HYPERTENSIVE DISORDERS IN PREGNANCY

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Writings on Eclampsia date back to 2200 B.C.

Zweifel first termed ‘toxaemia’ the disease of theories in 1916

NIGHTMARE FOR EVERY OBSTETRICIAN
ISSHP [1988]
ACOG [1996]
Working Group for High Blood Pressure in Pregnancy
of
NHBPEP [2000]
ICD [2003]
NHBPEP
(National High Blood Pressure Education Programme)

2000

Classification of hypertensive disorders complicating pregnancy
Classification

1. Gestational hypertension [formerly PIH that included Transient hypertension].

2. Preeclampsia.

3. Eclampsia.

4. Preeclampsia superimposed on chronic hypertension.

5. Chronic hypertension.
Diagnostic criteria as per NHBPEP Working Group (2000)

**Gestational hypertension**

BP $\geq 140/90$ mm Hg. for first time during pregnancy  
No proteinuria  
BP returns to normal $< 12$ weeks’ postpartum  
Final diagnosis made only postpartum  
May have other signs or symptoms of preeclampsia, e.g. epigastric discomfort or thrombocytopenia.
Preeclampsia

**Minimum criteria**

BP ≥ 140/90 mm Hg after 20 weeks’ gestation
Proteinuria ≥ 300 mg/24 hrs. or ≥ 1+ dipstick

*Increased certainty of preeclampsia*

BP ≥ 160/110 mm Hg
Proteinuria 2.0 gm/24 hrs. or ≥ 2+ dipstick
Serum creatinine > 1.2 mg/dl
unless known to be previously elevated
Platelets < 100,000/mm$^3$
Microangiopathic haemolysis (increased LDH)
Elevated ALT or AST
Persistent headache or other cerebral or visual disturbances
Persistent epigastric pain
Eclampsia

Seizures that cannot be attributed to other causes in a woman with pre-eclampsia

Superimposed Pre-eclampsia (on chronic hypertension)

New-onset proteinuria $\geq 300$ mg/24 hrs. in hypertensive women but no proteinuria before 20 weeks’ gestation

A sudden increase in proteinuria or BP or platelet count $< 100,000$/mm$^3$ in woman with hypertension and proteinuria before 20 weeks’ gestation
Chronic hypertension

BP $\geq$ 140/90 mm Hg before pregnancy or diagnosed before 20 weeks’ gestation not attributable to gestational trophoblastic disease

or

Hypertension first diagnosed after 20 weeks’ gestation and persistent after 12 weeks’ postpartum
Chronic hypertension

- **Essential hypertension**: systolic ≥ 140mmHg and/or diastolic ≥ 90mmHg confirmed before 20 weeks gestation, of unknown cause.
- **Secondary hypertension**: Raised blood pressure as above caused by known pre-existing medical conditions.
- **White coat hypertension**: A raised blood pressure as above, in the presence of a medical attendant.
High risk factors

- preeclampsia in a previous pregnancy
- multiple pregnancy
- pre-existing medical condition:
  - hypertension
  - diabetes
  - antiphospholipid antibody syndrome
  - renal disease
- obesity, BMI > 35
- vascular & connective tissue disorders
- maternal age <18 or >35
- nulliparity
- family history of preeclampsia
- new partner.
Preventative supplements for women with a high risk of preeclampsia

• low dose aspirin 75-150mg/day
• Calcium 2g/day.
Taking blood pressures

• appropriately sized cuff
• woman sitting with feet on a hard surface
• manual sphygmomanometer
• use Korotkoff 5 for diastolic reading
• take serial readings over several hours.
### Indicators of severity of Hypertensive disorders in Pregnancy

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic BP</td>
<td>&lt; 109 mm Hg</td>
<td>110 mm Hg or higher</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Trace to 1+</td>
<td>Persistent 2+ or more</td>
</tr>
<tr>
<td>Headache</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Convulsion (Eclampsia)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>Minimal</td>
<td>Marked</td>
</tr>
<tr>
<td>Fetal growth restriction</td>
<td>Absent</td>
<td>Obvious</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
HEL Provider Specific Syndrome

Haemolysis

- Schistocytes, burr cells in the blood smear
- Bilirubin $\geq 1.2$ mg/dl
- Absent or decrease plasma Haptoglobin

Elevated liver enzymes

- SGOT $> 72$ IU/Lt.
- LDH $> 600$ IU/Lt.

Low platelet count

- Platelet count $< 100 \times 10^3 / \text{mm}^3$. 
Consequences of HT in Pregnancy: Maternal effects

Maternal mortality

- Hypertension in Pregnancy [due to Pre-eclampsia/Eclampsia] is one among the leading causes.
  - In the early 20th century 10-15 % in the US.
  - Between 1991 and 1997 approx. 6 % [post Mg. Sulph. era]

[Berg and coworkers, 2003 ; quoted in Williams Obstetrics, 22nd. Edn.]
LONG TERM CONSEQUENCES

Increased incidence of Chronic Hypertension

Increased incidence of Death

[Observed more in Multiparas]
Consequences of HT in Pregnancy: Fetal effects

- IUGR
- IUD
- Abruptio placenta with rapid onset of fetal hypoxia
- Obligatory preterm delivery and dangers associated with prematurity
  - RDS
  - Hypoglycemia
  - Hyperbilirubinemia
Maternal Factors
- Genetics
- Underlying Medical Disorders [CHT, DM, Obesity, Hyperhcy, Hyperhcy, Hyperhcy]
- Immune-maladaptation

Placental Factors
- Inadequate Trophoblastic invasion
- Placental Ischaemia [Hypoperfusion]

Stage 1
Oxidative Stress
Free radicals (Oxidative stress markers: increased)
Antioxidants: decreased

Endothelial Dysfunction
Stage 2
Pre-eclampsia

- Good Endothelium
  - Mild Disease
- Bad Endothelium
  - Severe Disease
Principles of Management

If the observations lead to a diagnosis of severe pre-eclampsia, further management is the same as that for eclampsia.

These women are never “cured” because nearly 90 percent have recurrent hypertension before or during labour.

Almost certainly, the underlying disease persists even until after delivery!
Management

> Early prenatal detection <

> Antepartum management <

- Determination of severity of the disease
- Confirmation of Gestational Age
Maternal and fetal surveillance

Maternal: Frequency - daily to weekly.
• review for new symptoms or signs
• blood pressure
• urinalysis for protein
• preeclampsia blood screen. i.e. CBC, urea and creatinine, liver function tests.

Fetal: Frequency - daily to 2\textsuperscript{nd} weekly.
• CTG
• fetal umbilical artery Doppler
• AFI
• growth (2\textsuperscript{nd} weekly).
Decision regarding

> Continuation of pregnancy <
  • Monitoring of mother and fetus •

> Termination of pregnancy <
  • Fetal indications •
  • Maternal indications •
  • Condition of the cervix •
  • Route of delivery •
  • Use of glucocorticoids •

> Intrapartum management <
Objectives of treatment of severe pre-eclampsia/eclampsia

1. Control or prevention of convulsions by anticonvulsant: presently magnesium sulphate is the drug most commonly used.

2. Antihypertensive therapy to lower the BP whenever the DBP becomes dangerously high.

3. Avoidance of diuretics and limitation of intravenous fluid unless fluid loss is excessive. Hyperosmotic agents are avoided.

4. Delivery
Objectives contd....

- Termination of pregnancy with the least possible trauma to the mother and the fetus.
- Birth of an infant who subsequently survives.
- Complete restoration of health to the mother.
Aims of Antihypertensive treatment in Pregnancy

- Gentle reduction of BP to levels safe for mother and fetus
  - Avoid compromise of uteroplacental perfusion
  - Minimize end organ damage, prevent cerebrovascular events
- Reduce need for hospitalization by reliable long term control (managed safely at home)
- Prolong pregnancy to avoid hazards of prematurity
- Prevent of proteinuric deterioration
- Avoidance of hypertensive crises during labor and anesthesia
ANTIHYPERTENSIVES IN CHRONIC HYPERTENSION

GOALS

- Maintain BP at a level that minimises the risk of Cardio and or Cerebro-vascular accidents
- Prevention of Preclampsia

However current evidences do not show that either any specific BP targets or any specific antihypertensive agents modify the risk of super imposed pre-eclampsia.

Cochrane database of Systemic Reviews, 2007, Issue I, Art. No.: CD002252
Initial presentation

Categorize Hypertension

Patient Education

Maternal-fetal Investigation

Decision on Treatment

> History
> Examination
> Confirm Mild to Moderate Hypertension (ascertain cause if possible)

> Nutrition
> Stop smoking/illicit drugs
> Avoid strenuous
> Monitor weight
> Signs of severe hypertension
> Course of mild to moderate hypertension and treatment options

Any one of the following
> Uncomplicated hypertension with adequate monitoring possible
> Informed patient choice

Under-resourced region
> Proteinuria
> Chronic hypertension with target organ damage/previous Perinatal loss
> Informed patient choice

Intensive Maternal-fetal surveillance

Regular Monitoring

Antihypertensive agent

> Be ware of maternal complications
> Review mgt. at each AN visit
Antihypertensive agents Classified

1. **Central sympatholytics**
   - Metyldopa, Clonidine

2. **β adrenergic blockers**
   - Atenolol, Metoprolol

3. **β+α adrenergic blockers**
   - Labetalol, Carvedilol

4. **Calcium channel blockers**
   - Nifedipine

5. **Diuretics**
   - Hydrochlorothiazide
   - Frusemide

6. **Direct Vasodilators**
   - Hydralazine, Nitroglycerine
Antihypertensive agents contd....

7. Serotonin\textsubscript{2} receptor blockers
   - Ketanserine

8. ACE Inhibitors
   - Captopril, enalapril

9. Angiotensin receptor blockers
   - Losartan, Telmisartan

10. \textit{\alpha}-adrenergic blockers
    - Prazosin
Methyldopa

Widely used drug.
History of 40 yrs in use.

**Mode of Action:**
Centrally acting
$\alpha_2$-adrenergic agonist prodrug, metabolised to $\alpha$-methyl epinephrine which replaces norepinephrine in the neuro-secretory vesicles of adrenergic nerve terminals.

BP control is gradual over 16 – 18 hrs.
Methyldopa contd.:

- Rarely used in non-pregnant women
- Suggested as drug of choice in pregnancy
- Limited pharmacokinetic data in pregnancy
- No adverse fetal-neonatal effects
  - Birth weight
  - Doppler flow studies
  - Infant follow-up to 7.5 years
- Adverse maternal effects
  - Severe hepatitis
    - Death
    - Liver transplant
Methyldopa  

**Dose**: 250 to 750 mg. t.i.d. (Max. 2Gm./day).

No teratogenic effect (Cat. B, USFDA).
No adverse fetal-neonatal effects

- Birth weight
- Doppler flow studies
- Infant follow-up to 7.5 years

**Adverse Effects**: Decreased mental alertness, Impaired sleep, Decreased salivation and xerostomia, Liver enzyme increased, Hepatitis and Hepatic necrosis rarely. Some develop +ve ANA OR antiglobulin (Coomb’s) on chronic use.
Clonidine

Efficacy and safety similar to Methyl dopa.
Sleep disturbances in exposed infants reported.
Can be used as a third line drug in multi drug use.
Atenolol

**Mode of action**: Beta blocker. Central action. Reduces renin secretion

**Dose**: 25-100 mg i.v. once daily at 20 mg/hr or 50-100 mg b.d. orally

**Side effects**: Bradycardia, hypotension, hypoglycaemia, bronchospasm, neonatal hypoglycaemia, IUGR.

**Contraindications**: Asthma, DM, pulmonary edema, IUGR.
Labetalol

Racemic mixture of 4 isomers. (S,S) and (R,S) are inactive. (S,R) is powerful $\alpha_1$ blocker. (R,R) is mixed non selective $\beta$ blocker and selective $\beta_2$ agonist.
Site of action: Heart and Blood vessels

Mode of Action: Reduces HR, FOC & TPR

Preferred drug of choice in

Acute Hypertensive crisis and in moderate HTN

Pharmacokinetics described in few reports

No adverse fetal-neonatal effects

- Umbilical Doppler studies
- Neonatal outcome
Labetalol

Advantage:

More effective in lowering BP in comparison to Methyldopa.

Both parenteral and oral preparations available.

Lower incidence of maternal hypotension and other side effects in comparison to Hydralazine i.v. and Nifedipine orally in acute hypertensive crisis.
Onset of action: 1 - 2 min. (i.v), 2 - 4 hrs (oral)

Duration of action: 8 - 12 hrs

Beneficial effects: Peripheral vasodilator
- Cardiac output unaffected
- Causes reduction in B.P, HR & TPR

Drug Interaction - Nitroglycerine (blunts its reflex tachycardia)
Administration and Dosage

I.V. route:
As per the Working Group NHBPEP(2000),
20 mg. i.v. bolous stat. If not effective in 10 mins.
40 mg then 80 mg. every 10 mins. Total not to exceed 220 mg./per episode.

Oral route: 100 mg tid, maximum 1200 mg/day.

Time of effect: I.V. in 10 min., oral in 1 hr.

[Can be combined with Nifedepine 10 mg. but with caution]
Adverse Effects

[Cat. C, USFDA]

Maternal:
Bradycardia, flushing, hypotension, dizziness, headache, shakiness, tremors, heart block, nausea, vomiting,

Fetal:
Hypotension and hypoglycemia, bradycardia, respiratory depression, IUGR
Nifedepine

Mode of action

Relieves vasospasm, causes vasodilatation in various organs and uteroplacental circulation, improves renal and cerebral blood flow, reduces platelet aggregation.
Dose

10 mg orally to start may be repeated at 30 min intervals till desired effect may be increased to 120 mg /day in three divided doses for maintenance.

Never sublingually
Side effects

Hypotension, tachycardia, headache, decreased uterine activity, flushing, AMI combined with beta blocker, fetal anoxia. To be used with caution with Mag.sulph. And in fetal bradycardia.
Hydralazine

Mode of action
Direct acting vasodilatation
improves renal blood flow and cardiac output.

Dose
5 - 10 mg at 15-20 min. interval till response.
Then 10-20 i.v. b.d. for 48 hrs.
Orally 10 mg. t.i.d.

Side effects
Tachycardia, headache, skin reaction, vomiting,
dizziness, nasal congestion, SLE like syndrome, Fetal tachycardia and hypoxia. Not to be used in IUGR.
Nitroglycerine [NTG]

Non-specific vascular smooth m. relaxant

Onset of action - i.v. : 1-2mins lasts for 3-5mins

Adverse effects - Throbbing Headache, sweating, dizziness, tachycardia, palpitation, toxic to fetus, need for intra-arterial pressure monitoring.

Available - NTG 50mg/5ml (5mg/ml)

Dosage and administration

- i.v. infusion 2amp (50mg) in 500ml 5% DS, initially started @ 0.25-8µg/min with increments of 5µg/min till 50µg according to the response not more than 12-48hrs (maximum dose 250µg /min)
Frusemide

Mechanism of action

Decreases plasma volume and cardiac output
Decreased peripheral resistance
Decrease the renal blood flow
Beneficial effect
In acute hypertensive crisis
with pulmonary edema.
Used in the postpartum period
to help treat fluid overload.

Side effects
Electrolyte depletion
Fetal thrombocytopenia
Regimen and dosage

Available as Inj. Lasix 20 mg / ml

Used in pt with severe hypertension with pulmonary edema, in conjunction with other antihypertensives

Given as 40 mg i.v. stat, followed by 40 mg i.v., 8hrly
Diazoxide

**Mode of action**: Direct acting vasodilator Faster and longer acting than Hydralazine.

**Dose**: I.V. 50 mg bolus followed by Hydralazine.

**Side effects**: Hyperglycemia, hypotension, fetal hyperglycemia.

[Used only in acute and severe hypertension]

Isradepine
Verapamil
Nimodepine
Prazosine
Clonidine

**ACE inhibitors and ARBs**: ABSOLUTE C.I. in pregnancy
Mild HTN in pregnancy

- **First line drug:** Methyldopa
- **Second line drugs:** Labetalol/Pindolol/Oxprenolol/Nifedipine
- **Third line drugs:**
  - Hydralazine + clonidine
  - Hydralazine + metoprolol
  - Clonidine

Diuretics - only in specific situations

Keep SBP at 130-155mmHg and DBP at 80-105mmHg (III, C).
Postpartum treatment
Care in the six weeks postpartum

Recommendations

- BP should be measured during the time of peak postpartum BP, at days 3 to 6 after delivery (III, B).

Antihypertensive therapy may be restarted postpartum, particularly in women with severe pre-eclampsia and those who have delivered preterm.
Severe postpartum hypertension should be treated with antihypertensive therapy, to keep SBP <160mmHg and DBP <110mmHg (II-2, B).

Antihypertensive therapy may be used to treat non-severe postpartum hypertension, particularly in women with co-morbidities (III, A)
Antihypertensive agents acceptable for use in breastfeeding include: Labetalol, Nifedipine, Methyldopa, Captopril, and Enalapril (III, B).
Antihypertensive should be started in women with SBP over 160 mm Hg or DBP over 110 mm Hg.

Treatment can be considered with other markers of severe disease.

Labetalol, orally or i.v., Nifedepine orally or Hydrallazine i.v. can be used for acute management of severe hypertension.

In moderate hypertension treatment may assist prolongation of pregnancy and further research in this group required.

Clinicians should use agents with which they are familiar.

Nifedepine should be given orally not sublingually.

Labetalol should never be used in women with known asthma.

Atenolol may be avoided or used with caution for a brief period only.

ACE inhibitors and ARBs are contra-indicated in pregnancy.
Challenge is in deciding “when” and “how long” and some times “how much”? But the journey has to go on...
THANK YOU