Pharm-12A01 Outline the pharmacology of agents used in the management of pregnancy induced hypertension.

Background

Hypertensive disorders of pregnancy are one of the most common obstetric medical problems

Various types of hypertensive disorders of pregnancy:
(1) **chronic hypertension** – HTN present before 20 weeks gestation complicates 3 ~ 5% of pregnancies, doubles the risk of pre-eclampsia

(2) **pregnancy induced hypertension** – new HTN presenting after 20 weeks without significant proteinuria, usu. resolve within 6 weeks of delivery

(3) **pre-eclampsia** – new HTN presenting after 20 weeks with significant proteinuria (≥ 300 mg/day)

*(brief note on pre-eclampsia not part of answer to this question)*

Exact aetiology unclear

Possible autoimmune reaction against placenta + inadequate implantation → placental ischaemia → release of vasoactive substances → widespread endothelial damage and vasospasm → multiorgan involvement

Effects of pre-eclampsia
CVS – widespread vasoconstriction → ↑SVR → ↑BP
CNS – headache, visual disturbance, hyper-reflexia, convulsions
RESP – pulmonary + laryngeal oedema, ARDS
RENAL – proteinuria, ↓GFR, oliguria, renal failure
LIVER – abnormal LFTs, liver rupture + subcapsular haemorrhage
HAEM – ↓plt number and fn, ↑fibrinogen/fibrin turnover, DIC, HELLP
FETUS – ↓placental perfusion, IUGR, placental abruption, preterm labour

(4) **eclampsia** – convulsive condition associated with pre-eclampsia

may occur ante-partum (40%), intra-partum (20%) or post-partum (40%)
Commonly Used Antihypertensives in Pregnancy

All current antihypertensive drugs cross the placenta to various degrees
The aims of antihypertensive therapy are:
- protect mother from dangerously high BP
- maximise fetal maturity and minimise fetal harm

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism of Action</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Methyldopa</strong></td>
<td>1 ~ 3 g PO / day (3 ~ 4 divided doses)</td>
<td>dual mechanism of action: (1) DOPA decarboxylase inhibition → ↓dopamine and catecholamine synthesis (2) converted to α-methylnorad → direct α2-agonist → ↓SNS tone</td>
<td>S/fx: postural hypotension, sedation, depression, bradycardia, headache, haemolysis</td>
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<td><strong>Labetalol</strong></td>
<td>PO: 200~1600 mg/day IV: 50 mg q20min</td>
<td>Specific α1- and non-specific β-adrenoreceptor antagonist α:β blocking effect depends on route → PO 1:3 vs IV 1:7</td>
<td>S/fx: bradycardia, fatigue, bronchospasm</td>
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<tr>
<td><strong>Hydralazine</strong></td>
<td>IV: 5 mg slow bolus, repeat</td>
<td>Activate GC → ↑cGMP → ↓[Ca^{2+}] → vasodilatation</td>
<td>S/fx: headache, tremor, flushing, palpitations</td>
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<tr>
<td><strong>Magnesium sulfate</strong></td>
<td>IV: 4 g bolus over 10 min then 0.5 ~ 1 g/hr for 24 hrs Repeat 2 ~ 4 g bolus if seizures recur</td>
<td>Calcium channel antagonist → reduce systemic and cerebral vasospasm ↑endothelial prostacyclin → smooth muscle relaxation NMDA receptor antagonist → anti-epileptic</td>
<td>MgSO₄ used in treatment of pre-eclampsia/eclampsia S/fx: Therapeutic 2 ~ 4 mM, blurred vision &gt; 5 mM, respiratory depression &gt; 7 mM, cardiorespiratory arrest &gt; 10 mM Mg crosses placenta → neonatal hypotonia and respiratory depression May synergise with CCBs</td>
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<tr>
<td><strong>Nifedipine</strong></td>
<td>PO 20 ~ 90 mg/day</td>
<td>L-type calcium channel antagonist</td>
<td>S/fx: headache, tachycardia, peripheral oedema, visualΔ</td>
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<tr>
<td><strong>Sodium nitroprusside</strong></td>
<td>IV infusion starting at 0.25 mcg/kg/min and titrate</td>
<td>Direct vasodilator (arterial &gt; venous)</td>
<td>Rapid onset and offset Used for maternal hypertensive emergencies May result in ↓BP Risk of cyanide toxicity to fetus</td>
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</tbody>
</table>

**Contraindications**:
- Labetalol: asthma
- Hydralazine: severe tachycardia
- Magnesium sulfate: severe tachycardia
**Agents to avoid**

ACE inhibitors and ARBs → teratogenic during first trimester, fetal renal dysfunction, oligohydramnios

Diuretics → prevents physiological volume expansion of pregnancy

β-blockers (except labetalol) → fetal bradycardia and intrauterine growth retardation

**Examiner’s comments** – 15.5% of candidates passed this question.

The **adverse and teratogenic effects** of antihypertensive medication on the foetus needed to be considered. This needed to be balanced against the benefits of treating the maternal hypertension. ACE inhibitors can cause renal damage in the foetus, and are not recommended for use during pregnancy.

**Methyldopa** is a very safe drug in pregnancy; it has been used for a long time. The **main pharmacokinetic and dynamic features** should have been highlighted. It is used to treat chronic hypertension.

**Hydralazine, magnesium**, and to a lesser extent **labetalol** are the main drugs used for acute or severe hypertension. Once again a **brief outline of their main features** was expected. This should include more than just the mechanism of action. Extra marks were awarded for additional detail.

Some candidates spent a lot of time on nitrates, calcium antagonists, and other beta-blockers. The use of volatile agents, propofol, opioids, benzodiazepines, and local anaesthetics as treatment options rarely attracted marks. Discussion of the pathophysiology of pre-eclampsia did not attract marks. Please use the generic names of drugs.