Relevance of the topic

- Most common medical problem encountered during pregnancy (complicating 5-10% of all pregnancy)
- Considerable maternal and foetal morbidity.
- Remain a leading source of maternal mortality.
Hypertension is the most common medical problem encountered during pregnancy, complicating 5-10% of pregnancies.

Which causes maternal and fetal morbidity and remain a leading source of maternal mortality.

Integrated approach by physician and gynaecologist is essential, in the management of hypertension in pregnancy which will have an impact on reducing maternal mortality in Bangladesh.
Case definition & Classification

1. Chronic Hypertension (3-5%):
   - Hypertension prior to pregnancy
   - Gestational Hypertension which does not resolve within 12 weeks of delivery

2. Pre-eclampsia – eclampsia
   Pre-eclampsia (5-8%) - Triad of oedema, HTN & Proteinuria
   Eclampsia - Occurrence of seizure in a pre-eclamptic patient
3. Chronic Hypertension with Superimposed Pre-eclampsia (25% of CHTN): Worsening Hypertension (SBP > 30mmHg, DBP > 15mmHg) either non dependant oedema or proteinuria

4. Gestational Hypertension (6-7%): 
- Onset of hypertension without proteinuria after 20 wks of gestational with resolution to baseline by 12 wks postpartum

Group-2,3 and, 4 are combinedly designated as pregnancy induced hypertension (PIH)

Ref: ACOG Jan. 2002
Hypertension is defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg; or systolic blood pressure increase of >30 mmHg or diastolic blood pressure increase of >15 mmHg over first trimester of prepregnancy values.

Proteinuria refers to 24 hour urine protein >300 mg or dipstick protein >1 g/L

Ref: Hypertension in pregnancy American Heart Association.
# Differentiating points between groups

<table>
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<th>Clinical Finding</th>
<th>Chronic Hypertension</th>
<th>Gestational Hypertension</th>
<th>Pre-eclampsia</th>
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<tr>
<td>Time of onset of hypertension</td>
<td>&lt;20 Weeks of gestation</td>
<td>Usually in third trimester</td>
<td>&gt;20 Weeks of gestation</td>
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<tr>
<td>Degree of hypertension</td>
<td>Mild or severe</td>
<td>Mild</td>
<td>Mild or severe</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Absent</td>
<td>Absent</td>
<td>Usually present</td>
</tr>
<tr>
<td>Serum urate &gt;5.5 mg/dl (0.33 mmol/liter)</td>
<td>Rare</td>
<td>Absent</td>
<td>Present in almost all cases</td>
</tr>
<tr>
<td>Hemoconcentration</td>
<td>Absent</td>
<td>Absent</td>
<td>Present in severe disease</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Absent</td>
<td>Absent</td>
<td>Present in severe disease</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>Absent</td>
<td>Absent</td>
<td>Present in severe disease</td>
</tr>
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Chronic Hypertension

Incidence:
- Ranging from 0.5-4%, averaging 2.5%.
- Usually idiopathic 80%
- Renal cause 20%
- Incidence is high in black woman with +ve family history
Patient evaluation:

- Full medical history
- Meticulous physical examination
- Duration of HTN
- Anti hypertensive medication
- H/0 heart/renal disease
- Outcome of previous pregnancy
Physical examination:

Signs suggesting secondary medical cause

- Centripetal obesity, buffalohump, abdominal striae - Glucocorticoid excess
- A systolic bruit over abdomen or flank – Renal artery stenosis
- Radio femoral delay, decrease pulse in LL - Coarctation of aorta
- Clinical signs may demonstrate hypothyroidism, hyperthyroidism or growth hormone excess
Signs suggesting target organ damage (TOD)

LVH / diastolic dysfunction
- Shifting of apical impulse
- S4 on auscultation

Reflect atherosclerotic disease
- Decrease peripheral pulse
- Retinal change- on fundoscopic exam.
- Carotid bruit
Lab Test: To evaluate
- Test for TOD
- Potential secondary cause
- Other risk factors

In all patients:
- Urinalysis
- S. electrolyte
- S. creatinine
- E.C.G
- Lipid profile
In selected patient:

- CxR –P/A- To detect Cardiomegaly, heart failure, co-arctation of aorta
- Renal ultrasound: to detect renal disease
- Echocardiogram: to quantify LVH
- Renal duplex: to identify renal artery stenosis
- Urinary catecholamine: to detect phaeochromocytoma
- Urinary cortisol and dexamethasone suppression test: to detect cushing syndrome
- Plasma renin and aldosterone: to detect primary hyperaldosteronism
- Creatinine clearance
- 24 UTP
- S. uric Acid
- T.S.H
- OGTT
Complications:

Maternal
- Stroke/Heart failure
- DIC/ATN
- Abruptio placenta (0.4-10%)

Foetal
- Risk of prematurity (21-30%)
- Small for gestational age (10-15% risk)
- Intra uterine growth retardation
- Still birth
- Intrapartum foetal distress
Treatment of chronic hypertension in pregnancy

Three points to be considered

- When to start the treatment
- What drugs to be used
- Pregnancy category of the drug and level of recommendation
The FDA has a categorization of drug risks to the fetus that runs from: "Category A" (safest) to "Category X" (known danger--do not use!)

**Category A**

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
Pregnancy category of the drugs contd. 

**Category B**

Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
Pregnancy category of the drugs contd. .................

Category C
Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D
There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., 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).
Pregnancy category of the drugs contd. ........................

**Category X**

Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
When to start the treatment

a) Mild Hypertension (140-160/90-100)
   - If a woman is on drug, which is not recommended during pregnancy - switch to alternative drug preferred in pregnancy. (pregnancy category)
   - If a woman is on acceptable drug - (pregnancy category) continue her current medication.

b) Moderate – Severe hypertension: always treat the patient with drugs
Levels of evidence used to rate studies of the treatment of hypertensive disorder in pregnancy and to grade recommendations

Levels of evidence

I. Randomized controlled trial (RCT) that demonstrates statistically significant difference in at least 1 important outcome (e.g., survival or major illness)

OR

If difference is not statistically significant, an RCT with adequate sample size to exclude 25% difference in relative risk with 80% power, given the observed results
Levels of evidence contd. .............

III. Nonrandomized trial with contemporaneous control subjects selected by some systematic method (i.e., not selected by perceived suitability for one of the treatment options for individual patients) OR Subgroup analysis in an RCT

IV. Before–after study or case series (at least 10 patients) with historical control subjects drawn from other studies

V. Case series (at least 10 patients) without control subjects

VI. Case report (fewer than 10 patients)
Levels of evidence contd. ............

Grading system for recommendations
A. The recommendation is based on 1 or more studies at level I
B. The best evidence available was at level II
C. The best evidence available was at level III
D. The best evidence available was lower than level III and included expert Opinion

Recommended treatment of nonsevere hypertension in pregnancy

Treatment goal
- DBP 80–90 mm Hg (grade D)

First-line drug
- Methyldopa (grade A)

Second-line drugs
- Labetalol (grade A/B)
- Pindolol (grade A/B)
- Oxprenolol (grade A/B)
- Nifedipine (grade A/B)
Recommended treatment of nonsevere hypertension in pregnancy Contd. ……

Third-line drugs

Clonidine + hydralazine (grade A, but monotherapy preferable)

Metoprolol + hydralazine (grade A, but monotherapy preferable)

Clonidine (grade B)

Methyldopa + a second-line drug or hydralazine (grade D)

Special indications (renal or cardiac diseases)

Diuretics (grade D)

Drugs to avoid

Angiotensin-converting enzyme inhibitors (grade C)
Recommended treatment of nonsevere hypertension in pregnancy Contd. ..... 

Caution 
• Neuromuscular function and blood pressure should be closely monitored when using nifedipine + magnesium sulfate (grade D) 
• Foetuses and newborns of women taking atenolol, acebutolol or metoprolol should be observed for signs of β-blockage (grade D)
Recommended treatment of severe hypertension in pregnancy

First line drug

Hydralazine (grade-B)
Labetalol (grade-B)
Nifedipine (grade-B)

Refaractory to first line drugs

Diazoxide (grade-D)
Sodium nitroprusside (grade-D)
Groups of drugs

1. Alpha-adrenergic inhibitors
   Methyldopa (Dopegyt)
   **Adult Dose:**
   250mg PO bid/tid:
   Increase q2d prn; not to exceed 3g/d
   **Pregnancy category:** B. Usually safe

2. Centrally acting alpha-adrenergic agonists
   Clonidine
   **Adult dose:** Initial: 0.1mg PO bid
   Maintenance: 0.2-1.2mg/d bid/qid
   **Pregnancy category:** C
3. Beta-blockers

**Atenolol**
- **Adult dose**: 50-100mg PO qd
- **Pregnancy**: C - Last trimester

**Oxprenolol**
- **Adult dose**: 20-80 PO bid/tid
- **Pregnancy**: C - Last trimester

**Metoprolol**
- **Adult dose**: 50-400mg PO qd
- **Pregnancy**: C - Last trimester
Groups of drugs contd. ........

Labetalol

**Severe hypertension:** 100mg IV bid; not to exceed 2400mg/day BP 170/110mmHg: 20mg IV bolus subsequent dose-40mg followed by 80mg IV may be given 10-20mins interval. May also be administered as continuous IV infusion 1mg/kg/hr

**Non severe hypertension:** 200-600mg bid-tid

**Pregnancy:** C
4. Calcium channel blocker (CCB)

Nifedipine (Nifin)

**Adult Dose:** SR tab: 30-60mg PO qd; not to exceed 90-120mg/d

**Pregnancy:** C

Amlodipine

**Adult dose:** 2.5-10mg od

**Pregnancy:** C
Groups of drugs contd. .......

5. Diuretic

Hydrochlorothiazide

**Adult Dose:** 25-100mg PO qd; not to exceed 200mg/kg/d

**Pregnancy:** C

6. Vasodilator

Hydralazine (Apresoline)

**Severe hypertension:** 10-20mg/dose IV q4-6hr prn initial; increase to 40mg per dose prn. BP>170/110: 0.1-0.2mg/kg/day IV divided q4-6hr

**Non severe hypertension:** 10-50 mg bid-qid

**Pregnancy:** B usually safe
Pre-eclampsia

Incidence:
- 6% of all the general population
- Incidence varies with geographic location.

Predisposition:

a) Maternal personal risk factor
- First Pregnancy
- Age < 20yr. > 35yr.
- H/O Pre-eclampsia
Pre-eclampsia, predisposition contd. ......

- F/H of pre-eclampsia in a first degree relative
- Black race
- Obesity (BMI > 35)

b) Medical risk factor
- Ch.HTN
- Pre-existing DM
- Renal disease
- SLE
- Thrombophillia
c) Placental Risk factor
- Multiple gestation
- Hydrops foetalis
- Gestational trophoblastic disease
- Triploidy
Pre-eclampsia, pathogenesis

**Pathogenesis**: Disease of theories (chesley, 1978)

Some theories include:
- Endothelial cell injury
- Altered immune response
- **Imbalance between thromboxane & prostacyclin**
- Insufficient production of blocking antibody
- Compromised placental circulation
- Altered vascular reactivity
- Dietary & genetic factor
Clinical manifestation

Symptoms

- Visual disturbance
- New onset of headache
- Epigastric pain
- Non dependant oedema (may occur without oedema 39%)
- Wt gain 2 lb/ wk or sudden wt gain over 1-2 days
Clinical manifestation contd. ...

Physical Signs

• BP –
  
  SBP > 30mmHg or DBP > 25mmHg should be considered ominous

• Retinal vasospasm & oedema

• RUQ pain (Consider delivery)

• Clonus – Sign of severe pre eclampsia
Pre-eclampsia, prevention

Prevention:

1. **Aspirin**: Low dose (50-150mg) has been shown to be effective in the prevention of pre-eclampsia in high risk women (EBM).

2. **Calcium Supplement**: Controversial role.

3. **Fish oil supplement**: Not established yet. Trial is being conducted.
Treatment of hypertension in pre-eclampsia

Treatment:

Mild pre-eclampsia:
- Treatment of mother's pregnancy state
- Assessment of foetal status

Severe pre-eclampsia:
- Prevention of convulsion
- Control of maternal blood pressure
- Initiation of delivery
Eclampsia

Incidence:
- 0.2-0.5% of all deliveries
- May develop before 20wks of gestation
- 75% eclamptic seizure occur before delivery
- 50% post partum seizure occur in 1st 48hr after delivery, but may lasts as late as 6wks post partum.
Eclampsia clinical findings

- Seizure - One/ two/ many
- Hyperventillation
- Unconsciousness - lasts for variable time
- Fever is rare
- There may be seizure induced complication.
- Pulmonary oedema & retinal detachment may also be present.
Treatment of seizure in eclampsia

Magnesium Sulphate

**Dose:** Initial loading dose: 4-5gm Followed by maintenance dose: 2-3gm/hr to maintain levels 4-8gm/dl

**Precaution:** Causes loss of reflex, diplopia, flushing (8-12mg/dl)

Muscular paralysis, ventilatory failure (> 12mg/dl)

So require close monitoring

**Antidote:** I/V calcium gluconate-10%, 10-20ml

**Pregnancy:** A – safe in pregnancy
Treatment of seizure in eclampsia contd. ……

Phenytoin

**Dose:** 1000mg I/V over 1hr, followed by 500mg PO 10 hr later; not to exceed 50mg/min to avoid hypotension and arrhythmia

**Pregnancy:** C

Diazepam

- Initial I/V followed by continues I/V infusion
- Causes Respiratory depression, hypotonia, poor feeding, thermoregulatory problem in newborn
- Increases the incidence of kernicterus
Treatment of hypertension in eclampsia

All three drugs are grade – B recommendation

Hydralazine (Apresoline)

**Dose:** 10-20mg/dose IV q4-6hr prn initial; increase to 40mg per dose prn. BP>170/110: 0.1-0.2mg/kg/day IV divided q4-6hr

Nifedipine (Nifin)

**Dose:** SR tab: 30-60mg PO qd; not to exceed 90-120mg/d

Labetalol

**Dose:** 100mg IV bid; not to exceed 2400mg/day BP 170/110mmHg: 20mg IV bolus subsequent dose-40mg followed by 80mg IV may be given 10-20mins interval. May also be administered as continuous IV infusion 1mg/kg/hr
Post partum treatment of hypertension in eclampsia

- Hypertension may not resolved until 12wks post partum
- If DBP > 100mmHg post partum 24hrs antihypertensive can be prescribed
- At follow up after 1wk the need for antihypertensive medication may be re evaluated.

Recommended treatment option:

Methyldopa (grade-B)
Nifedipine (grade-B)
Timolol (grade-B)
Chr. Hypertension with super imposed pre-eclampsia

- Worsening HTN (SBP > 30mmHg, DBP > 15mmHg) with non dependant oedema and proteinuria – reflect development of super Imposed pre-eclampsia
- Usually occur early of pregnancy (26-34wk)
- Risk of super imposed pre-eclampsia is 25%
- Very difficult to differentiate from Ch. HTN
- Patient with LVH, cardiomegaly and increase creatinine are at risk for super imposed pre-eclampsia
Gestational Hypertension

• The level of blood pressure which requires treatment in pregnancy is not clear.

• Medication choices are similar to those used in ongoing treatment of pre-eclampsia.

• A suggested aim of treatment is to maintain blood pressure between 110 and 140 mmHg systolic and 80 to 90 mmHg diastolic without inducing undue side effects.
Summary

1. Prevention of maternal and perinatal complications and death is the main aim of treatment of hypertensive disorder of pregnancy.

2. An evidence based approach about pharmacologic treatment of hypertensive disorder in pregnancy provides a better opportunity for the physicians to address this problem.

3. Integrated approach by physicians and gynecologist for treating hypertension in pregnancy is required to reduce maternal mortality in Bangladesh.
Thank You