Hypertensive Drugs using during pregnancy and breast feeding

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REVIEW

Treatment options for hypertension in pregnancy and puerperium

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Definitions

Table 1. Diagnostic criteria (ACOG).

	Elevated BP	Proteinuria	Severe features (SF)
Chronic HTN (CHTN)	<20 weeks GA	—	—
Gestational HTN	>20 weeks GA	—	—
Preeclampsia	>20 weeks GA	+	—/+
CHTN with superimposed preeclampsia	** diagnosed with CHTN <20wks GA, with possible worsening >20 wks GA	—/+	—/+

BP: blood pressure, HTN: hypertension, GA: gestational age.
**Elevated BP is >140/90 mmHg on two separate occasions at least 2 h apart
**Proteinuria is 24 h urine protein >300 mg or spot urine protein: creatinine ratio >0.3 mg/dL
**Severe features:

- Systolic BP >160/110 mmHg on two occasions at least 4 h apart while patient is on bed rest
- Thrombocytopenia (Platelet count <100,000)
- Impaired liver function (elevated liver enzymes ×2 normal concentration)
- Progressive renal insufficiency (serum creatinine >1.1, or doubling of serum creatinine in the absence of other renal disease)
- Severe persistent right upper quadrant pain or epigastric pain (not improving with medication, and not accounted for by any other diagnosis)
- Pulmonary edema
- New onset cerebral or visual disturbances

Goals of treatment

- we should be mindful that outside of pregnancy, the management of hypertension is targeted at decreasing future cardiovascular, neurological, and renal risks.
- While in pregnancy treatment goals are tailored to acute complications and fetal well-being

Pregnancy-related changes

- Pregnancy is associated with changes that impact medications, pharmacodynamics, and pharmacokinetic properties.
- These changes include delayed gastric emptying, thus affecting absorption of drugs.
- Increased plasma volume thus increasing the drug's volume of distribution.
- Decrease in plasma albumin concentration thus decreasing plasma protein binding of certain drugs.

- Liver metabolism and Renal elimination are also increased. Specifically, the activity of cytochrome P450 (CYP) is variable.
- This increases the metabolism of lipophilic drugs and the elimination of watersoluble drugs.
- Overall, these pregnancy-related physiological
- changes typically will cause a Decrease in drug plasma concentration, Decreased half life, and Increased clearance .

Table 4. Pharmacokinetics.

	Mode of excretion	Metabolizing enzyme	Vd (L/kg)	Elimination t1/2
Nifedipine	>90% metabolism	CYP3A4	1.4–2.2	2.5–3.4 h for oral capsule, 6–11 h for oral tablet
Labetalol	95% metabolism	UGT1A1, others	5.1–9.4	8 h
Methyldopa	50% renal elimination, 50% metabolism	Sulfation, other	0.6	10 h

T1/2: half-life, h: hour, CYP: cytochrome P450, UGT: uridine diphosphate glucuronosyltransferase, Vd: apparent volume of distribution [9,15,16].

- The medication dosages however that are used in pregnancy are inferred from studies done on nonpregnant
- patients.

le 2. Drugs for Gestational or Chronic Hypertension in Pregnancy

g (FDA Risk)*	Dose	Concerns or Comments
erred agent		
lethyldopa (B)	0.5 to 3.0 g/d in 2 divided doses	Drug of choice according to NHBEP; safety after first trimester well documented, including 7 years follow-up of offspring
ond-line agents†		
abetalol (C)	200 to 1200 mg/d in 2 to 3 divided doses	May be associated with fetal growth restriction
ifedipine (C)	30 to 120 mg/d of a slow-release preparation	May inhibit labor and have synergistic action with magnesium sulfate in BP lowering; little experience with other calcium entry blockers
ydralazine (C)	50 to 300 mg/d in 2 to 4 divided doses	Few controlled trials, long experience with few adverse events documented; useful in combination with sympatholytic agent; may cause neonatal thrombocytopenia
-Receptor blockers (C)	Depends on specific agent	May decrease uteroplacental blood flow; may impair fetal response to hypoxic stress; risk of growth restriction when started in first or second trimester (atenolol); may be associated with neonatal hypoglycemia at higher doses
ydrochlorothiazide (C)‡	12.5 to 25.0 mg/d	Majority of controlled studies in normotensive pregnant women rather than hypertensive patients; can cause volume contraction and electrolyte disorders; may be useful in combination with methyldopa and vasodilator to mitigate compensatory fluid retention
ontraindicated ACE-Is and angiotensin pe 1 receptor antagonists (D)‡		Leads to fetal loss in animals; human use associated with cardiac defects, fetopathy, oligohydramnios, growth restriction, renal agenesis and neonatal anuric renal failure,

Medication administered during pregnancy

- Calcium chanel blockers:
- Mechanism of action Calcium channel blockers are frequently used in obstetrics; they are utilized for BP control and tocolysis.
- There are two subtypes: dihydropyridine (nifedipine) and non-dihydropyridine
- (verapamil, diltiazem)
- They act by blocking the transmembrane
- calcium influx at voltage-gated L-type channels

- They also increase renal blood flow and improve urine output and inhibit release of ADH.
- Therefore, causing a decrease in systemic vascular resistance, arterial pressure and causing uterine relaxation.

- The most commonly used CCB is nifedipine; it is also the
- most extensively studied. It is available in three formulations:
- Immediate release,

- PA tablet,

- long-acting tablet.
- The immediate release tablet's onset of action is within 30 min,

  PA tablet's onset of action is within hours.
-
- long-acting tablet continues to have an effect on BP over 24 h.

- They are considered safe in pregnancy (category C)

- After oral administration, nifedipine is almost completely absorbed from the GI tract; however, only 60% will remain active since 40% of the drug will be converted to inactive
- products in the liver.

- The onset of action is similar in pregnant and nonpregnant patients.
- However, when compared to nonpregnant patients, it is noted that there is a lower peak serum concentration and higher elimination half-life in pregnant patients, and therefore higher doses and more frequent administrations is recommended

- The duration of action for short-acting nifedipine is 4–6 h in pregnant women .

- Current recommended starting dose for nifedipine PA is 10–20 mg orally three times daily (maximum does or 180 mg/
- day),
- Nifedipine XL formulation is usually dosed once daily (starting at 30–60 mg and maximum of 120 mg/day.

Beta blocker (Labetalol)

- There are various beta blockers that differ in their selectivity to beta1 and beta 2 adrenoreceptors.
- While beta 1 blockade causes :

decrease in renal sympathetic output and cardiac output,

beta 2 blockade causes a decrease in systemic vascular resistance.

- Labetalol is a third-generation beta blocker that is nonselective in its actions against Beta 1 and beta 2 adrenoreceptors.
- It also has Alpha 1 adrenoreceptor blockade properties, which causes vasodilation.
- It has more beta blocking effect than alpha blocking effect (3:1 ratio).

- Regarding its pharmacokinetics, labetalol has been reported to have extensive first-pass hepatic metabolism, with a bioavailability of 20–35% after oral administration.
- Only 5% is eliminated in urine, indicating that it is mostly metabolized by the liver and absorbed via the intestinal wall It was noted that peak concentrations of labetalol were reached at 1 h after administration.
- In pregnancy, labetalol's half-life ranges from 4.3 to 6.9 h

Methyldopa

- Methyldopa acts as a centrally acting alpha 2 adrenergic
- receptor agonist, which in turn decreases sympathetic outflow
- from the brain.
- It also decreases peripheral vascular resistance
- Methyldopa is excreted 50% unchanged in the urine.
- Due to the effect of pregnancy changes on an increase in renal clearance,
- then renal clearance of methyldopa would be expected to
- increase in pregnancy however, there is no data at this time to
- that effec
- At this time, recommended doses of methyldopa in pregnancy are similar to those used in the nonpregnant population.
- A dosing of 2–4 times daily is recommended
- Therefore, a once-daily dosing is not recommended; instead a dosing of 2–4 times daily is recommended

Direct Vasodilators

- Hydralazine selectively relaxes arteriolar smooth muscle by an as-yet-unknown mechanism.
- It is effective orally, intramuscularly, or intravenously; parenteral administration
- is useful for rapid control of severe hypertension.

- Adverse effects are mostly those due to excessive vasodilation or sympathetic activation and include headache, nausea,
- flushing, or palpitations.
- Chronic use can lead in rare cases to a pyridoxine-responsive polyneuropathy or to immunologic reactions, including a drug-induced lupus syndrome.

- Hydralazine has been used in all trimesters of pregnancy, and data have not shown an association with teratogenicity, although
- neonatal thrombocytopenia and lupus have been reported.

Clinical applications

- Calcium channel blocker:

- Nifedipine is currently considered a first-line agent for
- treatment of hypertensive disorders in pregnancy.
- That is due to the fact that there was no increase in adverse perinatal outcomes noted when compared to other antihypertensive agents.
- Furthermore, nifedipine does not affect uterine or umbilical blood flow

- Beta blocker:Labetalol is considered to be first-line therapy for management of hypertensive diseases of pregnancy

- Methyldopa
- Methyldopa used to be a first-line agent for treatment ofh hypertensive disorders in pregnancy.
- That was likely due to the fact that it was a well-studied antihypertensive medication with a well-documented safety profile. However, recent evidence is suggesting that it is no longer the drug of choice forBP control in pregnant and nonpregnant patients.
- This is due to the fact that it is not as efficacious as other readily available antihypertensive agents

Table 5. Dosage.

Labetalol	200–2400 mg/d PO Q8-12 H
Nifedipine	30–120 mg/d of slow-release PO QD
	10–20 mg Q8-12 H for Nifedipine PA
Methyldopa	0.5–3 g/d PO Q8-12 H

Table 6. Hypertensive emergencies management (Hypertension Task Force).

Drug	Dose
Labetalol	10–20 mg IV, then 20–80 mg every 20–30 min (maximum dose of 300 mg). OR Continuous infusion 1–2 mg/min IV
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 min (to a maximum of 20 mg) OR Continuous infusion 0.5–10 mg/h
Nifedipine	10–20 mg orally, repeat in 30 min, then 10–20 mg every 2–6 h

American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy [1].

Table 2. Different alternatives for acute antihypertensive treatment in pregnancy

Drug	Dose
Dihydralazine	2.5–5 mg intravenously, repeat after 15–20 min if necessary or 0.5–10 mg/h by infusion
Labetalol	20 mg intravenously, then 20–80 mg every 20–30 min if necessary or 0.5 mg/min by infusion
Nifedipine	8–10 mg sublingual, repeat after 20–30 min then 10–20 mg every 3–6 h up to a total dose of 1 mg/kg body weight

Table 3. Drugs for Urgent Control of Severe Hypertension in Pregnancy

Drug (FDA Risk*)	Dose and Route	Concerns or Comments†
Labetalol (C)	10 to 20 mg IV, then 20 to 80 mg every 20 to 30 minutes, maximum of 300 mg; for infusion: 1 to 2 mg/min	Because of a lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine; avoid in women with asthma or congestive heart failure
Hydralazine (C)	5 mg, IV or IM, then 5 to 10 mg every 20 to 40 minutes; once BP controlled repeat every 3 hours; for infusion: 0.5 to 10.0 mg/h; if no success with 20 mg IV or 30 mg IM, consider another drug	A drug of choice according to NHBEP; long experience of safety and efficacy
Nifedipine (C)	Tablets recommended only: 10 to 30 mg PO, repeat in 45 minutes if needed	We prefer long-acting preparations; although obstetric experience with short acting has been favorable, it is not approved by the FDA for management of hypertension
Diazoxide (C)	30 to 50 mg IV every 5 to 15 minutes	Use is waning; may arrest labor; causes hyperglycemia
Relatively contraindicated nitroprusside (C)‡	Constant infusion of 0.25 to 5.00 μg/kg per minute	Possible cyanide toxicity if used for >4 hours; agent of last resort

Table 7. Other drugs.

	Fetal side effects
ACEI and ARB	Fetal hypotension, oligohydramnios, growth restriction, pulmonary hypoplasia, renal tubular dysplasia, hypocalvaria. Contraindicated
Thiazide	Theoretical concern for volume depletion and subsequent FGR. Second-line agents

Breastfeeding

- Thomas Hale is the leading expert on breastfeeding and medications
- The risk categories that were developed
- range from L1 to L5, with L1 being safest in breast feeding and L5 contraindicated in breastfeeding based on studies that
- have demonstrated a negative impact on the infant

Antihypertensive treatment during the postnatal period, including during breastfeeding

- antihypertensive medicines can pass into breast milk
- • most antihypertensive medicines taken while breastfeeding only lead to very low
- levels in breast milk, so the amounts taken in by babies are very small and would be
- unlikely to have any clinical effect

- Antihypertensive medications such as : labetalol, nifedipine, methyldope and hydralazine are in the L2 category,and consider safe.
- While the following antihypertensives: lisinopril, valsartan and chlorothiazide
- are in the L3 category, and therefore are considered “moderately safe”

Table 4. Maternal Antihypertensive Medications Usually Compatible With Breastfeeding

Captopril
Diltiazem
Enalapril
Hydralazine
Hydrochlorothiazide
Labetalol
Methyldopa
Minoxidil
Nadolol
Nifedipine
Oxprenolol
Propranolol
Spironolactone
Timolol
Verapamil

- Where possible, avoid using diuretics or angiotensin receptor blockers[5]
- to treat
- hypertension in women in the postnatal period who are breastfeeding or
- expressing milk

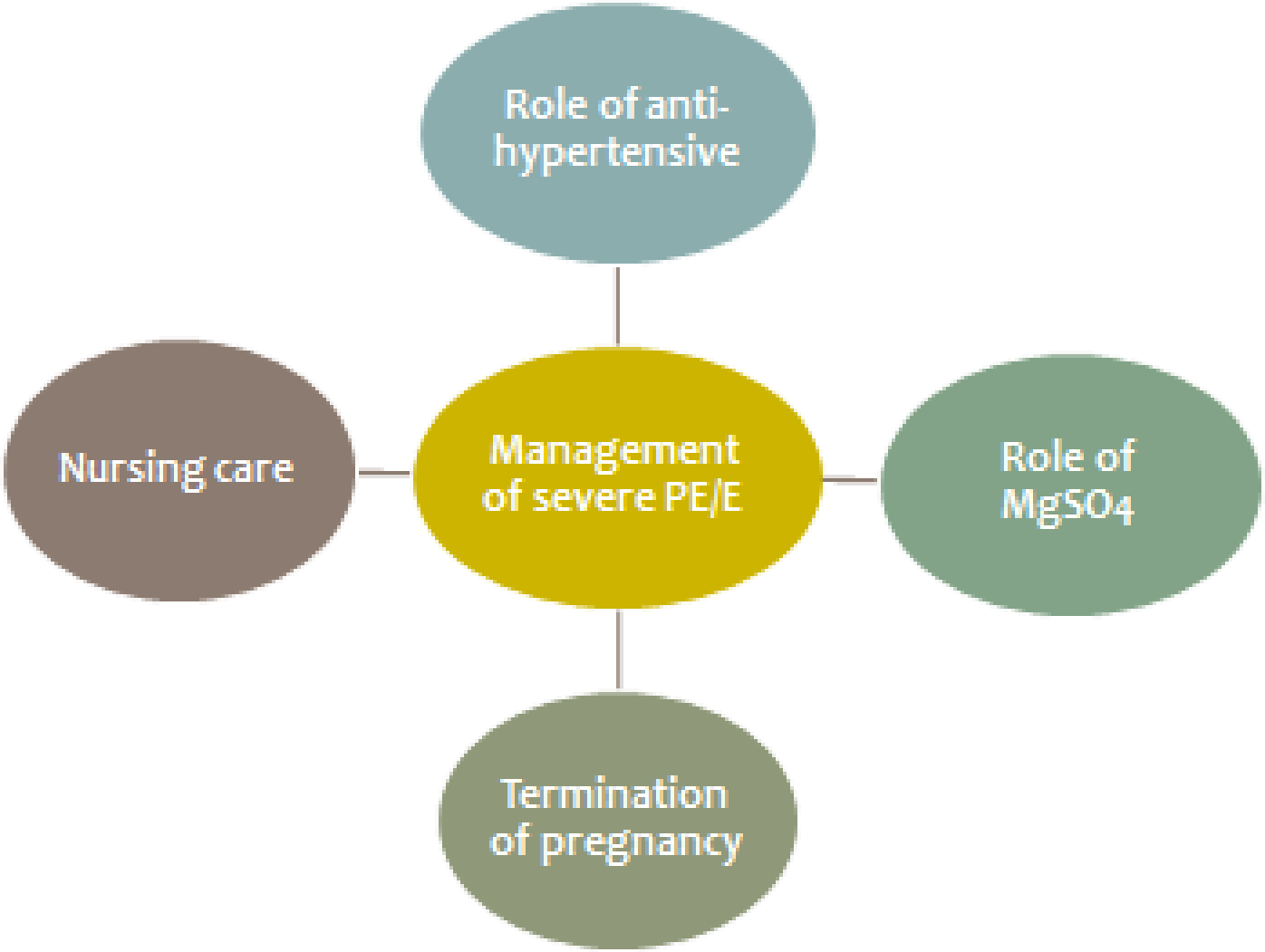
- Expert opinion
- we do not initiate pharmacological
- therapy unless BP approaches severe range (SBP of 160 mmHg or higher or DBP of 105 mmHg or higher).
- Our first-line agent is labetalol, followed by calcium channel blockers

- If BP is uncontrolled after administration of the maximal dose of the combination therapy, then the hypertension is considered uncontrolled and consistent with severe features.

- Intravenous labetalol, hydralazine, and oral nifedipine are first-line agents for lowering BP in the acute hospital settings.
- Thiazide diuretics have a clinical value, and we reserve their use to resistant hypertension in the African-American population.

- Where possible, avoid using diuretics or angiotensin receptor blockers to treat hypertension in women in the postnatal period who are breastfeeding or
- expressing milk

Management of Severe PE/E



To Terminate the Pregnancy or Not

If she is already in labour, let her progress in labour

DIAGNOSIS	Pregnancy of <23 Weeks	Pregnancy of 24-34 Weeks	Pregnancy of 35-36 Weeks	Pregnancy of ≥37 Weeks
GESTATIONAL HYPERTENSION	✗	✗	✗	✓
PRE-ECLAMPSIA	✗	✗	✗	✓
SEVERE PRE-ECLAMPSIA	✓	✓ If unstable, give antenatal corticosteroids and terminate within 24hrs ✗ If stable	✓ If unstable, do not give antenatal corticosteroids and terminate within 24hrs ✗ If stable	✓
ECLAMPSIA	✓	✓	✓	✓

In all cases of eclampsia terminate pregnancy within 12 hrs