

# HYPERTENSIVE DISORDERS OF PREGNANCY



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# OVERVIEW

- Spectrum of Hypertensive Disease and Pregnancy
  - Preeclampsia
  - Gestational Hypertension
  - Chronic Hypertension
  - Medical Treatment of Hypertension in Pregnancy
  - Breastfeeding on Antihypertensives
  - Fetal Evaluation
  - Delivery Timing
-

# HYPERTENSIVE DISEASE IN PREGNANCY

**Chronic  
Hypertension**

**Gestational  
Hypertension**

**Preeclampsia  
HELLP  
Eclampsia**

# HYPERTENSIVE DISEASE IN PREGNANCY

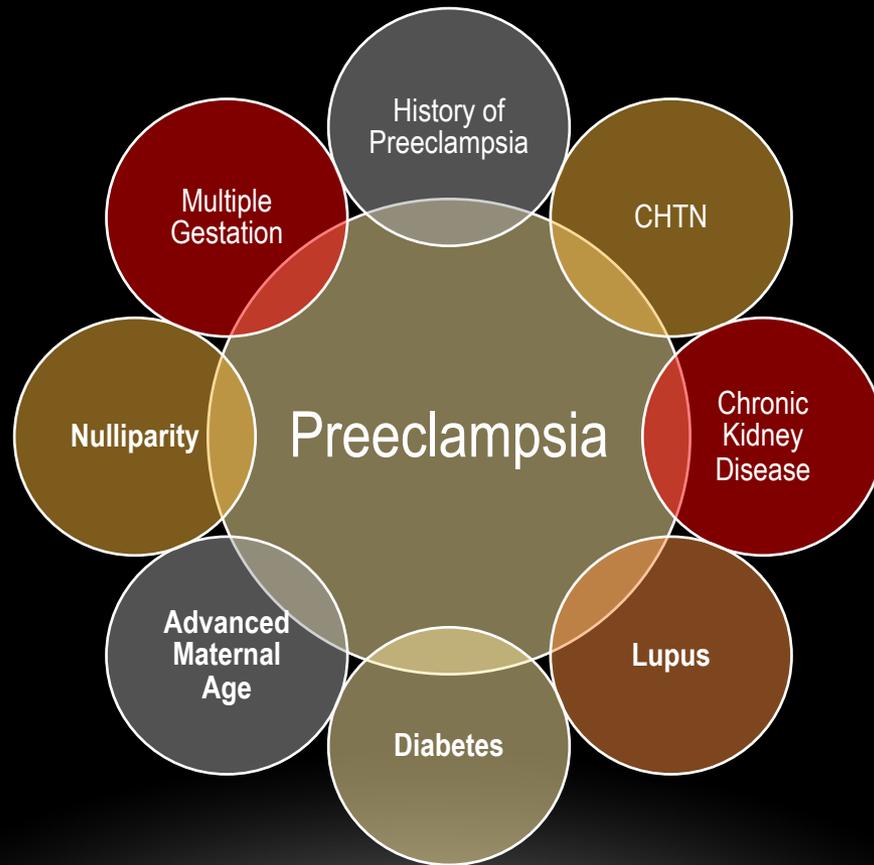
- **Preeclampsia-eclampsia**

- syndrome of new onset of hypertension and either proteinuria or end-organ dysfunction
- most often after 20 weeks of gestation in a previously normotensive woman
- Eclampsia – involvement of seizures
- HELLP

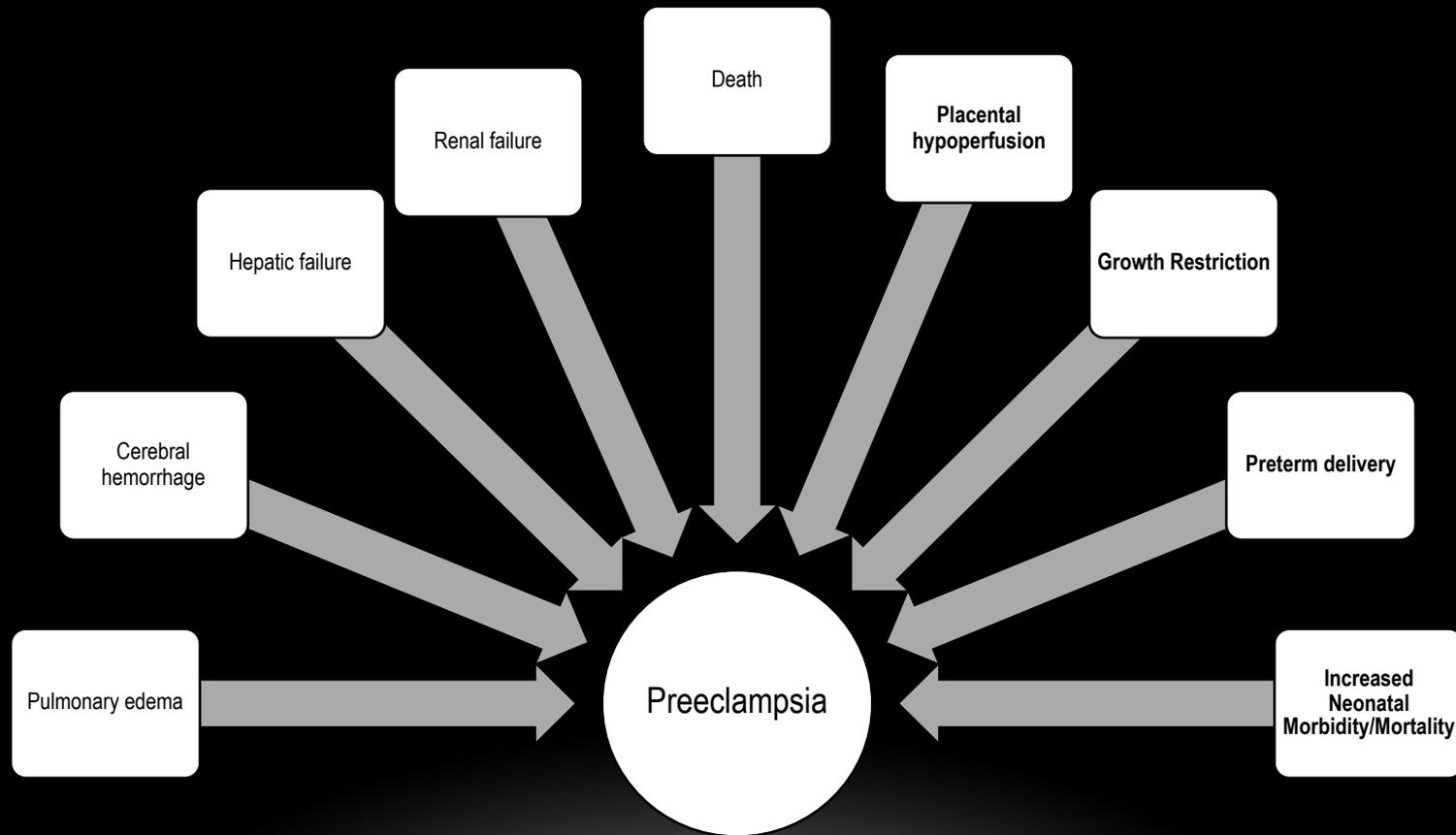
- **Gestational hypertension**

- elevated blood pressure after 20 weeks of gestation in the absence of proteinuria or other diagnostic features of preeclampsia

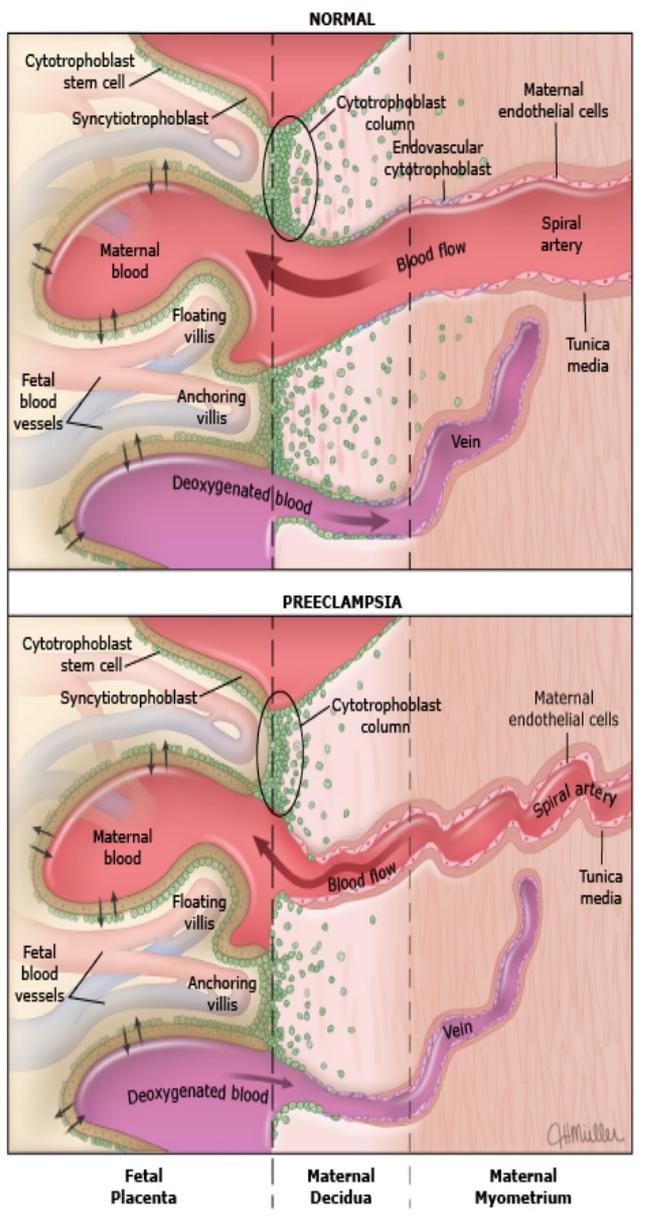
# PREECLAMPSIA: RISK FACTORS



# PREECLAMPSIA



Sibai BM, Caritis S, Hauth J, National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. What we have learned about preeclampsia. Semin Perinatol 2003; 27:239.



Abnormal  
Placental  
Development

Placental  
Hypoperfusion,  
hypoxia,  
ischemia

Release of  
Antiangiogenic  
factors

Effect maternal  
endothelial  
function

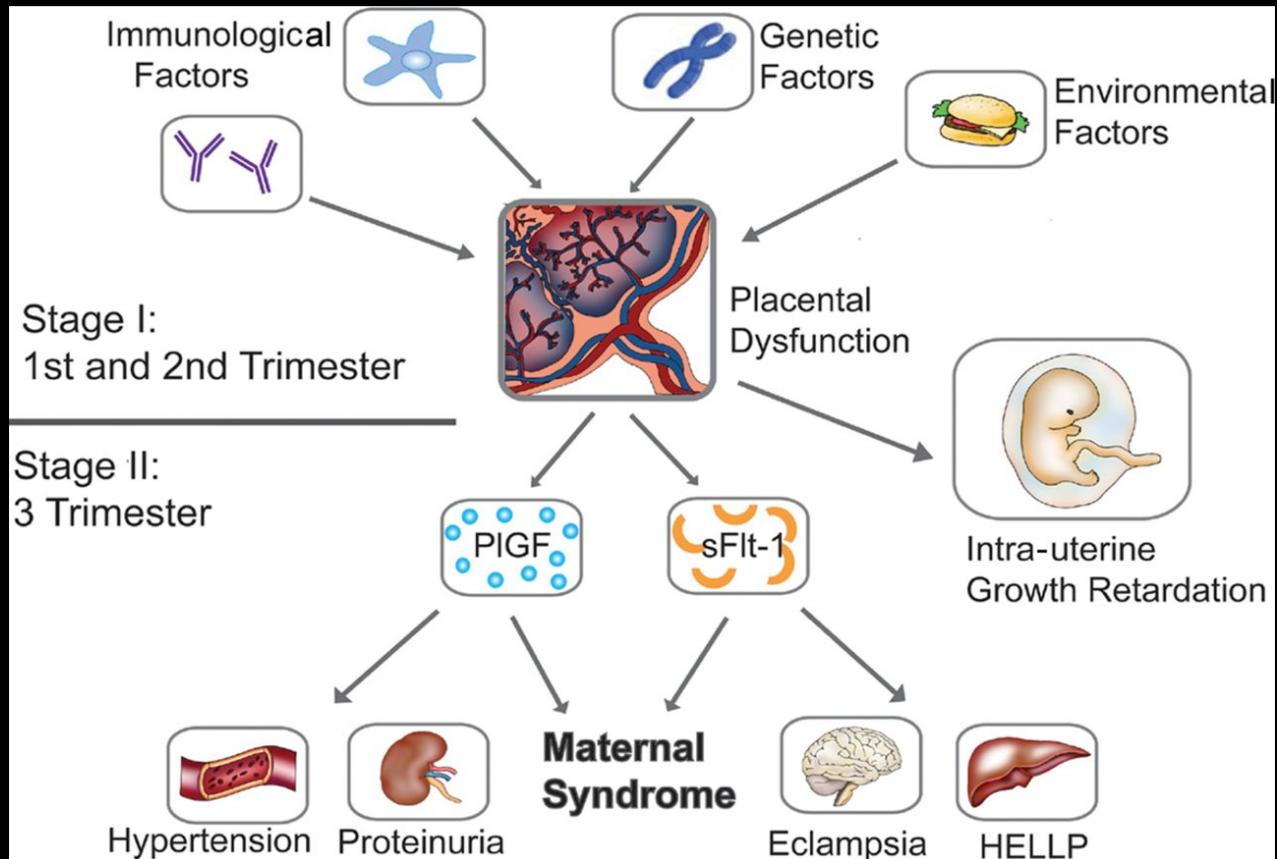
HTN,  
DISEASE  
STATE

- Abnormal development of spiral Arteries, poor placentation

- sFlt-1, VEGF, PlGF
- Antiangiogenic factors

- Endothelial Dysfunction: increased vascular permeability, vasoconstriction, activation of coagulation system, microangiopathic hemolysis

# PATHOPHYSIOLOGY OF PREECLAMPSIA



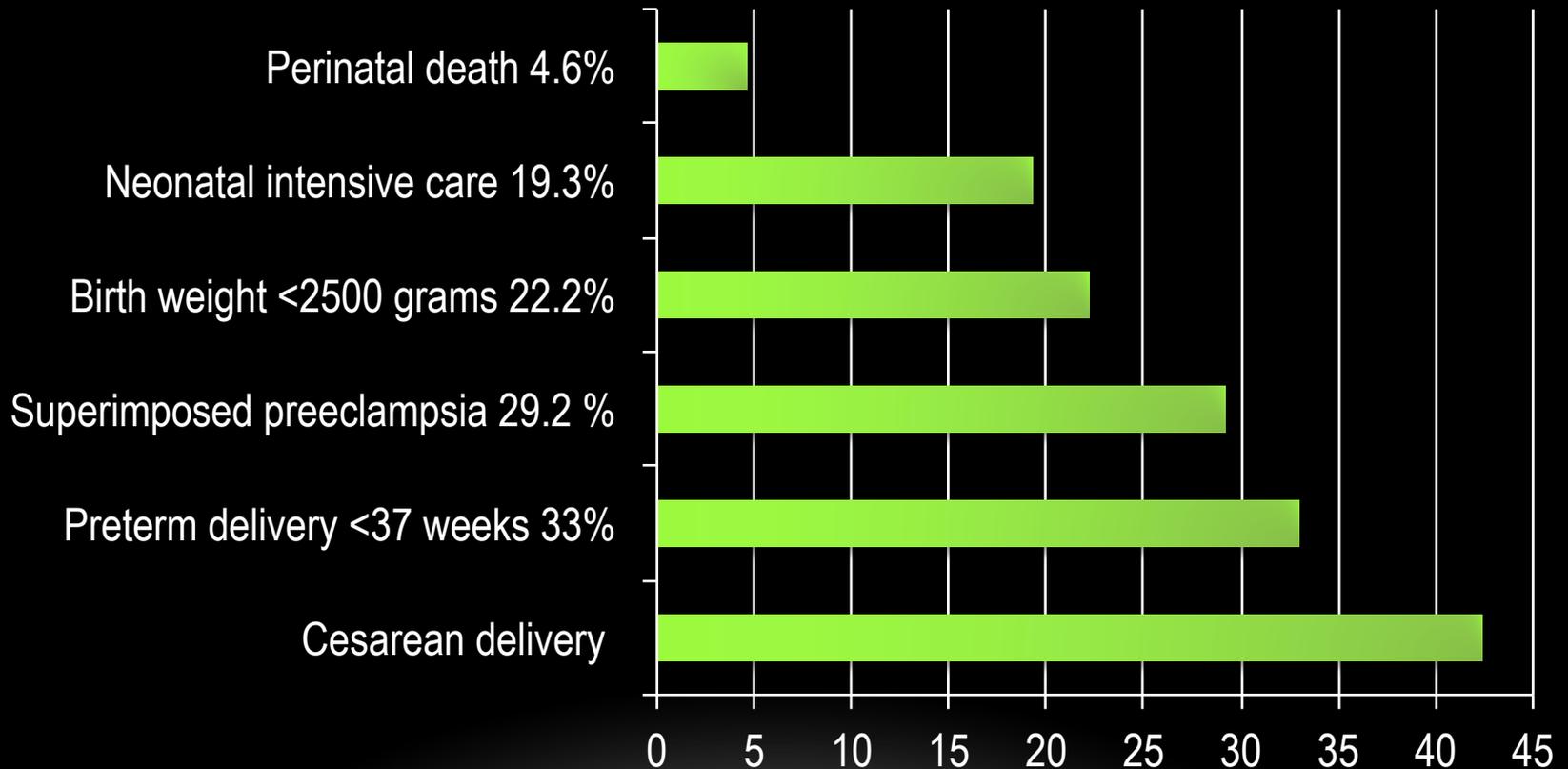
# HYPERTENSIVE DISEASE IN PREGNANCY

- **Chronic Hypertension**
  - systolic pressure  $\geq 140$  mmHg and/or diastolic pressure  $\geq 90$  mmHg before the 20<sup>th</sup> week of pregnancy
  - Or persists longer than 12 weeks postpartum.
- **Chronic hypertension with superimposed Preeclampsia-eclampsia**
  - worsening hypertension with new onset proteinuria or other features of preeclampsia

# CHRONIC HYPERTENSION IN PREGNANCY

- with or without antihypertensive drug treatment is associated with adverse pregnancy outcome (Fetal and Maternal) compared with normotensive pregnancies:
  - poor fetal growth
  - stillbirth
  - iatrogenic preterm birth
  - pulmonary edema
  - stroke
  - superimposed preeclampsia
  - cesarean delivery

CHRONIC HYPERTENSION AND PREGNANCY OUTCOMES: SYSTEMATIC REVIEW AND META-ANALYSIS.  
BRAMHAM K, PARNELL B, NELSON-PIERCY C, SEED PT, POSTON L, CHAPPELL LC  
BMJ. 2014;348:G2301.



# MEDICAL TREATMENT HYPERTENSIVE DISEASE IN PREGNANCY

## Methyldopa (Aldomet)

- widely used in pregnant women
- long-term safety for the fetus has been demonstrated
- mild antihypertensive agent and has a slow onset of action (three to six hours).
- Limited effectiveness and sedative at high doses

Cockburn J, Moar VA, Ounsted M, Redman CW.

Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children.  
Lancet 1982; 1:647.

# MEDICAL TREATMENT HYPERTENSIVE DISEASE IN PREGNANCY

## Beta Blockers

- The safety is somewhat controversial
- reports of premature labor, fetal growth restriction, and neonatal apnea, bradycardia, and hypoglycemia

## Labetalol

- both alpha- and beta-adrenergic blocking activity, and may preserve uteroplacental blood flow to a greater extent than traditional beta-blockers.
- A retrospective population-based cohort study (2014) observed slightly more adverse outcomes (respiratory distress syndrome, sepsis, seizure) among infants exposed in utero to labetalol than those exposed to methyldopa, but only when maternal treatment was for chronic hypertension rather than an acute pregnancy-related hypertensive disorder

[Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet 1982; 1:647.](#)

Association between labetalol use for hypertension in pregnancy and adverse infant outcomes.  
Xie RH, Guo Y, Krewski D, Mattison D, Walker MC, Nerenberg K, Wen SW  
Eur J Obstet Gynecol Reprod Biol. 2014;175:124.

# MEDICAL TREATMENT HYPERTENSIVE DISEASE IN PREGNANCY

## Calcium channel blockers

- Calcium channel blockers appear to be safe for use in pregnancy
- Long-acting Nifedipine has been used without major problems.

Other drugs commonly used:

- Hydralazine
- Clonidine
- Thiazide Diuretics

Cockburn J, Moar VA, Ounsted M, Redman CW.

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# LIMITED USE ANTIHYPERTENSIVES

- **ACE inhibitors, ARBs, direct renin inhibitors**
  - direct renin inhibitors are contraindicated at all stages of pregnancy
  - Second/Third Trimester Use - associated with significant fetal renal abnormalities
  - First trimester Use/Exposure - has been associated with fetal cardiac abnormalities.
- **Nitroprusside**
  - Limited clinical experience
  - Small studies - 22 pregnancies and an association with fetal cyanide poisoning have restricted the use
  - Nitroprusside is a last resort for urgent control of refractory severe hypertension; its use should be limited to a short period of time

# SEIZURE PROPHYLAXIS

- Magnesium Sulfate
  - The only medication known to decrease frequency and severity of eclamptic seizures
  - MOA not completely understood
    - raising the seizure threshold by its action at the n-methyl d-aspartate (NMDA) receptor, membrane stabilization in the central nervous system secondary to its actions as a non-specific calcium channel blocker, as well as decreasing acetylcholine in motor nerve terminals
    - vasodilatation of constricted cerebral vessels by opposing calcium-dependent arterial vasospasm, thereby reducing cerebral barotrauma
  - Significant dosing
    - 4-6gram loading dose, continuous dose of 1-2 grams/hr based on renal function

# BREASTFEEDING ON ANTIHYPERTENSIVES

## Beta-blockers and alpha/beta-blockers (Labetalol, Propranolol, Metoprolol)

- have the **lowest transfer** into milk
- relative infant doses of less than 2 percent.
- No associated adverse events in infants.
- Atenolol/Acebutolol relatively extensively excreted into breast milk and beta-blockade in nursing infants has been reported

## Calcium channel blockers

- Diltiazem, Nifedipine, Nicardipine, Verapamil associated with a relative infant dose of **less than 2 percent**.
- The American Academy of Pediatrics (AAP) lists all three as compatible with breastfeeding.



# BREASTFEEDING ON ANTIHYPERTENSIVES

## (ACE) inhibitors

- These drugs are transferred into milk at very low levels.
- Captopril/Enalapril have been reviewed by the AAP and are compatible for use in lactation.
- Can be associated with hemodynamic effects such as hypotension, and sequelae such as oliguria and seizures.
- Therefore, we suggest that the hemodynamic status of the infant be taken into account when deciding whether women taking these drugs should

## Diuretics

- Theoretically, diuretics may reduce milk volume
- AAP considers their use compatible with breastfeeding.

# Fetal Evaluation



- There is **no consensus** on antepartum fetal assessment in management of pregnancies complicated by mild maternal hypertension
- A baseline ultrasound examination at **16 to 20 weeks of gestation** is recommended to confirm gestational age.
- A second ultrasound in the third trimester is suggested to **screen for fetal growth restriction** .
- Close **fetal surveillance** is warranted when there is a high potential for uteroplacental vasculopathy, as with superimposed preeclampsia or intrauterine growth restriction.

# DELIVERY

- There are **no RCTs** evaluating optimal timing
- ACOG – suggests
  - **38 to 39<sup>6/7</sup>ths** weeks of gestation for women not requiring medication
  - **37 to 39<sup>6/7</sup>ths** weeks for women with hypertension controlled with medication
  - **36 to 37<sup>6/7</sup>ths** weeks for women with severe hypertension difficult to control



# DELIVERY

- Based on **HYPITAT trial** (Hypertension and Preeclampsia Intervention Trial At Term)
  - women with gestational hypertension or mild preeclampsia had better maternal outcomes and equivalent neonatal outcomes with **induction at  $\geq 37$  weeks** compared with **expectant** management
  - The ACOG Task Force on Hypertension in Pregnancy :
    - **avoiding delivery before 38<sup>0/7</sup>ths weeks in women with uncomplicated chronic hypertension in whom blood pressure remains controlled**

# WHEN TO DELIVER PRETERM?

## Severe Features of Preeclampsia (Any of these findings) ⇄

- Systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher on two occasions at least 4 hours apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
- Thrombocytopenia (platelet count less than 100,000/microliter)
- Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
- Progressive renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema
- New-onset cerebral or visual disturbances

# PREVENTION

- Low-dose aspirin is the only drug for which there is some evidence of benefit in reducing the risk of preeclampsia
  - Benefits seen in delaying preterm delivery
    - The Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) trial
    - 9364 women at 12 to 32 weeks of gestation at increased risk of developing preeclampsia or fetal growth restriction



# Perinatal and Hemodynamic Evaluation of Sildenafil Citrate for Preeclampsia Treatment

## *A Randomized Controlled Trial*

*Alberto Trapani Jr, MD, PhD, Luis Flavio Gonçalves, MD, MSc, Thamyris Finger Trapani, MD, Simone Vieira, Pharm, Marilen Pires, Pharm, PhD, and Maria Marlene de Souza Pires, MD, PhD*

Green Journal, Aug 2016

- OBJECTIVE: To evaluate whether therapy with sildenafil citrate prolongs gestation in women with preeclampsia.
- randomized double-blind, placebo-controlled trial, n= 100 with preeclampsia (24-33 wks), randomized to 50 mg oralsildenafil citrate every 8 hours or placebo.
- Results:
- Pregnancy duration was on average 4 days longer (14.4 days, 95% confidence interval [CI] 12.5–16.6 days compared with 10.4 days, 95% CI 8.4–12.3 days,  $P=.008$ )
- Improvement in uterine and umbilical artery dopplers
- Maternal blood pressure lower
- There was **no difference in perinatal morbidity, mortality, or adverse effects** between groups.

# QUESTIONS?

