# OBSTETRIC ANAESTHESIA AND ANALGESIA

## OBSTETRIC ANAESTHESIA AND ANALGESIA

## OBSTETRIC PHYSIOLOGY – MATERNAL
- Describe the physiological changes and their implications for anaesthesia that occur during pregnancy, labour and delivery, in particular the respiratory, cardiovascular, haematological and gastrointestinal changes.
- Respiratory changes during pregnancy
- Cardiovascular changes in pregnancy
- Endocrine changes during pregnancy
- Other systems changes during pregnancy
- Outline the reference ranges for physiological and biochemical variables in pregnancy
- Describe the mechanism and consequences of aorto-caval compression in pregnancy
- Describe the changes in the anatomy of the maternal airway and their impact on airway management during anaesthesia
- Describe the changes in the anatomy of the maternal vertebral column, the spinal cord and meninges relevant to the performance of a central neuraxial block including epidural, spinal and combined spinal-epidural, with appropriate surface markings (refer to the Regional and local anaesthesia clinical fundamental)
- Describe the anatomy and physiology of pain in labour and childbirth

## OBSTETRIC PHARMACOLOGY
- Describe the influence of pregnancy on the pharmacokinetics and pharmacodynamics of drugs commonly used in anaesthesia and analgesia
- Describe the pharmacology of oxytocic agents with special reference to oxytocin derivatives, ergot derivatives and prostaglandins
- Describe the pharmacology of tocolytic agents with particular reference to beta 2 agonists, calcium antagonists, magnesium, inhalational anaesthetics, nitrates and NSAIDS
- Describe the pharmacology of agents used for the treatment of pre-eclampsia including magnesium, hydralazine and labetalol
- Outline the pharmacology of agents used in the management of pregnancy induced hypertension: PAST QUESTION 15%
- Explain the factors which influence the transfer of drugs across the placenta to the foetus
- Methods of transfer of substances across placenta:
- Write short notes on placental transfer of drugs: PAST QUESTION
- Outline the potential effects on the foetus and neonate of drugs administered during pregnancy
- Outline the potential effects on the neonate of drug administration in association with lactation

## NEONATAL PHYSIOLOGY
- Describe the transition from foetal to neonatal circulation and the establishment of ventilation
- Describe the utero-placental circulation and the principles of placental physiology as related to placental gas exchange and regulation of placental blood flow
- Foetal circulation
- Foetal O2 delivery
- Functions of placenta
- Describe the factors affecting the diffusion of gas at the placenta, including the Bohr and Haldane effects: PAST QUESTION 50%
- Explain the Bohr and Haldane effects in trans-placental gas exchange: PAST QUESTION 42%
- The foetus requires an O2 supply as it grows. How are these demands met? PAST QUESTION
OBSTETRIC PHYSIOLOGY – MATERNAL

Describe the physiological changes and their implications for anaesthesia that occur during pregnancy, labour and delivery, in particular the respiratory, cardiovascular, haematological and gastrointestinal changes.

- Changes begin from week 8 and † to plateau at 32 weeks → return to normal 2-8 weeks post delivery
- Changes due to:
  - Hormonal changes: circulating concentrations of oestrogen, progesterone, hCG
  - Mechanical effects: gravid uterus
    - Anatomical compression of chest
    - Diaphragm pushed upwards by 4cm
    - †AP + transverse diameter of chest wall (2-3cm)
  - †metabolic demand esp. during labour: –760% O2 consumption/ CO2 production during labour
  - placental circulation: †pressure, †resistance AV shunt

Respiratory changes during pregnancy

Describe the physiological changes that occur in respiratory function during pregnancy and what significance these changes have to anaesthesia: PAST QUESTION 44%

<table>
<thead>
<tr>
<th>Background</th>
<th>- Changes begin from week 8 and † to plateau at 32 weeks → return to normal 2-8 weeks post delivery</th>
</tr>
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<tbody>
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<td>- Changes due to:</td>
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<tr>
<td></td>
<td>- placental circulation: †pressure, †resistance AV shunt</td>
</tr>
</tbody>
</table>

Respiratory changes

1. **Anatomical**
   - Cephalad displacement of diaphragm (~4cm at term). In compensation → †diaphragmatic excursion → diaphragmatic breathing
   - Airway dilation → †airway resistance by ~35%
   - Progesterone → dilation of large airways → †anatomical dead space → †airway resistance
   - Upper airway oedema: oestrogen + progesterone → engorgement of blood vessels surrounding upper airway
   - Respiratory compliance: Lung compliance unaffected; †thoracic wall compliance by 20%
   - Relaxin → †AP/ transverse diameter of thoracic cage by 2-3cm → partially compensates for cephalad migration of diaphragm

2. **Lung volumes + capacities**
   - Increased:
     - MV: †TV (40%), †RR (10%)
     - resp drive 2o progesterone
     - Inspiratory capacity †10%
   - Decreased
     - FRC: effect of uterus; 420% erect and 450% sup
     - †RV
     - TLC 4.5% (doesn’t change much due to †AP + †IAP)
     - Expiratory capacity 430%
   - Unchanged: VC, CC, airways closure, Flow vol curves

3. **Ventilation**
   - †Minute ventilation + †resp alkalosis
     - Progesterone: stimulates resp centres shifts O2
     - MV †50% (†RR 10%; †VT 40%) → †70% during labour
     - Poco2 ↓ to 26-32mmHg with compensatory 4[Hb]
   - O2 consumption: †20% at term → †during labour 2o uterus
   - Other
     - Desat: cessation of uterine contractions are followed by hypoventilatory period producing desat
     - Dyspnœa: 2o progesterone + †metabolic demand unable to be compensated by †CO alone

**Implications**
- †tendency to hypoxia: †FRC; preox less effective + †risk basal atelectasis; †MRO2 with †metabolic rate
- †wash in of volatiles: †alveolar vent 50-70% †term + †FRC (partly offset by †CO)
- †risk awareness in GA
- †aspiration risk: †pressure, †LES time, †gastric emptying
- Difficult airway → †failed intubations + difficult BVM, may be due to:
  - Airway oedema + friability
  - Bleeding with NPA
  - †mucosal vascularity
  - weight gain, breast enlargement, †chest diameter
  - poorly applied cricoid pressure
- maintenance of “normal” lowered levels of PaCO2 during mechanical ventilation
- Consider valsalva

**ABG in pregnancy**
- Respiratory alkalosis with complete renal compensation
Implications

- Spinal/ epidural → SY block effects BP significantly (as SNS activation maintaining CO and BP)

After birth

- FRC + RV return to normal <48hrs
- TV returns to normal <5days

Cardiovascular changes during labour

- PaO2: normal to slightly < despite TO2 consumption
  - O2 flux measured as CO x blood O2 content
  - PaCO2 < 40 by 10%
  - Hb decreased by 20%
  - 2,3DPG: maintains OHDC despite CO2 production
  - Hypermetabolic state
  - Base deficit reflects renal loss of HCO3
    - HCO3 excretion by 10%
    - CO2 production by 20%

- 1200-1500ml by term
  - SVR by 35%
  - DBP > SBP
  - HR by 25%
  - Hb by 20%
  - Progesterone induced vasodilation

- PaCO2, cardiac output, and alveolar gas equation
  - PaCO2 ~32mmHg
  - PaO2 ~102mmHg

- Hb by 20%
  - Myocardial contractility unchanged
  - AV shunt
  - Impaired VR

- Urinary output
  - ↑plasma vol (45%) > RBC vol → dilutional anaemia
  - ↓intravascular vol → ↑VR

- Haemodynamic changes:
  - ↓SVR by 25% → reflex response to ↓BP
  - ↓afterload by 30%

- preload (NB gravid uterus can compress IVC → impaired VR)

- ↑blood volume
  - ↑circulatory concentrations of oestrogen, progesterone, hCG
  - Elevated cardiac output
  - Anatomical compression of chest
  - ↑transverse diameter of chest wall (2-3cm)

- ↑metabolic demand esp. during labour: ↑60% O2 consumption/ CO2 production during labour

- placental circulation: ↓pressure, ↓resistance AV shunt

- ↓placental perfusion
  - ↓placental circulation
  - ↓VR + transverse diameter of chest wall (2-3cm)
  - ↑uterine venous pressure

- ↑oxygen consumption/ CO2 production during labour

- ↓TPR
  - ↓SVR by 35% → ↓DBP > 4SBP, ↓MAP by 10% (despite ↑in CO)
  - ↓vasodilation (2% progesterone, prostaglandins, down regulation of α R's → ↓flow to kidneys, gut, heart, breasts, skin)
  - ↓placenta → ↓pressure, ↓resistance AV shunt → flow passive + pressure dependent
  - ↓uteroplacental circulation by 10%
- significant in fixed CO states esp. labour e.g. AS, MS, HOCM
- requires left tilt between 15-30° to avoid aorto-caval compression

After birth
- return to non-pregnant levels <2 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Direction</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume</td>
<td>↑</td>
<td>35%</td>
<td>45%</td>
<td>50%</td>
<td>Peaks between 32-36th week, decreases slightly thereafter</td>
</tr>
<tr>
<td>Blood volume</td>
<td>↑</td>
<td>5%</td>
<td>15%</td>
<td>20%</td>
<td>Increases less than plasma volume, resulting in the fall in haematocrit to 33%</td>
</tr>
<tr>
<td>HR</td>
<td>↑</td>
<td>15%</td>
<td>18%</td>
<td>25%</td>
<td>Increases progressively throughout</td>
</tr>
<tr>
<td>SV</td>
<td>↑</td>
<td>20%</td>
<td>25%</td>
<td>30%</td>
<td>Increases progressively throughout</td>
</tr>
<tr>
<td>CO</td>
<td>↑</td>
<td>20%</td>
<td>40%</td>
<td>45%</td>
<td>Increases throughout and dramatically in labour</td>
</tr>
</tbody>
</table>

Endocrine changes during pregnancy

**Main hormones involved:**
- **B-human chorionic gonadotropin (bHCG)**
  - Glycoprotein secreted by placenta similar to LH, FSH, and TSH
  - Life of corpus luteum (secretes progesterone + oestrogen. If no embryo then progesterone secretion stops + corpus luteum degenerates)
- **hPL (human placental lactogen)**
  - Polypeptide hormone similar to GH
  - Secreted by syncytiotrophoblast cells of placenta
  - hPL ↑s throughout pregnancy ∝ foetal + placental growth
  - Function: nutrients for foetus through manipulation of maternal metabolism:
    - ↑maternal lipolysis → ↑FFAs
    - ↓maternal peripheral insulin sensitivity → ↓peripheral utilisation of glucose + ↑ maternal plasma BSL
  - breast growth / development: mimics action of PRL
- **Progesterone**
  - Steroid hormone
  - Secreted by corpus luteum in early pregnancy, and by placenta in 2nd + 3rd trimesters
  - Functions:
    - Prepares endometrium for implantation + promotes growth of endometrium following implantation
    - Uterine muscle relaxation → ↓myometrial contractions + preventing miscarriage
    - Cervical mucus plug – protects foetus from ascending infection
    - Development of milk glands
- **Oestrogen**
  - 3 oestrogens synthesised by placenta: oestradiol, oestrone, oestriol
  - Oestriol: produced from foetal adrenal precursor dehydroepiandrosterone sulphate; main role is to ↑uteroplacental blood flow
  - Functions:
    - Synthesis of uterine growth
    - Sensitisation of myometrium to oxytocin in preparation for labour

Other pregnancy related endocrine changes:
- **RAAS**
- **Thyroid hormones**
  - Oestriol stimulates liver to synthesise additional thyroxine binding globulin → ↑TRH secretion 2+ to →ve feedback loop → ↑TSH secretion by pituitary → ↑T3 + T4
- **Prolactin**
  - Oestrogen stimulates ↑pituitary secretion of prolactin
  - Function: prepares breasts for lactation
- **PTH**
  - Ca2+ transported across placenta for foetus → maternal absorption of dietary Ca2+ cannot meet placental loss → ↑PTH secretion → ↑bone reabsorption, renal tubular Ca2+ reabsorption + activation of vit D → ↑Ca2+ to normal

Other systems changes during pregnancy

**GI**
- ↑risk GORD due to:
  - ↓LOS tone: progesterone induced smooth muscle relaxation
  - gravid uterus displaces stomach + diaphragm upwards → ↓angle of oesophagus as it passes through diaphragm
  - ↑intraabdominal pressure
  - delayed gastric emptying in labour
  - gastric pH: ↑gastric vol, ↓gastric pH → aspiration has ↑degree of lung injury (Mendelson’s syndrome – pneumonitis from pulmonary aspiration of acidic gastric contents under GA)
- **Liver**:
  - glycogen depletion, fatty changes, ↑TALP
  - **Implications**:
    - ↑aspiration risk
    - ↓metabolism of drugs

**Haemalogical**
- Physiological anaemia: plasma vol ↑ > RBC vol → dilutional anaemia
  - ↑plasma vol 2o oestrogen activation RAAS → Na + H2O retention
  - ↑RBC vol 2o EPO synthesis
- ↑WCC due to ↑oestrogen → ↑neutrophils + monocytes
- ↓platelet count due to haemodilution + shorter platelet lifespan
- hypercoagulable state: ↑IFI, VII, VIII, IX, X + ↓ATII
plasma oncotic pressure
- ESR 2o plasma globulin + fibrinogen

Implications:
- DV due to plasma vol
- ↑risk VTE
- ↑edema due to oncotic pressure
- ↓albumin = ↓PB of drugs

Renal
- anatomical + physiological changed to kidneys + ureters
- dilution of ureters + renal pelvis: 2° mechanical obstruction by gravid uterus + progesterone mediated smooth muscle dilatation → ↑risk UTI + pyelo
- ↑GFR: ↑RBF by 50% due to ↑CO
- ↓serum Cr and ↓urea
- initially ↓uric acid 2° ↑GFR then hyperuricaemia 2° tubular reabsorption of uric acid
- glycosuria: tubular reabsorption of glucose cannot keep up with ↑GFR
- proteinuria: tubular protein reabsorption mechanisms insufficient to match 50% ↑in GFR

- Implications
  - ↑clearance of drugs

CNS
- ↑size pituitary: sheehans syndrome
- ↓MAC of volatile anaesthetics 45°-40% due to:
  - Progesterone: sedative effects
  - B-endorphins: analgesic in labour

- Epidural and subarachnoid space
  - ↑Epidural pressure to +1cmH₂O 2° engorgement of epidural veins 2° to mechanical compression of IVC by gravid uterus
  - ↑risk accidental venous cannulation when doing epidural
  - ↑CSF pressure changed during pregnancy byt ↑ up to 70cmH₂O in 2° stage of labour

Hepatic
- ↑GGT, ALT, LDH
- ↑ALP (originates from liver + placenta)
  - Hepatic protein production does not keep pace with ↓plasma vol → ↓plasma [protein]; ↓albumin; ↓plasma cholinesterase (prolonged sux action)

MSK
- ligaments lax due to placental secretion of relaxin

Outline the reference ranges for physiological and biochemical variables in pregnancy

<table>
<thead>
<tr>
<th>Value</th>
<th>Pregnancy RR</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>11-15</td>
<td>Dilutional anemia</td>
</tr>
<tr>
<td>Hct</td>
<td>32-36%</td>
<td>↓</td>
</tr>
<tr>
<td>WBC</td>
<td>6-20</td>
<td>↑</td>
</tr>
<tr>
<td>Plt</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Total protein conc</td>
<td>↓</td>
<td>↑amt, ↓conc</td>
</tr>
<tr>
<td>Albumin</td>
<td>↓</td>
<td>↑amt ↓conc</td>
</tr>
<tr>
<td>Globin</td>
<td>0</td>
<td>↑amt and ↑conc</td>
</tr>
<tr>
<td>Na</td>
<td>↓</td>
<td>↑body water</td>
</tr>
<tr>
<td>Osmol</td>
<td>↓</td>
<td>↑body water</td>
</tr>
<tr>
<td>Urea</td>
<td>↓</td>
<td>↑filtration</td>
</tr>
<tr>
<td>Creat</td>
<td>↓</td>
<td>↑filtration</td>
</tr>
<tr>
<td>Uric acid</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>↓</td>
<td>↑utilization</td>
</tr>
<tr>
<td>PaO₂</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>PCO₂</td>
<td>↓</td>
<td>Progesterone</td>
</tr>
<tr>
<td>HCO₃</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>BE</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>↑glucose ↑protein</td>
<td>Saturation</td>
</tr>
</tbody>
</table>

Describe the mechanism and consequences of aorto-caval compression in pregnancy

Aorto-caval compression:
- compression of IVC + aorta by gravid uterus → ↓VR + ↓CO → nausea, pallor, hypotension, cardiovascular collapse when supine (resolves in lateral position)
- ↓placental blood flow 2o ↑uterine venous pressure → ↓uteroplacental circulation
- VR via collaterals of paravertebral epidural veins → azygous
- Most non-anaesthetised patients are able to compensate to some degree for aortocaval compression through 2 mechanisms:
  - 1. ↑SY outflow → ↑SVR + ↑HR
  - 2. Some blood bypasses compressed IVC through collateral pathways: azygous, paravertebral, epidural veins
- NB: GA + neuraxial block abolish SY response to aortocaval compression → severe hypotension or cardiac arrest may develop when patient supine
Describe the changes in the anatomy of the maternal airway and their impact on airway management during anaesthesia

Changes begin from week 8 and ↑ to plateau at 32 weeks → return to normal 2-8 weeks post delivery

Changes due to:
- Hormonal changes: ↑ circulating concentrations of oestrogen, progesterone, hCG
- Mechanical effects: gravid uterus
  - Anatomical compression of chest
  - Diaphragm pushed upwards by 4cm
  - ↑ AP + transverse diameter of chest wall (2-3cm)
- ↑ metabolic demand
- Placental circulation: low pressure, low resistance AV shunt

Anatomical
- Cephalad displacement of diaphragm (~4cm at term). In compensation → ↑ diaphragmatic excursion → diaphragmatic breathing
- Relaxin → ↑ AP/ transverse diameter of thoracic cage by 2-3cm → partially compensates for cephalad migration of diaphragm
- Progesterone → dilation of large airways
- Respiratory compliance: Lung compliance unaffected; ↓ thoracic wall compliance by 20%
- Upper airway oedema: oestrogen + progesterone → engorgement of blood vessels surrounding upper airway
- Airway dilatation → ↓ airway resistance by ~35%
- Breast enlargement, ↑ chest diameter, airway oedema + friability → intubation + BVM ↑ difficulty

Impact on airway management
- difficult airway + ↑ failed intubations
- difficult BVM
- difficult laryngoscopy
- bleeding with NPA

Describe the changes in the anatomy of the maternal vertebral column, the spinal cord and meninges relevant to the performance of a central neuraxial block including epidural, spinal and combined spinal-epidural, with appropriate surface markings (refer to the Regional and local anaesthesia clinical fundamental)

Changes in maternal anatomy lead to:
- difficulties in performance of regional techniques (spinal, epidural, CSE)
- less LA required for spinal/ epidural
- changes to pattern of spread → ↑ cephalad spread (↑ lumbar lordosis, ↓ thoracic kyphosis, ↑ vol and ↑ density of CSF)

Changes in anatomy of:
1. Vertebral column
   - Superficial: ↑ fat → ↓ landmarks; ↑ distance to space; PET related oedema
   - Ligamentous: hormones → softening of ligaments → poorer sensation of LOR → ↓ dural puncture
   - Skeletal:
     - ↑ lumbar lordosis → ↓ space between vertebrae → difficult to find space
     - Tuffiers line (L4) moves cephalad due to ant pelvic tilt
     - Apex of lordosis moves cephalad; ↓ thoracic kyphosis → ↑ spread of spinal
   - Functional
     - Functional limitation of vertebral column 2o gravid uterus → positioning more difficult; flexion of lumbar spine more difficult
     - Labour pain: unable to maintain ideal position
2. Epidural space:
   - Engorged venous plexus 2o ↑ circulating vol + aortocaval compression → worse during contraction + obesity; ↑ risk of intravascular catheter + bloody tap
3. Spinal cord / meninges
   - ↑ sensitivity to LA: progesterone mediated (↑ dose 25%)
     - direct effect on membrane excitability
     - indirect action on NTs
     - ↑ permeability of neural sheath
     - potentiation of endogenous opioids
     - potentiation of GABA-mediated ↑ Cl- conductance
   - bulging of meninges during contraction → ↑ risk dural puncture
   - CSF: ↑ pressure; ↓ density; ↑ baricity of LA → ↑ cephalad spread; ↓ vol? → ↑ cephalad spread
Describe the anatomy and physiology of pain in labour and childbirth

**Labour stages**
- dilation of cervix
- full cervical dilation until delivery of baby
- delivery of placenta

1st stage
- pain impulses: uterine contraction + cervical dilation
  - myometrial ischaemia → release bradykinin, histamine, 5HT
  - stretch + distension lower uterine segment → mechanoRs
- afferent: Ad + C fibres via SV chain → T10-L1
- visceral → dull, poorly localised, referred (back), + N&V, rhythmic

2nd stage
- impulses: distension of pelvic floor, vagina, perineum
- afferent: pudendal nerves: S2-4 (large so poorly blocked by LA)
- somatic: well localised, sharp or burning; not referred; constant; not usual

**Effect of labour pain on maternal physiology**
- CVS: TC0 25-50% 2o tachycardia 2o pain; epidural → ↓Cl by 3-6% and
- SNS: ↑circulating catecholamines
- Resp: ↑MV = ↓maternal PaCO2 → maternal alkalosis → LEFT shift OHDC → ↓O2 released to foetus and ↓CO2 carried → risk of fetal hypercapnoea + hypoxia

**Factors affecting pain in labour**
- Physical: age, parity, infant size, foetal presentation, speed of dilation, frequency of contractions, stage of labour, maternal positioning in labour
- Psychological: knowledge/ preparation for childbirth, expectation of pain, prior experience, fear + anxiety, education, birthing partner, culture/ beliefs
**OBSTETRIC PHARMACOLOGY**

Describe the influence of pregnancy on the pharmacokinetics and pharmacodynamics of drugs commonly used in anaesthesia and analgesia

**Outline the influence of pregnancy on pharmacokinetics: PAST QUESTION 64%**

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
<td><strong>VD</strong></td>
<td><strong>Progestrone: oestrogen ratio</strong></td>
<td><strong>RBF (75%) and GFR (50%)</strong></td>
</tr>
<tr>
<td>PO absorption</td>
<td>↑ plasma vol: ↓VD polar drugs e.g. NDMRs</td>
<td>→ progesterone → induces hepatic enzymes</td>
<td>→ clearance of drugs dependent on renal excretion (polar, water soluble drugs e.g. enoxaparin)</td>
</tr>
<tr>
<td>gastric motility</td>
<td>↑ body fat (important for lipid soluble drugs)</td>
<td>→ oestrogen → inhibits hepatic enzymes</td>
<td></td>
</tr>
<tr>
<td>intestinal absorption 2→ intestinal blood flow</td>
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</tr>
<tr>
<td>↑ risk aspiration → ↑ absorption PO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N+V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhalational</strong></td>
<td><strong>plasma protein 2 diffusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑M/SC / transdermal absorption</td>
<td>4albumin → ↑free % acidic drugs; ↓dose required; ↑transplacental transfer of drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓</td>
<td>4A1AGP by 30% → ↑free %basic drugs; ↓dose required; ↑transplacental transfer of drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ IV: ↑onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epideral/spinal</strong></td>
<td><strong>Ionisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uptake of volatiles due to: ↑CO, ↑alveolar ventilation, ↓FRC. Net effect minimal</td>
<td>↓pH alters ionisation based on pKa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓MAC (progestosterone effect)</td>
<td>↑MV = mild resp alkalosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>engorged epidural veins esp. during contractions → systemic absorption + potential toxicity of LAs + ↑ plasma protein→ 4CC/ CNS ratio</td>
<td>↑transplacental transfer of drugs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacodynamics Background**

- may pharmacodynamics issue with pregnancy is whether drugs have effect on:
  - uterus
  - foetus (via placental drug transfer)
  - lactation
- route
  - may be less inclined to use PO given change to pharmacokinetics: (↓PO absorption, ↓gastric motility, ↑↑N+V)
  - ↑Skin blood flow → ↑absorption through skin
  - IV route has faster onset
  - ↑uptake of inhalational
  - Epidural/ spinal routes common
- Dose
  - Changes to VD + plasma protein binding + ionisation → change in dose required
  - ↑plasma vol → ↓VD polar drugs like NDMR so ↓dose
  - ↑Body fat → ↑dose lipid soluble drugs required
  - ↓plasma protein → ↓free % acidic drugs → ↓dose
  - oestrogen + progestosterone have effects on live enzymes for metabolism → may need dose change
- toxicity / side effects
  - be aware of transplacental transfer of drugs

After epidural injection in a healthy term pregnant woman, discuss the factors influencing the distribution of bupivacaine to a) the maternal CSF and spinal cord, b) the maternal circulation, c) the foetus: PAST QUESTION

**Background:**

- Bupivacaine = long acting amide LA
- epidural route of LA (+/- opioid) = common method of labour analgesia
  - MoA: LA → epidural space → diffuse into CSF → diffuse into SC → block pain transmission
  - Mechanism of toxicity: LA doses → epidural space →
    - ascends CSF → brainstem → high block
    - maternal systemic circulation → foetal circulation
- diffusion of bupivacaine across all membranes follows Fick's law of diffusion

\[
D = \frac{\text{sol} \times \Delta \text{conc}}{\sqrt{MW \times \text{surf area}}} \times \frac{1}{\text{thickness}}
\]

- there is constant diffusion between the 4 compartments:
  - Epidural
  - CSF/ spinal cord
  - Maternal circulation
  - Foetal circulation

**a) maternal CSF/ spinal cord**

- Diffusion to CSF/ spinal cord is 1+ mode of therapeutic effect of LA
- Dependent on conc gradient between CSF + spinal cord
  - Dose: ↑dose or ↑concentration → ↑diffusion
  - Volume: ↑vol → ↑arachnoid membrane area in contact with LA → ↑diffusion
  - solubility
    - protein binding: bupivacaine = 98% PB (including tissue protein) → remains at site of administration and limits absorption
    - ionisation: bupivavaine ~15% unionised at pH 7.4 (pKa 8.1) → only unionised will diffuse → (NB NaHCO3 → ↑pH →...
### Obstetric Anaesthesia and Analgesia (Inc Neonatal)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF bulk flow</td>
<td>Maintain conc gradient + facilitates ongoing diffusion</td>
</tr>
</tbody>
</table>
| **b) Maternal circulation** | - To reach maternal systemic circulation, bupivacaine must cross epidural space into epidural veins  
- Dependent on conc gradient between epidural space + vein  
- **Dose**: ↑ dose → ↑ conc gradient → ↑ diffusion into blood  
- **SA**: pregnancy → ↑ CO → engorgement of epidural vessels → ↑ SA → ↑ diffusion into circulation; use of vasoconstrictor will ↓ A → ↓ diffusion  
  - NB coadministered adrenaline → vasoconstriction → ↓ SA → ↓ diffusion into systemic circulation  
  - ↓ blood flow (↑ CO during labour) or ↑ epidural venous drainage with aorto-caval compression → ↓ P2 → maintain conc gradient for diffusion |
| **c) Fetus** | - Transfer dependent on conc gradient between maternal circulation and placenta  
- **Dose**: ↑ dose → ↑ conc gradient → ↑ diffusion across placenta  
- **Maternal protein binding**: ↑ PB (98%) but ↑ competition binding sites on AAG by progesterone → ↑ free fraction ↑ P2  
- Unionised fraction; maternal alkalosis during labour (↑ MV) → ↑ unionised portion → ↑ solubility → ↑ diffusion  
- Foetal acidosis → ion trapping |

*↑ unionised fraction*
### Outline briefly the pharmacology of oxytocin: PAST QUESTION 54%

Drugs used to *produce uterine tone (induction/acceleration of labour/treatment of PPH) = oxytocics*

<table>
<thead>
<tr>
<th>Oxytocin</th>
<th>Ergometrine</th>
<th>PGF2α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>Ergot alkaloid</td>
<td>Prostaglandin</td>
</tr>
<tr>
<td>Uses</td>
<td>PPH (2&lt;sup&gt;nd&lt;/sup&gt; line)</td>
<td>PPH (3&lt;sup&gt;rd&lt;/sup&gt; line)</td>
</tr>
<tr>
<td>Pres</td>
<td>CCS or IV&lt;-&gt;IM, intranasal 5 or 10 IU/ml → syntocin 1ml injection + 500ug ergometrine for PPH (intrauterine) → syntometrine</td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>Binds to GPCR on smooth muscle cells  - ↑permeability of myometrial cell membrane to K&lt;sup&gt;+&lt;/sup&gt; → ↓membrane potential + ↑cell membrane excitability → ↑ contraction  - opening of Ca&lt;sup&gt;2+&lt;/sup&gt; channels → ↑Ca&lt;sup&gt;2+&lt;/sup&gt; influx → release of Ca&lt;sup&gt;2+&lt;/sup&gt; by SR → smooth muscle contraction  Dose related ↑amplitude + frequency of contraction no ↑basal tone (i.e. complete relaxation between contractions)  Structurally similar to ADH  Lactation via contraction of myoepithelial cells in mammary glands</td>
<td>Acts on α + 5HT2 Rs on uterine + vascular smooth muscle → uterine contraction with ↑basal tone  Activation of adrenergic + 5HT R + D2 Rs (emesis)  Act via GPCR on myometrial cells → ↑Ca&lt;sup&gt;2+&lt;/sup&gt; → cervical ripening + uterine contractility with ↑basal tone + relaxation of cervix  Classes: - PGE1 analogues: misoprostol - E type (PGE2) e.g. Dinoprost: tablet/ pessary; induction of labour/ ripening of cervix - F type (PGF&lt;sub&gt;2α&lt;/sub&gt;) e.g. Dinoprost: myometrial injection only as if given IVI → PGs metabolized in pulmonary circuit → ↑↑PVR → ↑↑bronchospasm → DEATH</td>
</tr>
<tr>
<td>CNS</td>
<td>headache, N+V</td>
<td>N+V</td>
</tr>
<tr>
<td>CVS</td>
<td>↓MAP post bolus 2° vasodilatation → ↓SVR → reflex ↑HR  ECG: ↑QT, T wave flattening (2° perfusion coronary arteries)</td>
<td>Vasoconstriction → ↑SVR, ↑BP  coronary vasoconstriction  bradycardia 2o TVA tone  ↑BP. NB arge doses can vasodilate → 4SVR, 4BP  Dinoprost can cause CVS collapse if enters circulation after amniotic injection</td>
</tr>
<tr>
<td>Resp</td>
<td>Pulmonary oedema</td>
<td>Pulmonary oedema</td>
</tr>
<tr>
<td>AS</td>
<td>↑uterine tone; ↑frequency at low dose, tetanic contraction at high dose) foetal distress; lactation  ↑force + frequency of uterine contraction  ↑uterine tone; ↑contraction of cervix</td>
<td>Vomiting +++  Bronchospasm/ bronchoconstriction/ worsening asthma</td>
</tr>
<tr>
<td>Other</td>
<td>minimal ADH action</td>
<td>Uterine pain, uterine rupture, foetal distress</td>
</tr>
<tr>
<td>Feotal</td>
<td>In distressed foetus → ↓uterine blood flow, ↑distress, uterine spasm/rupture / ↑risk of foetal asphyxia  Ultrasound/ foetal non-stress test</td>
<td>Uterine spasms  Uterine pain, uterine rupture, foetal distress</td>
</tr>
<tr>
<td>Toxicity/ SE</td>
<td>NB synthetic syntocin doesn’t exhibit ADH action  Uterine rupture (foetal asphyxia) NB cannot be administered in same line as blood / plasma products → rapid plasma hydrolysis (oxytocinase) + inactivation</td>
<td>Cl in preeclampsia due to HTN  N+V 2° stimulation of CTZ, blurred vision/ headache 2o vasoconstriction, seizures  AMI, APO 2o ↑TSVR → ↑artery tension + coronary artery vasoconstriction  N+V; diarrhoea; bronchoconstriction  Vasodilation at large doses → 4SVR, 4BP  Genital oedema / anaphylaxis  Diarrhoea 2o stimulation of intestinal smooth muscle</td>
</tr>
<tr>
<td>Route/ dose</td>
<td>1V 5-10 IU bolus IV followed by titration of 1-2 units/hr q15-30mins until uterine contraction occurring every 2-3 mins IV1 / IM1 / intranasal  500microg IMI avoid IV due to N+V+++  Intramyometrial injection  Misoprostol: PO/ SL/ PV: 400-800microg  Dinoprostone: 10-20mg PV</td>
<td>Misoprostol: 2-3r (peak plasma time 14mins)  Dinoprostone: 10min</td>
</tr>
<tr>
<td>Onset</td>
<td>Minutes 1min IV; 5min IM; 10min PO</td>
<td>Misoprostol: 3hr  Dinoprostone: 2-3hr</td>
</tr>
<tr>
<td>Duration</td>
<td>1hr</td>
<td>PO 3-6hr</td>
</tr>
<tr>
<td>A</td>
<td>no PO bioavailability → broken down by chymotrypsin</td>
<td>Misoprostol: 80% PB</td>
</tr>
<tr>
<td>D</td>
<td>Vd 0.3L/kg</td>
<td>Misoprostol: 20-40min; urine 80%  Dinoprostone: ½ life 3-5mins; urine (small amount in faeces)</td>
</tr>
<tr>
<td>M</td>
<td>Rapid via oxytocinases in liver + kidney + ?plasma</td>
<td>Liver  Misoprostol: ↑+ rapid 1° pass metabolism → misoprostol acid (active)  Dinoprostone: maternal lungs, spleen, tissues via oxidation of side chains to 9 inactive metabolites</td>
</tr>
<tr>
<td>E</td>
<td>t1/2 1-7mins urine</td>
<td>Bile  Misoprostol: 3hr  Dinoprostone: 2-3hr</td>
</tr>
</tbody>
</table>

**Chem**
- Endogenous nonpeptide hormone produced in hypothalamus and stored / released from posterior pituitary  
- Syntocin = synthetic form (minimal ADH action)

**Uses**
- Augmentation of labour (accelerate / induce)  
- Tuterine tone + PPH aid lactation

**Pres**
- CCS or IV<->IM, intranasal 5 or 10 IU/ml → syntocin 1ml injection + 500ug ergometrine for PPH (intrauterine) → syntometrine

**Action**
- Binds to GPCR on smooth muscle cells  
  - ↑permeability of myometrial cell membrane to K<sup>+</sup> → ↓membrane potential + ↑cell membrane excitability → ↑ contraction  
  - opening of Ca<sup>2+</sup> channels → ↑Ca<sup>2+</sup> influx → release of Ca<sup>2+</sup> by SR → smooth muscle contraction  
  - Dose related ↑amplitude + frequency of contraction  
  - no ↑basal tone (i.e. complete relaxation between contractions)  
  - Structurally similar to ADH  
  - Lactation via contraction of myoepithelial cells in mammary glands

**Uses**
- Syntocin = synthetic form (minimal ADH action)  
- from posterior pituitary  
- Endogenous nonapeptide hormone produced in hypothamalus and stored / released

**Toxicity/ SE**
- NB synthetic syntocin doesn’t exhibit ADH action  
- Uterine rupture (foetal asphyxia)  
- NB cannot be administered in same line as blood / plasma products → rapid plasma hydrolysis (oxytocinase) + inactivation

**Misoprostol**
- 20-40min; urine 80%  
- Dinoprost: maternal lungs, spleen, tissues via oxidation of side chains to 9 inactive metabolites

**Dinoprostone**
- ½ life 3-5mins; urine (small amount in faeces)

**Misoprostol**
- 80% PB  
- Misoprostol: 20-40min; urine 80%  
- Dinoprostone: ½ life 3-5mins; urine (small amount in faeces)

**Dinoprost**
- Maternal lungs, spleen, tissues via oxidation of side chains to 9 inactive metabolites

**Misoprostol**
- 80% PB  
- Misoprostol: 20-40min; urine 80%  
- Dinoprostone: ½ life 3-5mins; urine (small amount in faeces)
Give a brief account of the pharmacological actions and side effects of prostaglandins used in obstetrics: PAST QUESTION

**Prostaglandin**
- an eicosanoid
- hormone like lipid compounds derived from FAs
- 20 carbon atoms
- formed from arachadonic acid via COX enzymes
- MOA: Act via GPCR
  - cervical ripening + T
erine contractility
- Coordinated contractions of uterus with Tbasal tone + relaxation of cervix

**PGE1**
- PGE1 analogues: misoprostol
- Side effects:
  - GIT: diarrhea, vomiting, abdo pain, flatulence
  - Dizziness
  - Rashes

**PGE2**
- E type (PGE2) e.g. Dinoprostone:
  - tablet/ pessary; induction of labour / ripening of cervix
- F type (PGF2α) e.g. Dinoprost:
  - myometrial injection only as if given IVI
  - PGs metabolised in pulmonary circuit
  - PVR → death
- Side effects:
  - CVS: acute HTN, cardiac arrhythmia
  - Resp: bronchoconstriction/ pulmonary oedema/ hypoxia (caution in asthma)
  - GIT: smooth muscle contraction, vomiting, diarrhea
  - Temperature, shivering
  - Uterine rupture
  - ↑IOP: beware glaucoma

Describe the pharmacology of tocolytic agents with particular reference to beta 2 agonists, calcium antagonists, magnesium, inhalational anaesthetics, nitrates and NSAIDS

Tocolytics are agents which ↓uterine tone. Rarely successful >24-48hrs
- β2-agonists (A)
- Ca2+-channel antagonists (A)
- COX Inhibitors
- MgSO4 (A)
- Nitrates (A)
- Volatile anaesthetic agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>B2 agonist</th>
<th>Ca2+ channel antagonist</th>
<th>COX inhibitors</th>
<th>MgSO4</th>
<th>Nitrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Salbutamol</td>
<td>Nifedipine</td>
<td>Indomethacin</td>
<td>Mg2+</td>
<td>GTN, amyl nitrate</td>
</tr>
<tr>
<td>MoA</td>
<td>Activate GPCR, ↑cAMP → intracellular Ca2+ relaxation</td>
<td>Block L type Ca2+ channels → relaxation</td>
<td>Inhibit prostaglandin synthesis (vital for uterine contraction)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Describe the pharmacology of agents used for the treatment of pre-eclampsia including magnesium, hydralazine and labeltol

**Preeclampsia**
- Hypertensive disease of pregnancy
- Associated with widespread endothelial dysfunction → placent al ischaemia + multi-organ dysfunction
- Associated with impairment in:
  - CVS/ resp: vasoconstricted, hypovolaemic, ↓CO, ↑risk APO, ↑vascular permeability, narrow airways
  - Haem: ↑hypercoagulable → thrombocytopenia, DIC
  - Renal: ↓renal tubular function
  - Hepatic: abnormal LFTs
  - Neuro: headaches, visual disturbances, hyperreflexia

**MoA**
- Unknown
- Structure + function of uteroplacental circulation = consistently abnormal in pre-eclampsia → normal conversion of fibro-elastic spiral arteries of non-preg uterus to low pressure, high flow circulation fails to occur → foetus fails to grow
- ↑oxidative stress → thromboxane + ↓prostacyclin → endothelial effects

**Diagnosis**
- HTN >140/90 on 2 occasions 4hrs apart >20 weeks gestation or postpartum that returns to normal 3 months post delivery with at least ONE of:
  - Proteinuria >300mg/24hrs or PCR>0.3
  - Oliguria or ↑Cr
  - ↑liver enzymes or RUQ pain
  - ↓platelets, ↑LDH, haemolysis, DIC
  - IUGR
- Severity determined by uric acid, LDH, LFTs
- HELLP syndrome – associated with preeclampsia
  - Haemolysis: ↑Br + abnormal blood smear
  - Elevated Liver enzymes: ↑AST ↑LDH
  - Low Platelets <100
- Risk ↑ by: chronic renal disease, antiphospholipid syndrome, HTN, FHx, multiple gestation, nulliparity, old maternal age, diabetes, African American

**Management**
- Aspirin for high risk from 12 weeks
- Delivery
- Antihypertensives
- MgSO4 infusion – for prevention + treatment of eclamptic seizures
Outline the pharmacology of agents used in the management of pregnancy induced hypertension: PAST QUESTION 15%

Background
- Hypertensive diseases of pregnancy = common cause of maternal death
- HTN occurs in 10% of pregnancies
- Main aim = prevent maternal complications (ICH, cardiac failure, placental abruption) while maintaining placental blood flow
- consider rx SBP >140-160mmHg, DBP >90-100mmHg
- NB: adverse and teratogenic effects of antihypertensive medication on the foetus need to be considered

Classification
- chronic HTN: precede conception or occur in 1st half of pregnancy. Classified as essential or secondary
- gestational HTN occurs >20 weeks gestation + returns to normal <3 months of delivery. No other features of preeclampsia
- eclampsia = occurrence of seizures in parturient who may have no underlying pathology
- pre-eclampsia = complex multi system disorder that may sometimes precede eclampsia

Drugs
- Mild-moderate/ chronic HTN
  o 1st line: methyl dopa
  o 2nd line: nifedipine, clonidine
- severe HTN
  o magnesium
  o hydralazine
  o labetalol
- NB ACEI and ARBs are CI in pregnancy → use in 3rd trimester = associated with foetal death + neonatal renal failure
### Centrally acting

<table>
<thead>
<tr>
<th>Clonidine</th>
<th>Methyldopa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chem</strong></td>
<td>Aniline derivative</td>
</tr>
<tr>
<td><strong>Category</strong></td>
<td>C</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>Antihypertensive + analgesia + sedative + anxiolytic</td>
</tr>
<tr>
<td>Intraoperative haemodynamic stability; ↓SNS outflow; blunt response to stimuli</td>
<td></td>
</tr>
<tr>
<td>Post op analgesia / shivering</td>
<td></td>
</tr>
<tr>
<td>Anaesthetic sparing</td>
<td></td>
</tr>
<tr>
<td>Migraine/ menopausal flushing/ chronic pain/ opiate or etoh withdrawal</td>
<td></td>
</tr>
<tr>
<td><strong>Pres</strong></td>
<td>Tablets: 100-300microg</td>
</tr>
<tr>
<td>CCS 150microg/ml clonidine hydrochloride</td>
<td>IV: 50mg/ml methyldopa hydrochloride</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>MuA: Partial α2 agonist; α2:01 selectivity 200:1</td>
</tr>
<tr>
<td>- ↓NAd release from SY nerve terminals</td>
<td></td>
</tr>
<tr>
<td>- ↓SY tone + ↑VA tone</td>
<td></td>
</tr>
<tr>
<td>α2 adrenoceptors:</td>
<td></td>
</tr>
<tr>
<td>- presynaptic peripheral SY nerve fibers; post synaptic within CNS/ SC (central); platelets</td>
<td></td>
</tr>
<tr>
<td>- GPCR Gi → adenyl cyclase inhibition → ↓cAMP</td>
<td></td>
</tr>
<tr>
<td>CNS Sedation + analgesia: via central α2 Rs in dorsal horn + ↓peripheral nociceptive input</td>
<td></td>
</tr>
<tr>
<td>↓adrenergic transmission in CNS</td>
<td></td>
</tr>
<tr>
<td>↓CBF ↓IOP</td>
<td></td>
</tr>
<tr>
<td>CVS ↓SNS outflow from BS vasomotor centre</td>
<td>↓SVR, ↓BP</td>
</tr>
<tr>
<td>↓HR ↓MAP</td>
<td>little change in HR or CO</td>
</tr>
<tr>
<td>initial ↑MAP 2° peripheral vasocostriction 2° α1 R stimulation → sustained ↓MAP with 2α central α2 activation (↓NAd release)</td>
<td></td>
</tr>
<tr>
<td>NB prolonged use: upregulate α-adrenoceptors → rebound HTN</td>
<td></td>
</tr>
<tr>
<td>4circulating catecholamines</td>
<td></td>
</tr>
<tr>
<td>AS ↓gastric + small bowel motility</td>
<td>Min effect on GFR, or FF</td>
</tr>
<tr>
<td>Antiemetic: ↓sensitivity of CTZ</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>4renovasc resistance</td>
</tr>
<tr>
<td>4plasma catecholamine activity</td>
<td></td>
</tr>
<tr>
<td>↑BSL (alpha)</td>
<td></td>
</tr>
<tr>
<td>Toxicity/ SE</td>
<td>Drowsiness + dry mouth 50%</td>
</tr>
<tr>
<td>CNS disturbance, fluid retention, constipation</td>
<td>CVS: Orthostatic hypotension, bradycardia, peripheral oedema</td>
</tr>
<tr>
<td>Rapid withdrawal → rebound HTN + ↑HR</td>
<td>GIT/ derm/ haem: 4platelets, haemolytic anaemia, hepatic damage</td>
</tr>
<tr>
<td><strong>Route/ dose</strong></td>
<td>PO: 50-600microg 8hrly</td>
</tr>
<tr>
<td>IV: 150-300microg</td>
<td>PO: 0.5-3g/day divided doses</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>IV: 10mins</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>IV: 3-7hrs</td>
</tr>
<tr>
<td>A</td>
<td>Bioavailability 100%</td>
</tr>
<tr>
<td>D</td>
<td>Very lipid soluble: penetrates BBB / 20% PB</td>
</tr>
<tr>
<td>Vd 2L/kg</td>
<td>Vd 0.2-0.3L/kg</td>
</tr>
<tr>
<td>M</td>
<td>50% liver to inactive metabolites</td>
</tr>
<tr>
<td>E</td>
<td>65% unchanged in urine</td>
</tr>
<tr>
<td>20% faeces</td>
<td>clearance 2-4ml/kg/min</td>
</tr>
<tr>
<td>elimination ½ life 6-23hrs</td>
<td>elimination ½ life 2.5hrs</td>
</tr>
<tr>
<td><strong>Special points</strong></td>
<td>↓MAC coadministered volatiles</td>
</tr>
<tr>
<td>prolongs duration of LA when coadministered for neural blockade</td>
<td></td>
</tr>
<tr>
<td><strong>OBSTETRIC ANAESTHESIA AND ANALGESIA (INC NEONATAL)</strong></td>
<td>Annelise Kerr</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

### Other

<table>
<thead>
<tr>
<th>Nifedipine</th>
<th>Hydralazine</th>
<th>Labetolol</th>
<th>Magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>Dihydropyridine</td>
<td>Phthalazine derivative</td>
<td>Non-cardioselective</td>
</tr>
<tr>
<td>Class</td>
<td>CB</td>
<td>CB</td>
<td>CB</td>
</tr>
<tr>
<td>Category</td>
<td>C</td>
<td>C</td>
<td>D (changed from A)</td>
</tr>
<tr>
<td>Uses</td>
<td>Antihypertensive + antianginal HTN/ angina/ Raynauds/ coronary artery spasm</td>
<td>HTN/ acute severe HTN/ pre-eclampsia/ CCF</td>
<td>HTN Hypotensive anaesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blunting SY response</td>
<td></td>
</tr>
<tr>
<td>Pres</td>
<td>Tablets: 5/10mg Slow release preparation</td>
<td>Tablets: 25/50mg Ampoules 20mg hydralazine hydrochloride White lyophilized powder reconstituted in water</td>
<td>Tablet: 100-800mg BD IV:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CCS 2.03mmol/ml ionic magnesium 50%</td>
</tr>
<tr>
<td>Action</td>
<td>competitive block of α1 subunit of L type Ca2+ channels → influx Ca2+ into vascular smooth muscle + myocardial cells → electromechanical decoupling + inhibition of contraction + relaxation of cardiac and smooth muscle fibres → coronary + systemic arterial vasodilation</td>
<td>Peripheral vasodilation</td>
<td>Selective antagonism of α1, β1, β2 adrenoceptors (1:3 when PO and 1:7 when IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Some intrinsic sympathomimetic activity at β2 adrenoceptors</td>
</tr>
<tr>
<td>CNS</td>
<td>Slight TCBF 2 cerebral vasodilation</td>
<td></td>
<td>Essential cofactor in &gt;300 enzyme systems</td>
</tr>
<tr>
<td>CVS</td>
<td>peripheral + coronary artery vasodilator -ve inotrope 4automaticity: 4SA node activity → 4HR 4conduction velocity vascular smooth muscle dilation: 4SVR, 4PVR TCO (2o 4allerload) trefractory period</td>
<td>Arteriolar vasodilations → 4SVR Compensatory ↑HR → ↑CO</td>
<td>Peripheral vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓HR ↓PVR ↓SVR ↓SBP ↓MAP/ ↓HR</td>
</tr>
<tr>
<td>Resp</td>
<td>Bronchodilator</td>
<td></td>
<td>Essential for production of ATP, DNA, RNA, protein function</td>
</tr>
<tr>
<td>AS</td>
<td>↓GUT contractility ↓LES pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetus</td>
<td>Relaxation of uterine muscle → may ↑Trisk PPH</td>
<td>crosses placenta – neonatal brady + hypoglycaemia rare no ↓uteroplacental flow</td>
<td>↓uterine tone ↑acontractility ↑placental perfusion</td>
</tr>
<tr>
<td>Other</td>
<td>No effect on renal blood flow ↑renin activity Tratecholamines impaired platelet aggregation</td>
<td>↑RBF 2o ↑TCO Na+ retention; ↑renin activity</td>
<td>Renal vasodilator + diuretic ↑clotting time, ↓TXA2</td>
</tr>
<tr>
<td>Toxicity/ SE</td>
<td>20%: flushing, dizziness, headache (vasodilation) oedema, gum hyperplasia</td>
<td>Headache, flushing, sweating, N+V May precipitate angina</td>
<td>↓HR, headache, nausea, scalp tingling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warmth, flushing, nausea, headache, dizziness</td>
</tr>
<tr>
<td>Route/ dose</td>
<td>PO: 10-20mg 8hrly IV: 2-50mg slowly</td>
<td>PO: 50-200mg/day divided PO: 100-800mg BD IV: 5-20mg titrated</td>
<td>IV: IM 10-20mmol over 20mins</td>
</tr>
<tr>
<td>Ossed</td>
<td>PO: 20min IV: 20min/ PO: 20-30min</td>
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</tr>
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<td>8hr (24hr SR)</td>
<td>1: 1-4 hr / PO: 3-8hr</td>
<td>3hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV: 30min / PO: 6hr</td>
</tr>
<tr>
<td>A</td>
<td>Completely absorbed Bioavailability 50-60%</td>
<td>Bioavailability 15-35%</td>
<td>Bioavailability 25%</td>
</tr>
<tr>
<td>D</td>
<td>95% protein bound Vd 1L/kg</td>
<td>90% protein bound Vd 4L/kg</td>
<td>50% protein bound Vd 3.5L/kg</td>
</tr>
<tr>
<td>M</td>
<td>95% liver to 3 inactive metabolites</td>
<td>Liver Acetylation + oxidation → conjugation NB fast + slow acetylators / metabolisers</td>
<td>Liver: conjugation to glucuronide metabolites</td>
</tr>
<tr>
<td>E</td>
<td>90% urine; 10% faeces clearance 30-60/hour elimination ½ life 1-10hr depending on route</td>
<td>50-90% urine (1-2% unchanged)(10% faeces clearance 1.4L/kg/hr elimination ½ life 0.7-3.6hours</td>
<td>½ life 6-8hr urine (60%); faeces via bile</td>
</tr>
</tbody>
</table>

### Magnesium

<table>
<thead>
<tr>
<th>Other</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chem</td>
<td>Dihydropyridine</td>
<td>Phthalazine derivative</td>
<td>Non-cardioselective</td>
</tr>
<tr>
<td>Class</td>
<td>CB</td>
<td>CB</td>
<td>CB</td>
</tr>
<tr>
<td>Category</td>
<td>C</td>
<td>C</td>
<td>D (changed from A)</td>
</tr>
<tr>
<td>Uses</td>
<td>Antihypertensive + antianginal HTN/ angina/ Raynauds/ coronary artery spasm</td>
<td>HTN Hypotensive anaesthesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blunting SY response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pres</td>
<td>Tablets: 5/10mg Slow release preparation</td>
<td>Tablets: 25/50mg Ampoules 20mg hydralazine hydrochloride White lyophilized powder reconstituted in water</td>
<td>Tablet: 100-800mg BD IV:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CCS 2.03mmol/ml ionic magnesium 50%</td>
</tr>
<tr>
<td>Action</td>
<td>competitive block of α1 subunit of L type Ca2+ channels → influx Ca2+ into vascular smooth muscle + myocardial cells → electromechanical decoupling + inhibition of contraction + relaxation of cardiac and smooth muscle fibres → coronary + systemic arterial vasodilation</td>
<td>Peripheral vasodilation</td>
<td>Selective antagonism of α1, β1, β2 adrenoceptors (1:3 when PO and 1:7 when IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Some intrinsic sympathomimetic activity at β2 adrenoceptors</td>
</tr>
<tr>
<td>CNS</td>
<td>Slight TCBF 2 cerebral vasodilation</td>
<td></td>
<td>Essential cofactor in &gt;300 enzyme systems</td>
</tr>
<tr>
<td>CVS</td>
<td>peripheral + coronary artery vasodilator -ve inotrope 4automaticity: 4SA node activity → 4HR 4conduction velocity vascular smooth muscle dilation: 4SVR, 4PVR TCO (2o 4allerload) trefractory period</td>
<td>Arteriolar vasodilations → 4SVR Compensatory ↑HR → ↑CO</td>
<td>Peripheral vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓HR ↓PVR ↓SVR ↓SBP ↓MAP/ ↓HR</td>
</tr>
<tr>
<td>Resp</td>
<td>Bronchodilator</td>
<td></td>
<td>Essential for production of ATP, DNA, RNA, protein function</td>
</tr>
<tr>
<td>AS</td>
<td>↓GUT contractility ↓LES pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetus</td>
<td>Relaxation of uterine muscle → may ↑Trisk PPH</td>
<td>crosses placenta – neonatal brady + hypoglycaemia rare no ↓uteroplacental flow</td>
<td>↓uterine tone ↑acontractility ↑placental perfusion</td>
</tr>
<tr>
<td>Other</td>
<td>No effect on renal blood flow ↑renin activity Tratecholamines impaired platelet aggregation</td>
<td>↑RBF 2o ↑TCO Na+ retention; ↑renin activity</td>
<td>Renal vasodilator + diuretic ↑clotting time, ↓TXA2</td>
</tr>
<tr>
<td>Toxicity/ SE</td>
<td>20%: flushing, dizziness, headache (vasodilation) oedema, gum hyperplasia</td>
<td>Headache, flushing, sweating, N+V May precipitate angina</td>
<td>↓HR, headache, nausea, scalp tingling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warmth, flushing, nausea, headache, dizziness</td>
</tr>
<tr>
<td>Route/ dose</td>
<td>PO: 10-20mg 8hrly IV: 2-50mg slowly</td>
<td>PO: 50-200mg/day divided PO: 100-800mg BD IV: 5-20mg titrated</td>
<td>IV: IM 10-20mmol over 20mins</td>
</tr>
<tr>
<td>Ossed</td>
<td>PO: 20min IV: 20min/ PO: 20-30min</td>
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Methods of transfer of substances across placenta:

1. **Passive diffusion:**
   - **Fick’s law:**
     - Rate of diffusion \( \propto \) to:
       - **Concentration:** based on – dose, plasma volume, foetal uptake
       - **Surface area** of placenta
       - **Solubility** of drugs: based on – lipid solubility; degree of ionisation (dependent on pKa and mothers pH); PB (only free drug crosses placenta)
     - Rate of diffusion inversely \( \propto \):
       - **Thickness** of placenta
       - **MW:** <500 Da cross easily, >1000 Da cross poorly

2. **Facilitated diffusion:** glucose via insulin independent glucose transport proteins GLUT-1 + GLUT-3. NB glucose transfer \( \propto \) maternal BSL

3. **Active transport:** amino acids by Na dependent active transport

4. **Transcytosis:** IgG endocytosed by syncytiotrophoblast cells \( \rightarrow \) transferred across placenta in vesicle and exocytosed into foetal circulation

5. **Bulk flow:** water passes between cells of placenta along osmotic gradient. Any small molecules dissolved in water are transported by solvent drag

Write short notes on placental transfer of drugs: PAST QUESTION

**Placental drug transfer**
- Placenta = phospholipid
- Passive diffusion \( \rightarrow \) Fick’s law:

**Factors that affect placental drug transfer**
- **Drug factors:**
  - Rate of diffusion \( \propto \) to:
    - **Concentration:** based on – dose, plasma volume, foetal uptake
    - **Surface area** of placenta
    - **Solubility** of drugs: based on – lipid solubility; degree of ionisation (dependent on pKa and mothers pH); PB (only free drug crosses placenta)
  - Rate of diffusion inversely \( \propto \):
    - **Thickness** of placenta
    - **MW:** <500 Da cross easily, >1000 Da cross poorly
- **Maternal factors**
  - Maternal protein binding: ↑PB \( \rightarrow \) ↓drug transfer
  - Maternal plasma pH
  - Placental blood flow: ↓in severe hypoxia, cord compression
  - Administration site
  - Placental metabolism
  - Duration of exposure
- **Foetal factors**
  - Foetal protein binding \( \rightarrow \) proteins available \( \rightarrow \) ↑%free drug
  - Plasma pH: ion trapping occurs on foetal side due to ↑acidity; relevant for weak bases (e.g. LAs) which ionised at pH below their pKas

**Foetal maternal ratio**
- the ratio between the [drug] in blood samples taken from umbilical cord and maternal veins
- based on single measurements of blood samples obtained at delivery
- ↑ratio = ↑drug transfer
- e.g. lignocaine = 0.6; bupivacaine =0.3

**Drugs of interest in anaesthetics**
- Glycopyrolate (charged quaternary NH4+ salt) cannot cross placenta; atropine (uncharged tertiary amine) can
- Muscle relaxants are charged \( \rightarrow \) do not cross placenta
- Thiopentone, ketamine, Propofol = highly lipophilic + readily transferred across placenta, however redistribution in foetus is rapid so residual effects are negligible following delivery
- Opioids: lipophilic \( \rightarrow \) diffuse readily across placenta.
- LA: placental transfer greatest for those with lower protein binding e.g. lignocaine. NB low foetal pH causes ionisation of any LA that crosses the placenta \( \rightarrow \) the LA is then unable to diffuse back into the maternal circulation

Outline the potential effects on the foetus and neonate of drugs administered during pregnancy

**General points:**
- Major malformation = defect which is either:
  - Incompatible with life e.g. anencephaly
  - Requiring major corrective surgery e.g. CHD, cleft palate
  - Significant impact on function: e.g. mental impairment
- Background risk of major malformation = 3-5% with 15% miscarriage risk
- **Teratogen:**
  - Agent capable of causing a birth defect
  - Not all drugs are teratogens, and exposure does not equal teratogenesis
  - Likelihood depends on drug selected, dose, and timing of exposure
  - Most susceptible period = critical period = 1st trimester (organogenesis)
- **Factors that influence drug transfer:**
  - Maternal: SBP, uterine blood flow, arterial concentration, uterine activity
  - Placental: membrane thickness, area, enzyme activity
  - Drug: lipid solubility, ionisation, PB, concentration gradient
- **Principles**
  - Generally drugs that cross BBB will cross placenta
  - Delay elective surg until post partum
Infant exposure

Outline the potential effects on the neonate of drug administration in association with lactation

Australian categories for prescribing medicines in pregnancy

- **Category A**
  - Drugs which have been taken by a large number of pregnant women / women of childbearing age...
  - No proven increase in malformations / direct / indirect harmful effects on fetus.
- **Category B1**
  - Taken by only a limited number of pregnant women / women of childbearing age
  - No ↑ in malformation / direct / indirect harmful effects on the human fetus
  - Studies in animals: no ↑ fetal damage.
- **Category B2**
  - Taken by only a limited number of pregnant women / women of childbearing age
  - No ↑ in malformation / direct / indirect harmful effects on the human fetus
  - Studies in animals: inadequate or lacking → available data show no ↑ fetal damage.
- **Category B3**
  - Taken by only a limited number of pregnant women / women of childbearing age
  - Studies in animals: occurrence of fetal damage → significance uncertain in humans.
- **Category C**
  - Have caused / suspected causing harmful effects on human fetus / neonate without causing malformations.
  - These effects may be reversible.
- **Category D**
  - Have caused / suspected fetal malformations or irreversible damage.
  - These drugs may also have adverse pharmacological effects.
- **Category X**
  - Such a ↑ risk of causing permanent damage to foetus; should not be used in pregnancy / possibility of pregnancy

NB:
- Human data are lacking or inadequate for drugs in the B1, B2 and B3 categories
- Subcategorisation of the B category is based on animal data
- The allocation of a B category does not imply greater safety than a C category
- Medicines in category D are not absolutely contraindicated during pregnancy (e.g. anticonvulsants)

**Examples**

- Inhalational agents
  - ↑ lipid solubility + ↓ MW → readily cross placenta
  - ↑ MAC + ↑ duration of exposure → ↓ Apgar score + uterine atony
  - CVS: maternal systemic vasodilation → ↓ MAP → ↓ uteroplacental perfusion pressure → ↓ foetal blood supply
  - N2O: ↓ foetal vascular resistance by 30%; neonatal depression + diffusion hypoxia
- IV agents
  - Propofol: neonatal sedation
  - Thio: min effect if dose <7mg/kg
- Benzols
  - ↑ unionised, ↑ lipid soluble; 95% PB
- Opiates
  - Easily cross placenta due to unionised fraction + ↑ lipid solubility
  - Prolonged use during pregnancy → ↑ risk neonatal withdrawal syndrome
  - If administered prior to delivery → resp depression risk
  - ↓ risk neonatal transfer when used via spinal / epidural
- NSAIDs
  - May induce premature closure of ductus arteriosus in 3rd trimester (cease by 32 weeks)
- Muscle relaxants
  - Don’t readily cross placental membrane due to fully ionised state
  - Neonatal blockade with repeated dose of sux in pts with pseudocholinesterase deficiency
- Anticholinergics
  - Highly ionised at physiological pH → doesn’t significantly cross placenta
- Anticoagulants
  - Warfarin in 1st trimester: ↑ rate fo foetal loss + major malformation
  - Heparin: highly charged and doesn’t cross BBB
  - LMWH: crosses placenta in limited amounts with no change in foetal antitha or antiXa activity

**Outline the potential effects on the neonate of drug administration in association with lactation**

- Nearly all drugs transfer into breast milk to some extent (exceptions: heparin, insulin – too large)
- Exposure depends on:
  - Degree of drug transfer into milk
  - Daily milk intake
  - Bioavailability of drug in infant
- Transfer highest with:
  - Low maternal PB
  - ↑ lipid solubility
  - Weakly basic drugs → become trapped in mild lipids to ionisation (pH of milk slightly acidic pH 7.2 vs. plasma 7.4)
  - Low MW

**Infant exposure**

\[ D = C x (M/P) x V \]

- Infant dose = maternal plasma concentration x ratio of milk/ plasma (M/P) concentration x vol of milk ingested per day by infant (usually 0.15L/kg/day)
- D (mg/kg/day) = C (mg/L) x M/PAUC x V (mg/kg/day)
- Arterial cut off = 10% of maternal dose. Lower for drugs with ↑ toxicity e.g. cytotoxics
- Potential to accumulate in neonate → toxicity e.g. amiodarone
- Immature infant drug clearance mechanisms
- Initial breast milk contains clostrum → low vol and low M/P ratio → ↓ exposure

Annelise Kerr
NEONATAL PHYSIOLOGY

Describe the transition from foetal to neonatal circulation and the establishment of ventilation

<table>
<thead>
<tr>
<th>Foetal/ neonatal circulatory changes that occur at birth:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth: foetal circulation [parallel] series circuit due to resistance changing throughout circulation</td>
</tr>
<tr>
<td>- Removal of low resistance placenta</td>
</tr>
<tr>
<td>- clamping of cord → ↑SVR, ↑LVEDP, ↑LAP + loss of VR from umbilical vessels + closure of ductus</td>
</tr>
<tr>
<td>- Inflation of the lungs</td>
</tr>
<tr>
<td>- Resp centre stimulation + ↑lung vol → ↓HPV → ↓PVR + ↑pulmonary blood flow</td>
</tr>
<tr>
<td>- Closure of PDA</td>
</tr>
<tr>
<td>- ↑PaO2 + 4 prostaglandins (PG1, PG2) → constriction of ductus arteriosus in 10-15hrs</td>
</tr>
<tr>
<td>- Permanent closure: 2-3weeks</td>
</tr>
<tr>
<td>- COX inhibitors prevent complete closure in pt with CHD (rely on shunt from PDA for O2 supply)</td>
</tr>
<tr>
<td>- Hypoxia in neonatal anaesthesia can trigger re-opening of PDA</td>
</tr>
<tr>
<td>- Closure of foramen ovale</td>
</tr>
<tr>
<td>- ↑pulmonary blood flow, ↑LAP = RAP → closure of foramen ovale</td>
</tr>
<tr>
<td>- permanent closure: 4-6weeks</td>
</tr>
</tbody>
</table>

Respiratory changes that occur with birth

First breath:

- trigger: relative asphyxia → central + peripheral chemoreceptor stimulation + sensory bombardment → stimulates resp centre + ventilation
- Lung vol: ↑lung vol + resistance of extra-alveolar vessels + ↑alveolar pO2 → ↓HPV
- ↓lung compliance
  - 1st breath requires a very large –ve intrathoracic pressure (-60cmH2O – 2poor compliance of lungs)
  - subsequent breaths are easier due to establishment of air-liquid interface + surfactant 4surface tension
- foetal lung fluid
  - before delivery: foetal lung contains 20ml/kg fluid → some expelled during vaginal delivery 2’ thoracic compression
  - ↓pulmonary vascular resistance → fluid shift into pulmonary vasculature → fluid reabsorption
- ↑chest wall compliance
- ↑in FRC: by 30mins almost adult value 30ml/kg

Neonatal lungs

- not viable <24 weeks: inadequate surface area / surfactant / control
- Airway: jaw angle 140 degrees, high larynx (C3-4); long epiglottis; narrow cricoid; short trachea (4cm); large nasal airway
- Control:
  - High RR ↓WOB
  - ↑ response to ↑PCO2
  - unreliable response to hypoxia
  - Transient apnoea is normal
  - true apnoea: >15sec, ↓PO2, ↓HR

Describe the utero-placental circulation and the principles of placental physiology as related to placental gas exchange and regulation of placental blood flow

Foetal circulation - Structure

- 2 umbilical arteries
  - arise from internal iliac a
  - return deoxygenated foetal blood to placenta
  - PaO2 18mmHg; SpO2 45%
- 1 umbilical vein
  - supplies oxygenated blood from placenta to foetus
  - PaO2 28mmHg; SpO2 70%
  - 60% of blood from umbi vein enters IVC; 40% enters liver
- 2 ducts
  - ductus venosus: shunts blood from umbi vein to IVC
  - ductus arteriosus: shunts blood from pulmonary trunk to descending aorta
- Foramen ovale
  - Shunts blood from RA to LA
- Immature myocardium
  - Does not obey Starlings Law
  - Does not adjust contractility for any given preload
  - SV is fixed; CO is HR dependent
  - Normal HR at term = 110-160

Foetal circulation – circulation:

- Oxygenated blood returns via umbi vein:
  - 40% flows to liver via portal vein → hepatic vein → IVC
  - 60% bypasses liver via ductus venosus → directly to IVC
- Blood reaches the heart → divided into 2 streams by interatrial septum:
  - 1. Oxygenated blood from IVC directed via Eustachian valve through foramen ovale → LA → LV → ascending aorta → O2 rich blood to head + upper body
  - 2. Blood returning from SVC (drains myocardium + upper body; ↓PaO2)
Mechanisms whereby O2 transfer is facilitated at placenta

- Placenta = large vol, low pressure, low resistance A-V shunt responsible for transfer of O2 and nutrients to meet demands of growing foetus
- tBb supply to placenta: uterine flow \( t \times 20 \) during pregnancy; not autoregulated and is pressure dependent
- tFoetal blood supply to placenta: umbilical arteries supply foetal deoxygenated blood to placenta; foetal CO is 1L/min (25-55% goes to placenta)
- tHbF: Taffinity for O2 than HbA; HbF = 2x affinity for O2; 2,3-DPG \( \rightarrow \) shifts HbF O2HDC to L \( \rightarrow \) HbF taffinity for O2 \( \rightarrow \) O2 loading in placenta; \( t \)saturation at given pO2 than adult Hb
- tHb: t[HbF] \( \rightarrow \) HbF tcarrying capacity
- 5. Double Bohr effect: Bohr effect operative in both maternal and foetal circulations

Physiological principles

- Bohr effect: describes how ∆pCO2 and pH affect O2 transport
  - tpcO2 and t4pH stabilises deoxy-Hb facilitating release of O2 \( \rightarrow \) R shift in OHDC
  - 4pCO2 and t4pH \( \rightarrow \) L shift OHDC
- Double Bohr effect: describes both effects happening on either side of placental gas exchange in mother + foetal circulations
  - tpcO2 in maternal intervillous sinuses assists O2 unloading \( \rightarrow \) 4pCO2 on foetal side assists O2 loading
  - Foetal blood flows from umbilical artery to umbilical vein \( \rightarrow \) releases CO2 to mother and tO2 uptake
- Haldane effect
  - Describes how changes in O2 saturation of Hb affect CO2 transport.
  - DeoxyHb is able to bind H+ improving carriage of CO2 as HCO3 and carbamino compounds
- Double Haldane effect:
  - As maternal blood unloads O2, it is able to take up more CO2 for a given change in pCO2
  - As foetal blood takes up more O2 it releases more CO2 for a given change in pCO2

Approximate values:

<table>
<thead>
<tr>
<th>PO2</th>
<th>Umbral vein</th>
<th>Umbilical artery</th>
<th>Maternal arterial</th>
</tr>
</thead>
<tbody>
<tr>
<td>30mmHg</td>
<td>15</td>
<td>~100mmHg</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>52</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>7.2</td>
<td>7.3</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>70</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Foetal O2 delivery

Foetal oxygenation is determined by:

- delivery of O2 to placenta
  - product of placental blood flow \( \times \) maternal blood O2 content (depends on maternal PaO2 and [Hb])
- transfer of O2 across placenta. Dependent on:
  - Large surface area of placenta
  - Large O2 pressure gradient across placenta:
    - intervillous blood PaO2 50mmHg cf foetal umbilical arterial PaO2 20mmHg
  - HbF O2HDC L shifted cf HbA curve
    - HbF has higher O2 binding affinity than maternal HbA \( \rightarrow \) L shift HbF O2HDC
    - Due to 2,3-DPG binding
    - Placenta produces 2,3-DPG: \( \rightarrow \) binds to b-globulin chains of HbA; cannot bind to y-globulin chains of HbF
    - 2,3-DPG shifts O2HDC of maternal HbA to R \( \rightarrow \) offloading additional O2 to HbF
  - Double Bohr effect
    - CO2 diffuses down conc gradient from foetus to mother
    - Bohr effect: ∆pCO2 and pH affect O2 transport
      - tpcO2 and t4pH \( \rightarrow \) R shift OHDC \( \rightarrow \) release of O2
      - 4pCO2 and t4pH \( \rightarrow \) L shift OHDC \( \rightarrow \) tO2 binding capacity
    - Double Bohr effect:
      - effect on sides of placenta
      - Bohr effect 1: placenta: foetus unloads CO2 in placenta \( \rightarrow \) placental CO2 \( \rightarrow \) RIGHT shift HbA O2HDC \( \rightarrow \) tHbA affinity for O2 \( \rightarrow \) tplacental O2 unloading
      - Bohr effect 2: foetus: foetus unloads CO2 \( \rightarrow \) tfoetal CO2 \( \rightarrow \) LEFT shift HbF O2HDC \( \rightarrow \) tHbF affinity for O2 \( \rightarrow \) tfoetal O2 binding/uptake
    - Foetal O2 carrying capacity
      - Foetus has t[Hb] than adults \( \rightarrow \) tO2 carrying capacity

Transfer of CO2

- Haldane effect
  - Describes how ∆O2 saturation of Hb affect CO2 transport
  - DeoxyHb has taffinity for CO2 than oxyHb
- Double Haldane effect
  - Haldane 1: placenta: placenta unloads O2 \( \rightarrow \) 4placental O2 \( \rightarrow \) deoxyHbA has taffinity of CO2 \( \rightarrow \) tplacental O2 uptake from foetus
  - Haldane 2: foetus: foetus takes up O2 \( \rightarrow \) tHbF O2 \( \rightarrow \) dHbF affinity for CO2 \( \rightarrow \) tHbF CO2 release to placenta
Functions of placenta

- Organ of foetal + maternal origin; supports developing foetus
- Low pressure, low resistance AV shunt that provides metabolic nutrients necessary for growing foetus
  - Functions = TIME
    - Transfer: gas exchange; nutrient + waste exchange; drugs; heat
    - Immunological barrier
    - Metabolic
    - Endocrine

1. Transfer
   a. Gas exchange
      - Diffusion dependent on Fick's Principle
      \[
      D = \frac{\text{sol} \times \Delta\text{conc}}{\sqrt{\text{MW} \times \text{thickness}}} 
      \]
      - Maternal placental flow ~600ml/min at term (2x foetal flow) \(\Rightarrow\) diffusion by \(\uparrow\) concentration gradient for solutes
      - Molecules <600Da more readily diffuse down concentration gradient
      - O2 diffusion
        - PO2 entering placenta via uterine artery = 18mmHg (SpO2 45%)
        - PO2 leaving placenta via uterine vein 28mmHg (SpO2 70%)
        - Foetus able to absorb large enough vol O2 despite low PO2 because:
          - Foetal Hb
            - 2 y subunits of \(\beta\) \(\Rightarrow\) prevent binding of 2,3-DPG \(\Rightarrow\) L shifted OHDC \(\Rightarrow\) favours O2 loading at \(\uparrow\) PaO2
            - [FHB] 50% > maternal [Hb]
          - Double Bohr effect
            - Describes Bohr effects happening on either side of placental gas exchange in mother + foetal circulations
            - Accounts for 2-8% of O2 transfer
            - Bohr effect 1: placenta: foetus unloads CO2 in placenta \(\Rightarrow\) \(\uparrow\) placental CO2 \(\Rightarrow\) RIGHT shift HbA OHDC \(\Rightarrow\) \(\uparrow\) HbA affinity for O2 \(\Rightarrow\) \(\uparrow\) placental O2 unloading
            - Bohr effect 2: foetus: foetus unloads CO2 \(\Rightarrow\) \(\downarrow\) foetal CO2 \(\Rightarrow\) LEFT shift HbF OHDC \(\Rightarrow\) \(\downarrow\) HbF affinity for O2 \(\Rightarrow\) \(\downarrow\) foetal O2 binding/uptake
      - CO2 diffusion
        - Foetal PaCO2 50mmHg; intervillous PCO2 37mmHg
        - CO2 offloading favoured in foetus by:
          - High foetal [Hb] \(\uparrow\) amount of CO2 that can be carried as carbaminoHb
          - Double Haldane effect
            - Haldane effect: describes how \(\Delta\)O2 sat of Hb affect CO2 transport: deoxyHb has \(\uparrow\) affinity for CO2 than oxyHb
            - Double Haldane: describes Haldane effects happening across the placenta
            - Accounts for 45% of CO2 transfer between maternal and foetal circulation
            - Haldane 1: placenta: placenta unloads O2 \(\Rightarrow\) \(\downarrow\) placental O2 \(\Rightarrow\) deoxyHbA has \(\uparrow\) affinity of CO2 \(\Rightarrow\) \(\uparrow\) placental CO2 uptake from foetus
            - Haldane 2: foetus: foetus takes up O2 \(\Rightarrow\) \(\uparrow\) HbF O2 \(\Rightarrow\) HbF affinity for CO2 \(\Rightarrow\) \(\uparrow\) HbF CO2 release to placenta
   b. Nutrient delivery
      - Nutrient diffusion
        - High foetal caloric requirements in late pregnancy
        - Facilitated diffusion of glucose via carrier molecules in trophoblasts
        - Active transport for amino acids, Ca2+, Fe, folate, vit A and C
      c. Waste removal
        - Urea; Br
      d. Heat transfer

2. Immunological function
   - Permeable to IgG via pinocytosis \(\Rightarrow\) allows maternal abs to provide passive immunity to foetus
   - Trophoblast cells lose many cell surface MHC molecules \(\Rightarrow\) making them less immunogenic; also cells cover themselves in mucoprotein which disguises them from maternal immune system
   - Chorionic cells act as immunological barrier – preventing maternal T cells and abs from reaching foetal circulation
     - Some bacteria (listeria) and viruses (rubella, parvovirus B19, HIV) can cross into foetal circulation
   - Progesterone + alpha-foetoprotein produced by yolk sac act as maternal immunosuppressive agents

3. Metabolic
   - Synthesis of glycogen, cholesterol, FA, enzymes

4. Endocrine function
   - Synthesis of 4 main hormones:
     - hHCG
     - hPL: human placental lactogen (human chorionic somatomammotropin)
     - Oestriol
     - Progesterone
   - Synthesis of other hormones and growth factors
     - Placental corticotrophin
     - Human chorionic somatomatostatin
     - Human chorionic thyrotropin
     - Epidermal growth factor
     - Somatomedin
Describe the factors affecting the diffusion of gas at the placenta, including the Bohr and Haldane effects: PAST QUESTION 50%
Explain the Bohr and Haldane effects in trans-placental gas exchange: PAST QUESTION 42%

Background

Maternal foetal O2 exchange
- placenta = organ that facilitates nutrient + waste exchange between mother + foetus
- at placenta, O2 and CO2 passively diffuse down respective concentration gradients
  - CO2 delivered from foetus via foetal umbilical artery to maternal uterine vein
  - O2 delivered to foetus via maternal uterine artery to foetal umbilical vein

Concentration gradient across placenta

<table>
<thead>
<tr>
<th>Flow (ml/min)</th>
<th>Uterine A</th>
<th>Uterine V</th>
<th>Umbilical A</th>
<th>Umbilical V</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO2 (mmHg)</td>
<td>100</td>
<td>40</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>32</td>
<td>45</td>
<td>55</td>
<td>35</td>
</tr>
</tbody>
</table>

- placental O2 consumption = 6ml/min
- foetal O2 consumption = 17ml/min

Bohr and Haldane effects

- Efficiency of gas diffusion across placenta
- Bohr effect
  - Describes how ΔpCO2 or pH influence Hb affinity for O2 and therefore O2 transport
  - ↑pCO2 → ↓Hb affinity for O2 → ↑O2 offloading + formation of deoxyHb
  - represented by a RIGHT shift on OHDC
  - Facilitated by ↓pH, ↑2,3DPG
  - Mechanism: O2 binding to Hb releases H+ (and vice versa) → H+ binding to Hb promotes O2 release
- Haldane effect
  - Describes how ΔO2 saturation of Hb affect CO2 transport
  - deoxyHb has ↑affinity for CO2 than oxyHb
  - Mechanism: deoxyHb is better buffer for H+ than oxyHb → deoxyHb shifts CO2 dissociation equation to right (CO2 + H2O → HCO3 + H+) → improves carriage of CO2 as HCO3 and carbamino compounds (bound to imidazole groups on histidine residues)

Double Bohr and Haldane effect
- Double Bohr effect
  - Describes the Bohr effects happening on either side of placental gas exchange in the mother and foetal circulations
  - Accounts for 2-8% of O2 transfer
Explain the mechanisms whereby O2 transfer is facilitated at the placenta: PAST QUESTION 59%
The foetus requires an ↑O2 supply as it grows. How are these demands met? PAST QUESTION

**Background**

- placenta = large vol, low pressure, low resistance A-V shunt that is responsible for transfer of O2 and nutrients to meet ↑demands of growing foetus

As pregnancy progresses, factors involved in meeting the ↑O2 demands include:

1. **↑blood supply to the placenta**
   - uterine flow ↑20x during pregnancy from 6-8weeks; plateau at 32 weeks to max 750ml/min (85% to placenta)
   - not autoregulated → pressure dependent

2. **↑foetal blood supply to placenta**
   - umbilical arteries supply foetal deoxygenated blood to placenta
   - foetal CO 1L/min at term; 25-55^ to placenta
   - O2 and CO2 exchange

3. **foetal Hb (HbF)**
   - ↑affinity for O2 than HbA
   - 4haem moieties – proco-porphyrin based ring with central ferrous (Fe2+) molecule bound to 4 globin chains
   - HbF = 2α2y vs. HbA = 2α2β
   - Does not bind 2,3DPG → Left shifts HbF O2Hb dissociation curve with p50 19mmHg (vs. 27mmHg) → foetal Hb has ↑O2 affinity → assists it to load O2 in placenta while maternal Hb is unloading O2
   - ↑saturation at given pO2 than adult Hb

4. **Hb concentration**
   - ↑[HbF] than maternal Hb
   - ~180g/dL → ↑O2 carrying capacity

5. **Double Bohr effect**
   - Bohr effect describes how ApCO2 and pH affect O2 transport: ↑pCO2 and ↓pH stabilise deoxy(T) conformation of Hb facilitating release of O2 → RIGHT shift of OHDC. Opposite occurs with ↓pCO2 and ↑pH
   - Bohr effect 1: placenta: foetus unloads CO2 in placenta → ↑placental CO2 → RIGHT shift HbA OHDC → ↓HbA affinity for O2 → ↑placental O2 unloading
   - Bohr effect 2: foetus: foetus unloads CO2 → ↓foetal CO2 → LEFT shift HbF OHDC → ↑HbF affinity for O2 → ↑foetal O2 binding/uptake
   - Double Bohr effect refers to situation in placenta where Bohr effect is operative in both maternal and foetal circulations
     - ↑pCO2 in maternal intervillous sinuses assists O2 unloading
     - ↓pCO2 in foetal circulation assists O2 loading
     - Means that OHDC for maternal HbA and foetal HbF move apart