis → increased renal vascular resistance
- This causes reduced renal blood flow and decreased GFR.

Glomerular Endotheliosis



Glomerular Endotheliosis

- Endotheliosis seems to be responsible for the decreased GFR noted in preeclampsia, primarily through reduction in the ultrafiltration (convection) coefficient as opposed to diminished plasma/blood flow.

Glomerular Endotheliosis

- The glomeruli are enlarged as a result of narrowed or occluded capillary lumens that are the result of swelling of the native endothelial cells and, to a lesser extent, mesangial cells.

Glomerular Endotheliosis

- The endothelial changes are confined to the glomerular capillaries.
- Arterioles are typically unaffected.
- Unlike TMA, finding thrombosis in the microvasculature is rare.

Anti-angiogenic Factors

- Anti-angiogenic factors contribute to the pathophysiology of preeclampsia.
 - Increased expression of soluble fms-like tyrosine kinase-1 (sFlt1)
 - decreased expression of placental growth factor (PlGF)

Anti-angiogenic Factors

- sFlt1 binds and functionally inactivates both VEGF and PlGF.
- Circulating sFlt is elevated in preeclampsia and PlGF is depressed (and the ratio of circulating sFlt/PlGF is increased)

Anti-angiogenic Factors

- sFlt1, via functional VEGF deficiency, results in vasoconstriction and endothelial dysfunction in small arteries

Clinical Features

BP > 140/90 after 20 weeks gestation in a previously normotensive woman

And...

Proteinuria in excess of 300mg in 24 hours.

Clinical Features

- Primigravida
- Onset after 20 weeks
- Proteinuria
- Generalized edema
- Patients are at the extremes of age
- Hyper-reflexia
- Multisystem involvement
- No increased risk of HTN at follow-up

Severity of Preeclampsia

Preeclampsia: judging severity*		
	Less Severe	More Severe
Presentation	≥Gestational wk 34	<Gestational wk 35
Diastolic BP	<100 mm Hg	>110 mm Hg
Headache	Absent	Present
Visual disturbances	Absent	Present
Abdominal pain	Absent	Present
Oliguria	Absent	Present
S _{Creatinine} (GFR)	Normal	Elevated (decreasing)
LDH, AST	Normal	Elevated
Proteinuria	Mild to moderate	Nephrotic range (>3 g/24 h) [†]
Nonreassuring fetal testing [‡]	Absent	Present

AST, aspartate aminotransferase; BP, blood pressure; GFR, glomerular filtration rate; LDH, lactic acid dehydrogenase.

* Presence of convulsions (eclampsia), congestive heart failure, or pulmonary edema are always very ominous signs.

[†] Degree of proteinuria alone may not indicate seriousness unless accompanied by other ominous sign or symptom.

[‡] Growth restriction, adverse signs during periodic fetal testing including electronic monitoring and Doppler ultrasound.

The American College of Obstetrics and Gynecology bulletins utilize the terms “mild” and “severe” for our preferred “less” and “more” severe, so as to underscore diligence for any form of preeclampsia.

Pathophysiology

Cardiovascular manifestations

- Hypertension is due to severe vasoconstriction
- Arterial compliance and cardiac output are reduced.
- Increased sympathetic tone
- Increased insulin resistance

Pathophysiology

- Renal plasma flow and GFR decrease in preeclampsia
- The decrement in RPF is attributable to vasoconstriction, whereas the fall in GFR relates both to the decrement of RPF and the development of a glomerular lesion termed *glomerular endotheliosis* and reduced convective forces (ultrafiltration coefficient)

Pathophysiology

Placenta

- Shallow and abnormal placentation (possibly due to ischemia) is a hallmark of preeclampsia.
- Failure of the normal trophoblastic invasion of the spiral arteries to remodel and dilate.
- Anti-angiogenic substances that enter the maternal circulation deprive the glomerular endothelium of essential growth factors.

Pathophysiology

Neurological manifestations

- Major findings on autopsy were micro and macroscopic bleeding
- Studies using sophisticated imaging techniques reveal increased cerebral flow in preeclamptic women.
- Preeclamptic women may have increased perfusion pressures, perhaps exceeding the cerebral circulation's auto-regulatory capacity
- Their vessels “leak” at perfusion pressures lower than what would be expected in non-pregnant subjects.

Pathophysiology

Hepatic Manifestations

Preeclampsia is associated with activation of the coagulation system, with thrombocytopenia (usually mild) as the most commonly detected abnormality.

- There is increased platelet activation and size, plus decrements in their lifespan.
- The hypercoagulability of normal pregnancy is accentuated (eg, reduced antithrombin III, protein S, and protein C) even when platelet counts appear normal

Pathophysiology

Hepatic Manifestations

- The gross hepatic changes in preeclampsia are petechiae, liver infarction, and subcapsular hematomas, some of which rupture and death may result.
- endothelial injury may also become manifest as a low-grade coagulopathy with increased fibronectin, increased platelet aggregation, shortened platelet survival, and depressed antithrombin III levels.
- The HELLP syndrome develops in up to 10% of pregnancies with severe preeclampsia

Eclampsia

- New onset tonic-clonic seizures during pregnancy or within 4 weeks post-partum in a woman with preeclampsia.

Management of Preeclampsia/Eclampsia

- Delivery of the placenta remains the main “cure” for preeclampsia.
- Delivery is indicated at any stage of pregnancy if severe hypertension remains uncontrolled for 24 to 48 hours or at the appearance of certain “ominous” signs such as clotting or liver abnormalities, decreasing renal function, or impending seizure.

Management of Preeclampsia/Eclampsia

- Gestation is permitted to continue as long as BP is controlled, no ominous signs of life-threatening maternal complications occur, and in the absence of signs of nonreassuring fetal testing.

JOCG guidelines

- **Recommendations: Antihypertensive therapy for severe hypertension (BP of 160 mmHg systolic or 110 mmHg diastolic)**
- 1. BP should be lowered to <160 mmHg systolic and < 110 mmHg diastolic. (II-2B)
- 2. Initial antihypertensive therapy should be with labetalol, (I-A) nifedipine capsules, (I-A) nifedipine PA tablets, (I-B) or hydralazine. (I-A)
- 3. MgSO₄ is not recommended as an antihypertensive agent. (II-2 D)
- 4. Continuous FHR monitoring is advised until BP is stable. (III-I)
- 5. Nifedipine and MgSO₄ can be used contemporaneously. (II-2B)

JOCG guidelines

Recommendations: Antihypertensive therapy for non-severe hypertension (BP of 140–159/90–109 mmHg)

- 1. For women without comorbid conditions, antihypertensive drug therapy should be used to keep systolic BP at 130–155 mmHg and diastolic BP at 80–105 mmHg. (III-C)
- 2. For women with comorbid conditions, antihypertensive drug therapy should be used to keep systolic BP at 130–139 mmHg and diastolic BP at 80–89 mmHg. (III-C)
- 3. Initial therapy can be with one of a variety of antihypertensive agents: methyldopa, (I-A) labetalol, (I-A) other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol), (I-B) and calcium channel blockers (nifedipine). (I-A)
- 4. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers should not be used. (II-2E)
- 5. Atenolol and prazosin are not recommended. (I-D)

JOCG guidelines

Recommendations: Aspects of care specific to women with pre-existing hypertension

- 1. Pre-conceptual counseling for women with pre-existing hypertension is recommended. (III-I)
- 2. Discontinue ACE inhibitors and ARBs pre-pregnancy (or as soon as pregnancy is diagnosed). (II-2D)
- 3. If antihypertensive agent(s) are to be discontinued or changed to allow treatment to continue during pregnancy, then consider changing the agent(s) pre-pregnancy if the woman has uncomplicated pre-existing hypertension, or, if in the presence of comorbid conditions, she is likely to conceive easily (within 12 months). (III-I)
- 4. Consider discontinuing atenolol when pregnancy is diagnosed. (I-D)
- 5. A variety of antihypertensive drugs may be used in the first trimester of pregnancy (e.g., methyldopa, labetalol, and nifedipine). (II-2B)

Eclampsia

- Management of eclamptic convulsions requires parenteral magnesium sulfate administration, which is shown to be superior to either diazepam or phenytoin for both prevention and treatment.
- Some experts contend that IV magnesium, due to its intrinsic risks, should be reserved for patients with severe disease.

JOCG Guidelines

Recommendations: Magnesium sulphate (MgSO₄) for eclampsia prophylaxis or treatment

- 1. MgSO₄ is recommended for first-line treatment of eclampsia. (I-A)
- 2. MgSO₄ is recommended as prophylaxis against eclampsia in women with severe preeclampsia. (I-A)
- 3. MgSO₄ may be considered for women with non-severe preeclampsia. (I-C)
- 4. Phenytoin and benzodiazepines should not be used for eclampsia prophylaxis or treatment, unless there is a contraindication to MgSO₄ or it is ineffective. (I-E)

Treatment

Drugs for chronic hypertension in pregnancy

Drug (Food and Drug Administration risk)*	Dose	Concerns or Comments
Methyldopa (B)	0.5–3.0 g/d in 2 divided doses	Drug of choice according to NHBEP working group; safety after first trimester well documented, including 7-year follow-up evaluation of offspring.
Labetalol (C)†	200–1200 mg/d in 2–3 divided doses	Gaining in popularity as concerns relating to growth restriction and neonatal bradycardia do not seem to have materialized.
Nifedipine (C)	30–120 mg/d of a slow-release preparation	May inhibit labor and have synergistic interaction with magnesium sulfate; small experience with other calcium-entry blockers.
Hydralazine (C)	50–300 mg/d in 2–4 divided doses	Few controlled trials, long experience with few adverse events documented, useful only in combination with sympatholytic agent; may cause neonatal thrombocytopenia.
β-receptor blockers (C)	Depends on specific agent	May cause fetal bradycardia and decrease uteroplacental blood flow, this effect may be less for agents with partial agonist activity; may impair fetal response to hypoxic stress; risk for growth retardation when started in first or second trimester (atenolol).
Hydrochlorothiazide (C)	25 mg/d	Majority of controlled studies in normotensive pregnant women rather than hypertensive patients, can cause volume depletion and electrolyte disorders; may be useful in combination with methyldopa and vasodilator to mitigate compensatory fluid retention.
Contraindicated ACE inhibitors and AT1-receptor antagonists (D)‡		Use associated with major anomalies plus fetopathy, oligohydramnios, growth restriction, and neonatal anuric renal failure, which may be fatal.

ACE, angiotensin-converting enzyme; NHBEP, National High Blood Pressure Education Program.

Note: No antihypertensive drug has been proven safe for use during the first trimester. Drug therapy is indicated for uncomplicated chronic hypertension when diastolic blood pressure is ≥ 100 mm Hg (Korotkoff V). Treatment at lower levels may be indicated for patients with diabetes mellitus, renal disease, or target organ damage.

* U.S. Food and Drug Administration classification.

† We omit some agents (eg, clonidine, α -blockers) because of limited data on use for chronic hypertension in pregnancy.

‡ We would classify in category X during second and third trimesters.

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Treatment

Drugs for urgent control of severe hypertension in pregnancy

Drug (Food and Drug Administration risk)*	Dose and Rate	Concerns or Comments†
Labetalol (C)	20 mg IV, then 20–80 mg every 20–30 min, up to a maximum of 300 mg; or constant infusion of 1–2 mg/min	Experience in pregnancy less than with hydralazine; probably less risk for tachycardia and arrhythmia than with other vasodilators.
Hydralazine (C)	5 mg, IV or IM, then 5–10 mg every 20–40 min; or constant infusion of 0.5–10 mg/h	Drug of choice according to NHBEP working group; long experience of safety and efficacy.
Nifedipine (C)	Tablets recommended only; 10–30 mg orally, repeat in 45 min if needed	Possible interference with labor.
Relatively contraindicated nitroprusside (C)‡	Constant infusion of 0.5–10 µg/kg/min	Possible cyanide toxicity; agent of last resort.

IM, intramuscularly; IV, intravenously; NHBEP, National High Blood Pressure Education Program.

Note: Indicated for acute increase of diastolic blood pressure ≥ 105 mm Hg; goal is a gradual reduction to 90 to 100 mm Hg.

* U.S. Food and Drug Administration classification; C indicates that either that studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) or there are no controlled studies in women, or studies in women and animals are not available. Drugs only should be given if the potential benefits justify the potential risk to the fetus.

† Adverse effects for all agents, except as noted, may include headache, flushing, nausea, and tachycardia (primarily caused by precipitous hypotension and reflex sympathetic activation).

‡ We would classify as category D; there is positive evidence of human fetal risk, but the benefits of use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

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Gestational Hypertension

- Pregnant women with a blood pressure > 140/90, without proteinuria, and whose blood pressure was lower before pregnancy are described to have “gestational hypertension”
- Usually, there is no significant proteinuria
- The serum uric acid level is also not elevated

Gestational Hypertension

- There is evidence that transient hypertension of pregnancy occurs in women who eventually develop isolated primary hypertension later in life.

Gestational Hypertension

- Arises *de novo* after 20 weeks of gestation, returning to normal within 3 months post-partum.
- There is usually no maternal end-organ damage.

Gestational Hypertension

- A rare group of patients have an activating mineralocorticoid receptor mutations that result in an exaggerated sensitivity to progesterone, which has a weak mineralocorticoid effect.
- They manifest salt-sensitive hypertension, accompanied by hypokalemia. This worsens as pregnancy progresses (and progesterone levels rise).

Chronic Hypertension

- Most are of the “essential” variety
- Increased incidence of placental abruption, acute renal failure, cardiac decompensation, and cerebral accidents in the mother
- Increased incidence of growth retardation or unexplained mid-trimester fetal death.

Chronic Hypertension

- May occur in any pregnancy
- Before or anytime during pregnancy
- No proteinuria
- Mild pretibial edema
- More common in older age group
- Normo-reflexia
- Increased risk of placental abruption
- Hypertension present at follow-up

Chronic Hypertension

Risk of complications

- Age of mother
- Duration and degree of blood pressure
- Presence of end-organ damage

Chronic Hypertension

Systematic review of the literature suggests:

- Treatment of mild to moderate hypertension does not prevent superimposed preeclampsia.
- Treatment does show reduced hospitalization

Treatment of Chronic Hypertension

JCOG

- Guidelines suggest withholding anti-hypertensive treatment for DBP < 100 mmHg.
- “end points” for re-instating treatment include exceeding thresholds for BPs of 150-160mmHg systolic and 100-110 mmHg diastolic.
- Due to the propensity for pregnant women to develop cerebrovascular accident when SBP > 160 mmHg, it has been suggested that SBP be treated above this goal.

Treatment of Chronic Hypertension

Which anti-hypertensives to use or avoid?

- ACE/ARB should not be prescribed in pregnancy
- These medicines are safe during lactation, however.
- ACE/ARBs are important anti-proteinuric drugs in diabetes and be resumed immediately following delivery.

Treatment of Chronic Hypertension

- Diuretics can reduce breast milk production and should be avoided.
- The NHBPEP report named ***methyldopa***, a centrally acting adrenergic antagonist, as the “preferred” drug of choice to use for blood pressure control during pregnancy based on 20 years of experimental data.
- Adrenergic blockers can cause fetal growth restriction, although this effect is minimal.

Superimposed Preeclampsia with Chronic Hypertension

- 30% of women with chronic hypertension
- Difficult to distinguish clinically
- HTN before or early on in pregnancy
- Increase of 30 mmHg systolic or 15 mmHg diastolic blood pressure after 20 weeks gestation.
- Hyper-reflexia
- Generalized edema
- HTN at follow-up
- More common in older age group

Questions?

References

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