Hypertensive Disorders of Pregnancy: Definitions and Classification

HYPERTENSIVE DISORDERS ARE:

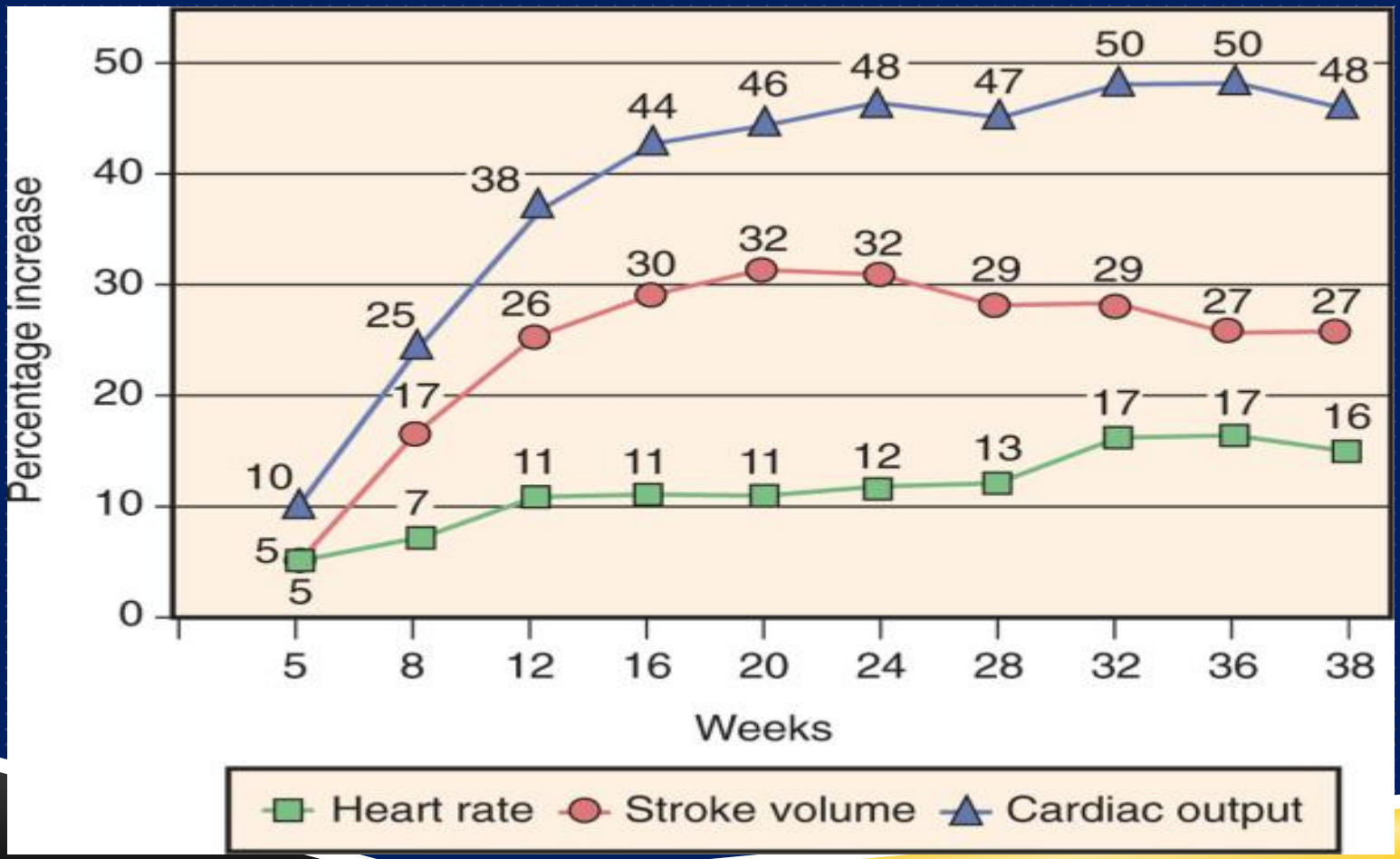
The most common complication during pregnancy

HYPERTENSION

In pregnancy cardiac output increases by :

- **40% most of which is due to an increase in stroke volume**
- **Heart rate increases by ~10 beats/min during the third trimester.**

Hemodynamic changes in pregnancy

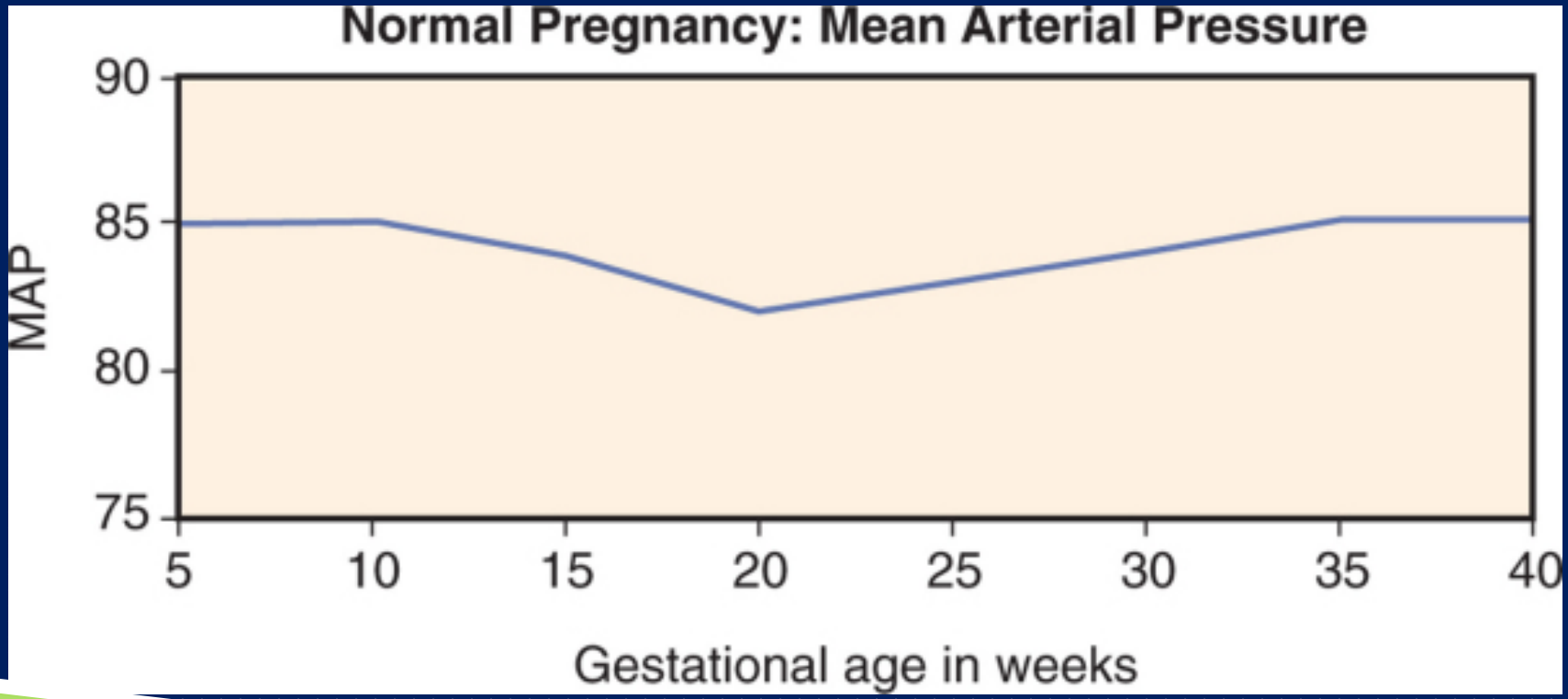


HYPERTENSION

In the second trimester systemic vascular resistance decreases and this is associated with a fall in blood pressure.

During pregnancy a blood pressure of 140/90 mmHg is considered to be abnormally elevated and is associated with an increase in perinatal morbidity and mortality.

CHANGES IN MEAN ARTERIAL PRESSURE IN NORMAL GESTATION



Thadhani R, Ecker JL, Kettyle E, et al: Pulse pressure and risk of preeclampsia: A prospective study. Obstet Gynecol 97(4):515–520, 2001

HYPERTENSION

In all pregnant women the measurement of blood pressure should be performed in the sitting position.

because the lateral recumbent position may result in a blood pressure lower than that recorded in the sitting position.

The diagnosis of hypertension requires the measurement of two elevated blood pressures at least 6h apart.

CLASSIFICATION

- **Mild – Systolic pressure 140 to 149 mmHg and/or diastolic pressure 90 to 99mmHg**
- **Moderate – Systolic pressure 150 to 159 mmHg and/or diastolic pressure 100 to 109 mmHg**
- **Severe – Systolic pressure ≥160 and/or diastolic pressure ≥110 mmHg**

HYPERTENSION

It has a bimodal frequency, being more common in young women in their first pregnancy and in older multiparous women.

What's the different type of HTN in PREGNANCY?

A RISE IN BLOOD PRESSURE IN PREGNANCY INDICATES ONE OF FOUR CONDITIONS:

- 1) Preeclampsia (toxemia)
- 2) Preeclampsia superimposed on chronic hypertension or renal disease
- 3) Chronic essential hypertension
- 4) Gestational hypertension.

PREECLAMPSIA

Describe the disease unique to pregnancy manifested by hypertension and multiple organ involvement.

PREECLAMPSIA

Approximately 5–7% of all pregnant women develop preeclampsia.

The new onset of hypertension (BP>140/90 mmHg) and proteinuria (>300 mg/24h) after 20 weeks of gestation.

In a patient with new-onset hypertension without proteinuria, the diagnosis of preeclampsia can still be made if any features of severe disease are present.

SEVERE PREECLAMPSIA

- Marked elevation of blood pressure (>160/110 mmHg),
- Evidence of central nervous system (CNS) dysfunction (headaches, blurred vision seizures,coma),
- Renal dysfunction (oliguria or creatinine > 1.1mg/dL),
- Pulmonary edema,
- Hepatocellular injury (ALT> 2-fold the upper limits of NL),
- Hematologic dysfunction (platelet count< 100,000/L or disseminated intravascular coagulation),

PREECLAMPSIA

- *HELLP syndrome*
  - target organ systems
    - liver
    - brain
    - kidneys
    - coagulation system

PREECLAMPSIA

- ***HELLP syndrome - diagnostic criteria***
  - **H**emolysis
    - abnormal peripheral smear
    - lactate dehydrogenase > 600 U/L
  - **EL**evated liver enzymes
    - serum aspartate aminotransferase > 70 U/L
    - lactate dehydrogenase > 600 U/L
  - **l**ow **P**latelets
    - platelet count < 100,000/mm^3

PREECLAMPSIA

- usually begins after the 32nd week of pregnancy but may begin earlier, particularly in women with pre-existing renal disease or hypertension.
- When it occurs in the first trimester, it is pathognomonic of a hydatidiform mole.

- The disease may be seen post partum, with hypertension and convulsions occurring within 24 to 48 hours after delivery, although it has been reported as late as 7 days post partum.

PREECLAMPSIA

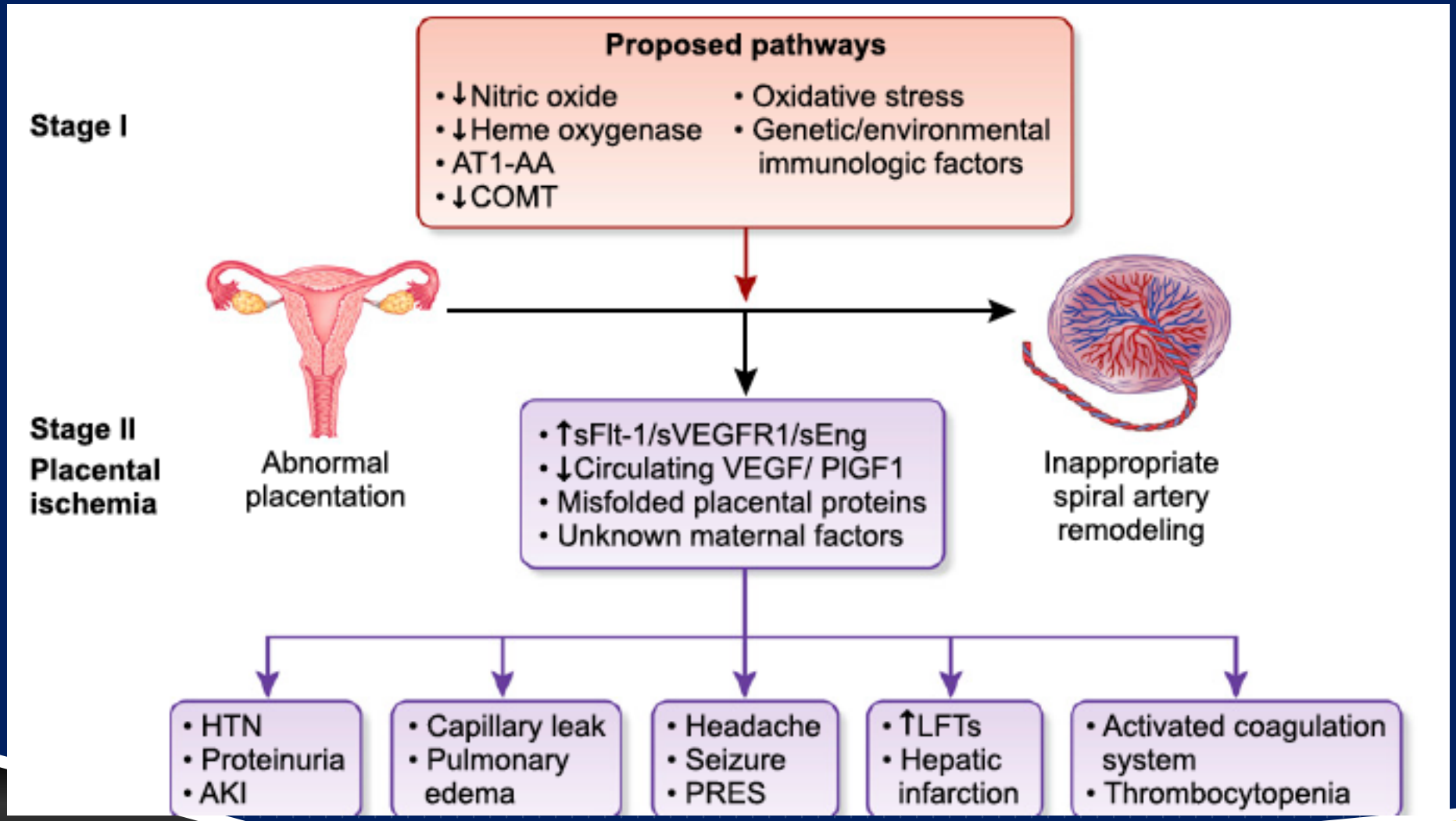
- ***The etiology is unknown***
- believed to be involved:
  - immune maladaptation
  - placental ischemia
  - oxidative stress
  - genetic susceptibility

PREECLAMPSIA

Pathophysiology :

excessive placental production of antagonists to both vascular epithelial growth factor(VEGF) (soluble fms-like tyrosine kinase 1and sflt-1) and transforming growth factor β(TGFβ) (endoglin).

These antagonists to VEGF and TGF βdisrupt endothelial and renal glomerular function resulting in edema, hypertension, and proteinuria.


Proposed pathways
• ↓Nitric oxide
• ↓Heme oxygenase
• AT1-AA
• ↓COMT
• Oxidative stress
• Genetic/environmental immunologic factors
Stage I
Stage II
Placental ischemia
Abnormal placentation
Inappropriate spiral artery remodeling
• ↑sFlt-1/sVEGFR1/sEng
• ↓Circulating VEGF/ PlGF1
• Misfolded placental proteins
• Unknown maternal factors
• HTN
• Proteinuria
• AKI
• Capillary leak
• Pulmonary edema
• Headache
• Seizure
• PRES
• ↑LFTs
• Hepatic infarction
• Activated coagulation system
• Thrombocytopenia

PREECLAMPSIA

Pathophysiology :

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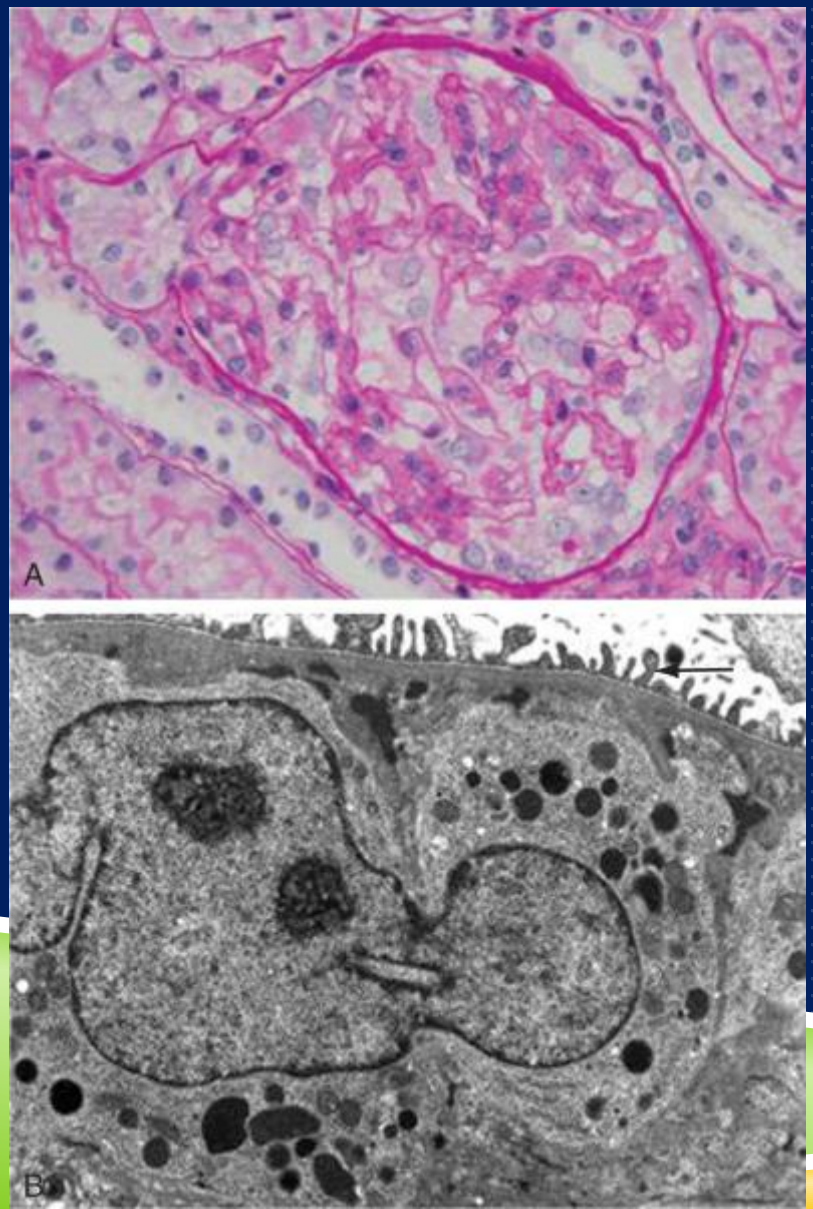
PREECLAMPSIA

The renal histological feature of preeclampsia is glomerular endotheliosis.

Glomerular endothelial cells are swollen and encroach on the vascular lumen

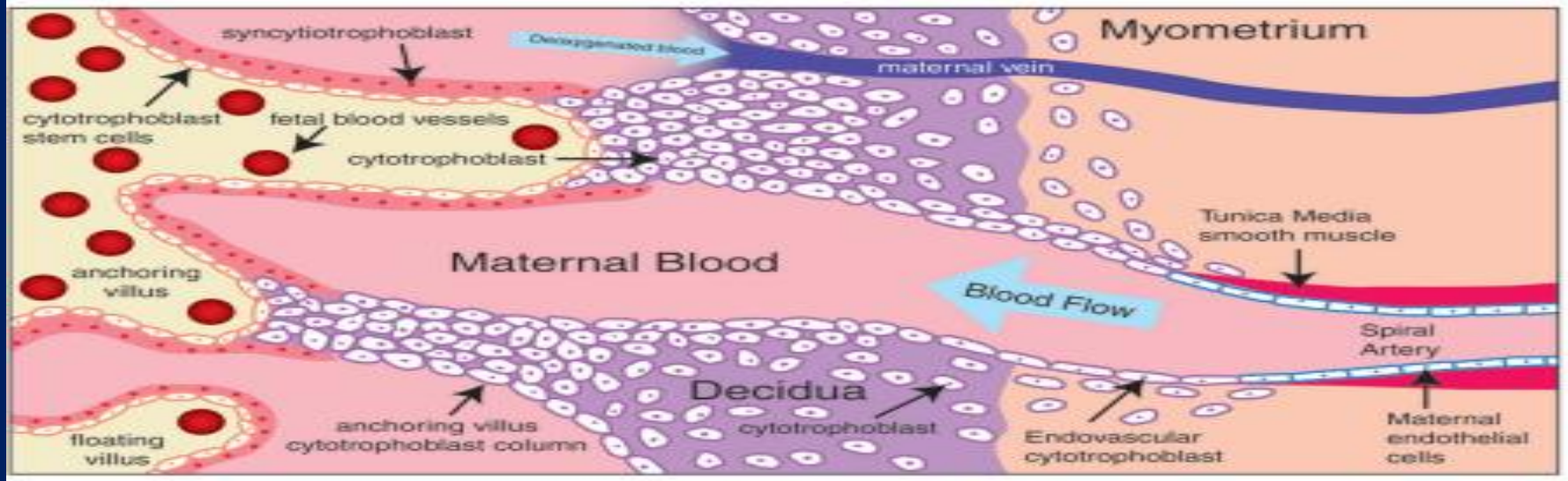
GLOMERULAR ENDOTHELIOSIS



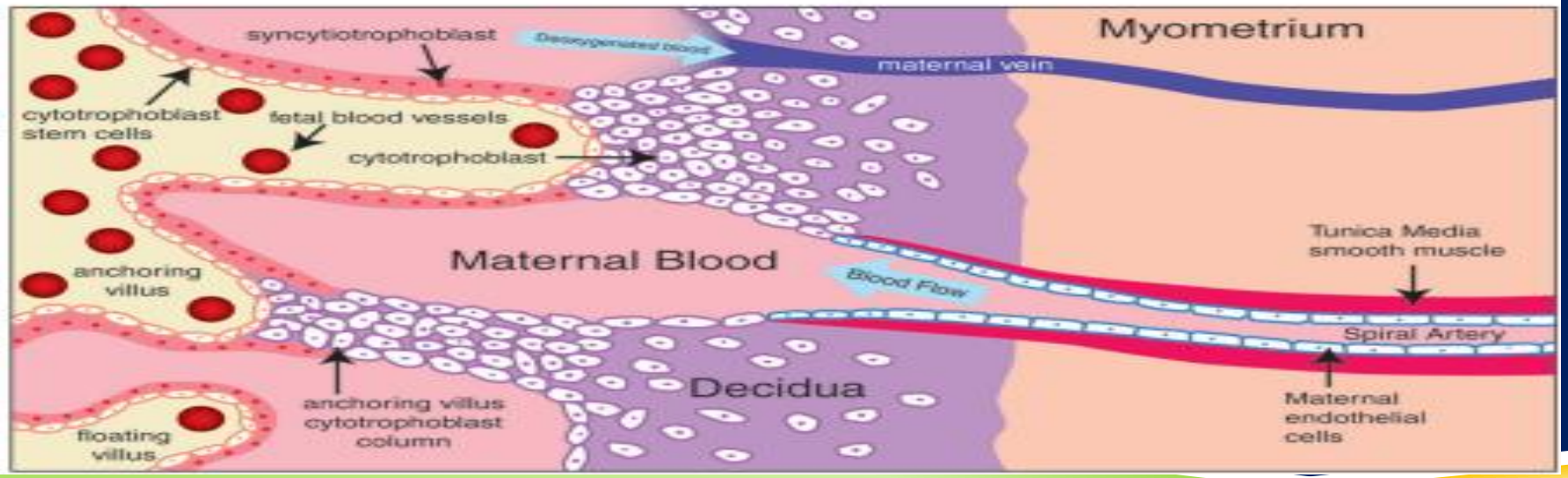
A, Human preeclamptic glomerulus, light microscopy. Renal biopsy findings of a 29-year-old woman with twin gestation and severe preeclampsia are shown. Patient's blood pressure was 170/112 mm Hg and random urine protein-to-creatinine ratio was 9.8. Note the "bloodless" appearance of the glomeruli and absent capillary Lumen.

B, Electron microscopy of glomerulus of the patient described in A. Note occlusion of capillary lumen cytoplasm and expansion of the subendothelial space with some electron-dense material. Podocyte cytoplasm shows protein resorption droplets and relatively intact foot processes

Normal



Preeclampsia



MAJOR RISK FACTORS FOR PREECLAMPSIA

OR or RR (95% CI)	Risk Factor
(۲۱,۷–۴,۳) ۹,۷	Antiphospholipid antibody syndrome
(۲۸,۲–۲,۲) ۷,۸	Renal disease
(۸,۸–۵,۸) ۷,۲	Prior preeclampsia
(۱۶,۲–۲,۰) ۵,۷	Systemic lupus erythematosis
(۱۰,۳–۲,۸) ۵,۴	Nulliparity
(۴,۳–۳,۴) ۳,۸	Chronic hypertension
(۵,۰–۲,۵) ۳,۶	Diabetes mellitus
(۱۱,۹–۱,۱) ۳,۶	High altitude
(۴,۲–۳,۰) ۳,۵	Multiple gestations
(۷,۷–۱,۴) ۳,۲	Strong family history of cardiovascular disease (heart disease or stroke in two or more first-degree relatives)
(۳,۷–۱,۷) ۲,۵	Obesity
(۳,۶–۱,۸) ۲,۶–۲,۳	Family history of preeclampsia in first-degree relative
1.68 (1.23–2.29) for nulliparas 1.96 (1.34–2.87) for multiparas[31]	Advanced maternal age (>40 yr)

PREECLAMPSIA

- ***Prevention of preeclampsia***
  - Antihypertensive drugs
  - Magnesium
  - zinc
  - Fish oil
  - Calcium
  - low-dose aspirin

ECLAMPSIA

New-onset grand mal seizures during pregnancy or within 4 wk postpartum in a woman with preeclampsia

GESTATIONAL HYPERTENSION

- New onset of SBP≥140 mmHg and/or DBP ≥90 mmHg on at least 2 occasions 4 hours apart after 20 weeks of gestation in a previously normotensive individual.

And:

- No proteinuria
- No signs/symptoms of preeclampsia-related endorgan dysfunction (eg, thrombocytopenia, acute kidney injury, elevated liver transaminases,

pulmonary edema, cerebral or visual symptoms)

GESTATIONAL HYPERTENSION

- Disappears post partum

Is frequent in:

- Multiparous
- overweight
- positive family history of hypertension;

CHRONIC (PREEXISTING)HYPERTENSION

- Diagnosed or present before pregnancy
- Or on at least two occasions before 20 weeks of gestation.

- Hypertension that is first diagnosed during pregnancy and persists for at least 12 weeks postpartum .

CHRONIC (PREEXISTING)HYPERTENSION

Blood pressure criteria during pregnancy are:

- **Systolic ≥140 mmHg and/or diastolic ≥90 mmHg**

Pre-pregnancy and 12 weeks postpartum blood pressure criteria are:

- **Stage 1 – Systolic 130 to 139 mmHg or diastolic 80 to 89 mmHg**
- **Stage 2 – Systolic ≥140 mmHg or diastolic ≥90 mmHg**

ESSENTIAL HYPERTENSION IN PREGNANCY

Have an increased risk of:

- preeclampsia
- Abruptio placenta
- Intrauterine growth retardation
- Second-trimester fetal death.
- Have a spontaneous reduction in pressure in the second trimester.

PREECLAMPSIA SUPERIMPOSED ON CHRONIC HYPERTENSION

If proteinuria prior to 20 wk is absent:

- New-onset proteinuria in a woman with chronic hypertension

If proteinuria prior to 20 wk is present, any of the following raise concern for superimposed preeclampsia:

- A sudden increase in proteinuria
- A sudden increase in hypertension, chronic hypertension develops worsening hypertension
- Thrombocytopenia
- Increased in liver enzymes

TREATMENT

MILD THN/CHRONIC HTN IN PREGNANCY

- **we recommend antihypertensive treatment**

results in more favorable pregnancy outcomes (reduction in

preeclampsia with severe features, medically indicated preterm birth <35 weeks,

abruption, or fetal or neonatal death) without increasing the frequency of small

for gestational age birth weight

MILD HTN /GESTATIONAL HTN OR PREECLAMPSIA

Initiating antihypertensive therapy if delivery is likely to be delayed for

- Several days or weeks.
- Even We may initiate treatment at lower levels (SBP 130 to 139 mmHg and/or DBP 80 to 89 mmHg) in patients with clinical signs and symptoms associated with elevated blood pressure:
- Evidence of heart failure or
- Cerebrovascular symptoms (eg, chest discomfort, shortness of breath, headache, visual disturbances, confusion)
- In younger patients whose baseline blood pressures were low (less than 90/75 mmHg), but

MODERATE HTN/GESTATIONAL/CHRONIC HYPERTENSION OR PREECLAMPSIA

We suggest initiating (or increase existing) antihypertensive therapy if delivery is likely to be delayed for more than 24 hours .

TARGET BLOOD PRESSURE/NON SEVER

our target blood pressure is <140/90 mmHg.

SEVERE HYPERTENSION IN PREGNANCY

- Prompt treatment (within 30 to 60 minutes of diagnosis) of acute severe hypertension is required

- We try to reduce mean arterial pressure by no more than 25 percent over two hours to achieve initial target blood pressures in the range of 130 to 150 mmHg systolic and 80 to 100 mmHg diastolic

DRUG DOSES FOR ORAL TREATMENT OF HYPERTENSION IN PREGNANCY

NON SEVER /FIRST LINE

Drug	Class	Initial dose	Usual effective dose range	Maximum suggested total daily dose
Nifedipine extended release (ER) ¶	Calcium channel blocker	30 to 60 mg once daily as an extended release tablet, increase at 7 to 14 day intervals	30 to 90 mg once daily	120 mg

DRUG DOSES FOR ORAL TREATMENT OF HYPERTENSION IN PREGNANCY

NON SEVER /FIRST LINE

drug	class	Initial dose	effective dose range	avoid
Labetalol	Combined alpha and beta blocker	100 mg 2 times daily, increase by 100 mg twice daily every 2 to 3 days as needed	200 to 800 mg in 2 divided doses	asthma, COPD, HF, bradycardia(HR <60), or greater than first degree heart block.

DRUG DOSES FOR ORAL TREATMENT OF HYPERTENSION IN PREGNANCY /BETA BLOCKERS

- **Carvedilol : beta blocker with alpha-blocking activity, but there is less**

information on outcomes with use in pregnancy

- **Metoprolol (beta-1 selective blocker) and pindolol considered acceptable alternatives to labetalol**
- **Atenolol and propranolol are generally avoided.**

DRUG DOSES FOR ORAL TREATMENT OF HYPERTENSION IN PREGNANCY

Drug	Class	Initial dose	Usual effective dose range	Maximum suggested total daily dose
Hydralazine **NOTE:** Due to reflex tachycardia, monotherapy with oral hydralazine is not recommended; hydralazine may be combined with methyldopa or labetalol if needed as add-on therapy	Peripheral vasodilator	Begin with 10 mg 4 times per day, increase by 10 to 25 mg/dose every 2 to 5 days	50 to 100 mg in 2 to 4 divided doses	200 mg*

DRUG DOSES FOR ORAL TREATMENT OF HYPERTENSION IN PREGNANCY/CC BLOCKERS

- **Nicardipine** is an effective treatment of hypertension in pregnancy, with a good maternal and fetal safety profile
- **Amlodipine** may not be associated with an increased risk of malformations.

- **verapamil** and **diltiazem**, have been used as well

DRUG DOSES FOR ORAL TREATMENT OF HYPERTENSION IN PREGNANCY

Drug	Class	Initial dose	Usual effective dose range	Maximum suggested total daily dose	Comments
Methyldopa	Centrally acting alpha agonist	250 mg 2 to 3 times daily, increase every 2 days as needed[Δ]	250 to 1000 mg in 2 to 3 divided doses	3000 mg	Sedation is a common side effect.

DRUGS TO AVOID IN PREGNANCY

- Selected beta blockers: Atenolol and propranolol
- ACE inhibitors, ARBs, direct renin inhibitors
- Mineralocorticoid receptor antagonists
- Nitroprusside
- Diuretics?

ACE AND ARBS

Are contraindicated at all stages of pregnancy because they are associated with

- **Significant fetal renal abnormalities when maternal exposure has been in the latter half of pregnancy,**
- **First trimester exposure has been associated with fetal cardiac abnormalities.**

THIAZIDE DIURETICS

- some guidelines suggest that these agents can be continued in women with chronic hypertension who were taking them prior to pregnancy

- Significant volume depletion is not likely in this setting, since all of the fluid loss occurs within the first two weeks of use, assuming that drug dose and dietary sodium intake are relatively constant.

- Diuretics are not generally used in women with preeclampsia unless pulmonary edema has developed.

NITROPRUSSIDE

- Is contraindicated in the later stages of pregnancy due to possible fetal cyanide poisoning if used for more than four hours.

However,

- Nitroprusside (0.5 to 10 mcg/kg/min) is the agent of last resort for urgent control of refractory severe hypertension.

PREECLAMPSIA/ INDICATIONS FOR ANTIHYPERTENSIVE THERAPY

Choice of drug and dose

- **Acute** management of severe hypertension, which may require **parenteral therapy**
- **Longer-term blood pressure control during expectant management of severe preeclampsia**

ACUTE THERAPY

- Labetolol
- Hydralazine
- Calcium channel blockers
- Nitroglycerin

PREECLAMPSIA/ ACUTE TREATMENT

Labetalol

- Has a rapid onset of action, and a good safety profile.
- Begin with 20 mg intravenously over 2 minutes followed at 10-minute intervals by doses of 20 to 80 mg up to a maximum total cumulative dose of 300 mg.

As an example, give 20 mg, then 40 mg, then 80 mg, then 80 mg, then 80 mg.

A constant infusion of 1 to 2 mg/min can be used instead of intermittent therapy.

The fall in blood pressure begins

- within 5 to 10 minutes and lasts from 3 to 6 hours. Continuous cardiac monitoring is not necessary routinely, but should be used in patients with relevant co-morbidities

PREECLAMPSIA/ ACUTE TREATMENT/HYDRALAZINE

- Begin with 5 mg intravenously over 1 to 2 minutes; if the blood pressure goal is not achieved within 20 minutes, give a 5 to 10 mg bolus depending upon the initial response.
- The maximum bolus dose is 20 mg. If a total dose of 30 mg does not achieve optimal blood pressure control, another agent should be used.
- The fall in blood pressure begins within 10 to 30 minutes and lasts from 2 to 4 hours.

PREECLAMPSIA/ ACUTE TREATMENT

- **Calcium channel blockers**
- Sustained release Nifedipine (30 mg) and immediate release nicardipine are other options.
- Nicardipine can be given intravenously.

- Target blood pressure was reached within 23 minutes in 70 percent of pregnant patients with severeHTN.

PREECLAMPSIA/ ACUTE TREATMENT CALCIUM CHANNEL BLOCKERS

- Safe for use in pregnancy
- Long-acting nifedipine (30 to 90 mg once daily as sustained release tablet, increase at 7- to 14-day intervals, maximum dose 120 mg/day) has been used without major problems

- Amlodipine is widely used in non-pregnant individuals with hypertension, there are sparse data of its use in pregnancy

Nondihydropyridine calcium antagonists such as verapamil and diltiazem have been used,

PREECLAMPSIA/ ACUTE TREATMENT CALCIUM CHANNEL BLOCKERS

- We do not use immediate release Nifedipine, either orally or sublingually, for treatment of hypertension because of the risk of acute, precipitous falls in blood pressure, which have been associated with serious cardiovascular morbidity

PREECLAMPSIA/ ACUTE TREATMENT

NITROGLYCERIN

- Is a good option for treatment of hypertension associated with pulmonary edema
- It is given as an intravenous infusion of 5 mcg/min and gradually increased every 3 to 5 minutes to a maximum dose of 100 mcg/min

LONG-TERM ORAL THERAPY

- Occasionally, preeclamptic women with severe hypertension remote from term are stabilized and not delivered immediately. Oral antihypertensive therapy is often indicated for these patients.

- Options for oral antihypertensive therapy are the same as for women with preexisting hypertension

GESTATIONAL HYPERTENSION

- The indications for and choice of antihypertensive therapy in women with gestational hypertension are the same as for women with preeclampsia.

CHRONIC ESSENTIAL HYPERTENSION

- **α-Methyldopa**
- **labetalol**
- **Nifedipine**

are the most commonly used medications for the treatment of chronic hypertension in pregnancy.

OPTIONS FOR BREASTFEEDING MOTHERS

- Propranolol , metoprolol , and labetalol

have the lowest transfer into milk, with relative infant doses of less than 2 percent. None has been associated with adverse events in infants.

- Atenolol

should be avoided in breastfeeding mothers, if possible; if used, the infant should be observed for signs of beta-blockade.

Carvedilol And bisoprolol

- Little to no published experience

OPTIONS FOR BREASTFEEDING MOTHERS

- **Calcium channel blockers** Diltiazem Nifedipine , nicardipine , and verapamil

are associated with a relative infant dose of less than 2 percent. The American Academy of Pediatrics (AAP) lists all three as compatible with breastfeeding.

OPTIONS FOR BREASTFEEDING MOTHERS

- **Angiotensin converting enzyme (ACE) inhibitors –**

- These drugs are transferred into milk at very low levels. Captopril and Enalapril are compatible for use in lactation.
- However, newborns may be more susceptible to the hemodynamic effects of these drugs, such as hypotension, and sequelae such as oliguria and seizures.

- There is no information on use of angiotensin II receptor blockers ARBs during breastfeeding.

OPTIONS FOR BREASTFEEDING MOTHERS

- **Diuretics**

- May reduce milk volume, but the AAP considers their use compatible with breastfeeding.

- Thank you…