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.

- 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: ~↑60% 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%

Background

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- ***Changes due to:***
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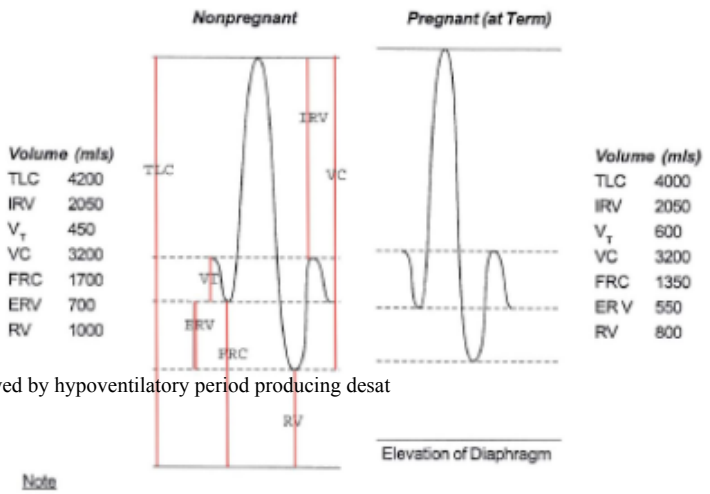
  - **↑metabolic demand** esp. during labour: ~↑60% O2 consumption/ CO2 production during labour
  - **placental circulation**: ↓pressure, ↓resistance AV shunt

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; ↓20% erect and ↓50% sup
     - ↓RV
     - TLC ↓5% (doesn't change much due to ↑AP + tr
     - Expiratory capacity ↓30%
   - 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% duri
     - PCO2 ↓ to 26-32mmHg with compensatory ↓[H
   - O2 consumption: ↑20% at term → ↑↑during labour 2° uterir
   - Other
     - Desat: cessation of uterine contractions are followed by hypoventilatory period producing desat
     - Dyspnoea: 2° progesterone + ↑metabolic demand unable to be compensated by ↑CO alone

Fig 11.1 Spirometry : Changes due to Pregnancy



Note
- Decreased FRC in pregnancy due to decreased RV & ERV
- TLC may be normal or slightly decreased (The decrease due to elevation of diaphragm is counteracted by increase in both AP & transverse diameters)
- Higher minute volume due increased V_T (and slight increase in repiratory rate).

(Values after Bo

Implications

- tendency to hypoxia: ↓FRC; preox less effective + ↑risk basal atelectasis; ↑MRO2 with ↑metbaolic rate
- ↑wash in of volatiles: ↑alveolar vent 50-70% t 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

- pH: ~7.44
- pCO2 ~32mmHg → ↑gradient for CO2 transfer from foetus
  - progesterone → ↑chemoreceptor sensitivity to CO2 → ↑MV by 50% (↑tidal vol by 35%)
  - ↑CO2 production 2° hypermetabolic state + foetal metabolism
- HCO3 ~20mmHg
  - Full metabolic compensation for chronic respiratory alkalosis occurs after 3 days
  - Due to: ↑HCO3 excretion 2° inhibition of renal secretion of H+ ions + ammonium
  - Base deficit reflects renal loss of HCO3
- PaO2: normal to slightly ↑despite ↑O2 consumption
  - Due to: ↑alveolar ventilation, ↓PaCO2, cardiac output, and alveolar gas equation
  - PAO2 = 0.21 (pATM – SVP) – PaCO2 / R → as PaCO2 ↓s → PAO2 ↑s. However there is ↑O2 consumption (15-30% above normal) in hypermetabolic state → PaO2 ~102mmHg
- NB maternal PO2 and PCO2 ↑gas exchange to foetus

After birth

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

Cardiovascular changes in pregnancy

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  - **placental circulation**: ↓pressure, ↓resistance AV shunt

Cardiovascular changes:

- **↑CO (50%)**
  - ↑SV by 30% 2° ↑circulating blood vol → ↑VR → ↑preload (NB gravid uterus can compress IVC → impaired VR)
  - ↑HR by 25% 2° reflex response to ↓BP
  - ↓afterload 2° ↓SVR 2° progesterone induced vasodilation
  - myocardial contractility unchanged
- **↑blood volume**
  - ↑blood vol by 1200-1500ml by term
    - ↑plasma vol (45%) > RBC vol → dilutional anaemia
    - ↑intravascular vol → ↑VR
  - ↑intravascular vol by 2 mechanisms:
    - ↑oestrogen → stimulates RAAS → ↑Na + H2O retention → ↑plasma vol → ↓capillary oncotic pressure (→ oedema; exacerbated by gravid uterus compressing IVC)
    - ↑EPO → ↑RBC vol by 30%
- **↓TPR**
  - ↓SVR by 35% → ↓DBP > ↓SBP; ↓MAP by 10% (despite ↑in CO)
    - vasodilation (2° progesterone, prostaglandins, down regulation of α Rs → ↑ flow to kidneys, gut, heart, breasts, skin)
  - placenta = ↓pressure, ↓resistance AV shunt → flow passive + pressure dependent
  - uteroplacental circulation ↑ x10
- **aortocaval compression**
  - compression of IVC + aorta by gravid uterus → ↓VR + ↓CO → nausea, pallor, ↓BP, CC when supine - resolves in lateral position
  - ↓placental blood flow 2° ↑uterine venous pressure → ↓uteroplacental circulation
  - VR via collaterals of paravertebral epidural veins → azygous
  - Most non-anaesthetised patients can compensate via:
    - 1. ↑SY outflow → ↑SVR + ↑HR. NB GA + neuraxial block abolish SY response → ↓↓BP, CC when supine
    - 2. Collateral pathways: azygous, paravertebral, epidural veins
- Other
  - Dilutional ↓albumin
  - ↑FI, VII, VIII, IX, X + ↓ATII → hypercoagulable
  - ↓pseudocholinesterase 30% (dilutional)
  - ECG: L) axis deviation 2o gravid uterus; non specific ΔST and T waves
  - Transient valvular incompetence → murmurs
  - Exaggerated splitting of heart sounds

Changes during labour

- ↑CO
  - uterine contraction → bolus ~300ml blood → ↑CO by 30% during active phase + 45% during ejection → ↑SBP + DBP by 10-20mmHg
  - ↑CO further 25-50% in response to catecholamine secretion
  - post partum CO up to 80% of pre-labour values due to ***autotransfusion***
- Other
  - ↑2,3DPG: maintains OHDC despite ↓pCO2
  - ↑cardiac work: ↑risk CCF/ APO
  - ↑venous plexus vol during ACC and labour: ↓epidural/ subarachnoid space → ↓dose neuraxial block, ↑risk bleeding

O2 flux

- measured as CO x blood O2 content
- ↑CO by 30%
- ↓blood O2 content: ↓Hb → 2o physiological anaemia of pregnancy
- ↑CO > ↓blood O2 content → ↑O2 flux by 10%

Implications

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

- significant in fixed CO states esp. labour e.g. AS, MS, HOCM
- requires left tilt between 15-30o to ↓aorto-caval compression

After birth

- return to non-pregnant levels <2 weeks

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

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 + corput lutum 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
  - ↑intragastric pressure
  - delayed gastric emptying in labour
  - gastric pH: ↑gastric vol, ↓gastric pH → aspiration has ↑degree of lung injury (Mendelsons syndrome – pneumonitis from pulmonary aspiration of acidic gastric contents under GA)
- Liver: glycogen depletion, fatty changes, ↑ALP
- **Implications**:
  - ↑aspiration risk
  - ↓metabolism of drugs

Haematological

- 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**: ↑FI, VII, VIII, IX, X + ↓ATII

- ↓plasma oncotic pressure
- ↑ESR 2o plasma globulin + fibrinogen
- **Implications**:
  - ↑DV due to ↑plasma vol
  - ↑risk VTE
  - ↑oedema due to ↑oncotic pressure
  - ↓albumin = ↓PB of drugs

Renal

- anatomical + physiological changed to kidneys + ureters
- **dilation** 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 ↓30-40% 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 2nd 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

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

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

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- 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 → ↑anatomical dead space + ↓airway resistance
- Respiratory compliance: Lung compliance unaffected; ↓thoracic wall compliance by 20%
- Upper airway oedema: oestrogen + progesterone → engorgement of blood vessels surrounding upper airway
- Airway dilation → ↓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

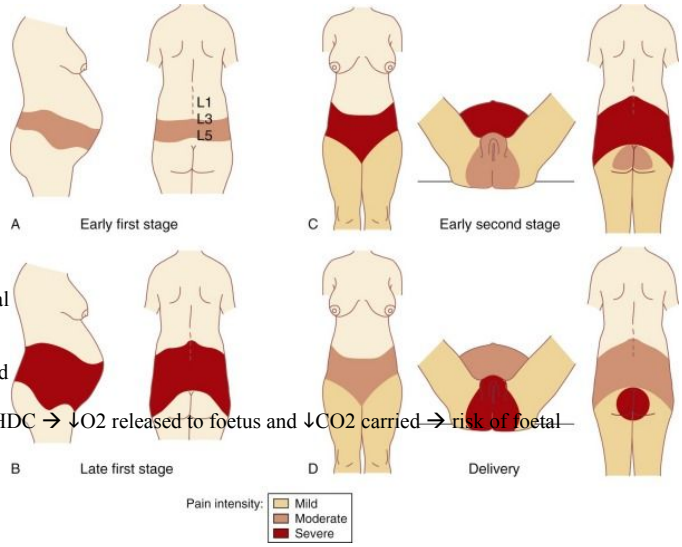
- dilation of cervix
- full cervical dilation until delivery of baby
- delivery of placenta

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 SY 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: ↑CO 25-50% 2o tachycardia 2o pain; epidural → ↓CI by 3-6% and
- SNS: ↑circulating catecholamines
- Resp: ↑MV = ↓maternal $PaCO_2$ → maternal alkalosis → LEFT shift OHDC → ↓O_2 released to foetus and ↓CO_2 carried → risk of foetal 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%

Pharmacokinetics

Absorption	Distribution	Metabolism	Excretion
↓PO absorption - ↓gastric motility - ↓gastric emptying during labour - ↓intestinal absorption 2° ↓intestinal blood flow - ↑risk aspiration + ↓absorption PO - N+V ***↑IM/ SC / transdermal absorption*** - ↑ skin blood flow - IV: ↑onset ***Inhalational*** - uptake of volatiles due to: ↑CO, ↑alveolar ventilation, ↓FRC. Net effect minimal - ↓MAC (progesterone effect) ***Epidural/ spinal*** - engorged epidural veins esp. during contractions → ↑systemic absorption + potential toxicity of LAs + ↓plasma protein → ↓CC/ CNS ratio	***VD*** - ↑plasma vol: ↓VD polar drugs e.g. NDMRs - ↑body fat (important for lipid soluble drugs) ***↓plasma protein 2` dilutional effect*** - ↓albumin → ↑free % acidic drugs; ↓dose required; ↑transplacental transfer of drug - ↓A1AGP by 30% → ↑free %basic drugs; ↓dose required; ↑transplacental transfer of drugs ***Ionisation*** - mild ↑pH alters ionisation based on pKa - ↑MV = mild resp alkalosis → ↑transplacental transfer of basic drugs; ↑ion trapping in more acidic foetus	***Progesterone: oestrogen ratio*** - progesterone → induces hepatic enzymes - oestrogen → inhibits hepatic enzymes ***↓Plasma cholinesterase*** ***Placenta metabolises some dugs*** ***Foetal liver has functioning CYP450*** - can metabolises some drugs	***↑RBF (75%) and GFR (50%)*** - ↑clearance of drugs dependent on renal excretion (polar, water soluble drugs e.g. enoxaparin) ***↑MV*** - ↑washout of volatile anaesthetics

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 inhalationals
  - 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 → ↑freee % acidic drugs → ↓dose
  - oestrogen + progesterone 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
  - $$D = \frac{sol \times \Delta conc}{\sqrt{MW}} \times \frac{surf\ area}{thickness}$$
  - 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 →

↑unionised fraction)
    - CSF bulk flow: maintain conc gradient + facilitates ongoing diffusion

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) foetus

- 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) → ↑unioinisd portion → ↑solubility → ↑diffusion
- foetal acidosis → ion trapping

Describe the pharmacology of oxytocic agents with special reference to oxytocin derivatives, ergot derivatives and prostaglandins

Outline briefly the pharmacology of oxytocin: PAST QUESTION 54%

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

	Oxytocin	**Ergometrine**	**PGF2a**
Chem	Endogenous nonapeptide hormone produced in hypothamalus and stored / released from posterior pituitary Syntocin = synthetic form (minimal ADH action)	Ergot alkaloid	Prostaglandin
Uses	Augmentation of labour (accelerate / induce) ↑uterine tone + PPH aid lactation	PPH (2nd line)	PPH (3rd line)
Pres	CCS or IV< IM, intranasal 5 or 10 IU/ml → syntocinon 1ml injection + 500ug ergometrine for PPH (intrauterine) → syntometrine		
Action	Binds to GPCR on smooth muscle cells - **↑permeability of myometrial cell membrane to K+** → ↓membrane potential + ↑cell membrane excitability → ↑ contraction - **opening of Ca2+ channels** → ↑Ca2+ influx → release of Ca2+ 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	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 → ↑Ca2+ → cervical ripening + ↑uterine contractility with ↑basal tone + relaxation of cervix ***Classes:*** - **PGE1** analogues: misoprostol - **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 metabolized in pulmonary circuit → ↑↑↑PVR → ↑↑bronchospasm → **DEATH**
CNS	headache, N+V	headache + nausea	N+V
CVS	↓MAP post bolus 2° vasodilation → ↓SVR → reflex ↑HR ECG: ↑QT, T wave flattening (2° ↓perfusion coronary arteries)	Vasoconstriction → ↑SVR, ↑BP coronary vasoconstriction bradycardia 2o ↑VA tone	↑BP. NB arge doses can vasodilate → ↓SVR, ↓BP Dinoprost can cause CVS collapse if enters circulation after amniotic injection
Resp		Pulmonary oedema	
AS	↑uterine tone; ↑frequency at low dose, tetanic contraction at high dose) foetal distress; lactation	↑force + frequency of uterine contraction ↑uterine tone; ↑constraction of cervix	
Other	minimal ADH action	Vomiting +++	Bronchospasm/ bronchoconstriction/ worsening asthma
Foetal	In distressed foetus → ↓uterine blood flow, ↑distress, uterine spasm/ rupture → ↑risk of foetal asphyxia	Uterine spasm	Uterine pain, uterine rupture, foetal distress
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	**CI in preeclampsia due to HTN** N+V 2° stimulation of CTZ, blurred vision/ headache 2o vasoconstriction, seizures AMI, APO 2o ↑↑SVR → ↑afterload + ↑wall tension + coronary artery vasospasm	N+V; diarrhoea; bronchoconstriction Vasodilation at large doses → ↓SVR, ↓BP Genital oedema / anaphylaxis Diarrhea 2o stimulation of intestinal smooth muscle
Route/ dose	IV 5-10 IU bolus IV followed by titration of 1-2 units/hr q15-30mins until uterine contraction occurring every 2-3 mins IVI / IMI / intranasal	500microg IMI avoid IV due to N+V+++	Intramyometrial injection Misoprostol: PO/ SL/ PV: 400-800microg Dinoprostone: 10-20mg PV
Onset	Minutes	1min IV; 5min IM; 10min PO	Misoprostol: 2-3r (peak plasma time 14mins) Dinoprostone: 10min
Duration	1hr	PO 3-6hr	Misoprostol: 3hr Dinoprostone: 2-3hr
A	no PO bioavailability → broken down by chymotrypsin		
D	Vd 0.3L/kg		Misoprostol: 80% PB
M	Rapid via oxytocinases in liver + kidney + ?plasma	liver	Misoprostol: ↑+ rapid 1st pass metabolism → misoprostol acid (active) Dinoprostone: maternal lungs, spleen, tissues via oxidation of side chains to 9 inactive metabolites
E	t1/2 1-7mins urine	Bile	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 + ↑uterine contractility
- Coordinated contractions of uterus with ↑basal 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 → ↑↑bronchospasm → 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

Drug	B2 agonist	Ca2+ channel antagonist	COX inhibitors	MgSO4	Nitrates
Example	Salbutamol	Nifedipine	Indomethacin	Mg2+	GTN, amylnitrate
MoA	Activate GPCR, ↑cAMP → ↓intracellular Ca2+ → relaxation	Block L type Ca2+ channels → relaxation	Inhibit prostaglandin synthesis (vital for uterine contraction)		

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

Preeclampsia

- Hypertensive disease of pregnancy
- Associated with widespread endothelial dysfunction → placental 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
  - **H**aemolysis: ↑Br + abnormal blood smear
  - **E**levated **L**iver enzymes: ↑AST ↑LDH
  - **L**ow **P**latelets <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 ½ of pregnancy. Classified as essential or secondary
- gestational HTN occurs >20weeks 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
    - 1st line: methyldopa
    - 2nd line: nifedipine, clonidine
- severe HTN
    - magnesium
    - hydralazine
    - labetalol
- NB ACEI and ARBs are CI in pregnancy → use in 3rd trimester = associated with foetal death + neonatal renal failure

Centrally acting

	Clonidine	**Methyldopa**
Chem	Aniline derivative	Phenylalanine derivative
Category	C	B
Uses	**Antihypertensive + analgesia + sedative + anxiolytic** Intraoperative haemodynamic stability: ↓SNS outflow; blunt response to stimuli Post op analgesia / shivering Anaesthetic sparing Migraine/ menopausal flushing/ chronic pain/ opiate or etoh withdrawal	HTN Pre-eclampsia
Pres	Tablets: 100-300microg CCS 150microg/ml clonidine hydrochloride	Tablets: 125/250/500mg IV: 50mg/ml methyldopa hydrochloride
Action	**MoA**: Partial **α2-agonist**; α2:α1 selectivity 200:1 - → ↓NAd release from SY nerve terminals → ↓SY tone + ↑VA tone - Analgesic: ↓NAd transmission at dorsal horn + ↑inhibitory descending pathway α2 adrenoceptors: - presynaptic peripheral SY nerve fibers; post synaptic within CNS/ SC (central); platelets - GPCR Gi → adenylyl cyclase inhibition → ↓cAMP	methyldopa metabolized to α-methyl NAd → stored in adrenergic nerve terminals within CNS α-methyl NAd = potent **α2 agonist** + ↓central SY discharge
CNS	Sedation + analgesia: via central α2 agonism → inactivate locus ceruleus + activation of descending inhibitory pain pathways Spinal analgesia: via spinal α2 Rs in dorsal horn → ↓peripheral nociceptive input ↓adrenergic transmission in CNS ↓CBF ↓IOP	
CVS	α2 agonist → ↓SNS outflow from BS vasomotor centre → ↓SVR ↓HR ↓MAP initial ↑MAP 2° peripheral vasoconstriction 2° α1 R stimulation → sustained ↓MAP with 2o central α2 activation (↓NAd release) NB prolonged use: upregulate α-adrenoceptors → rebound HTN ↓circulating catecholamines	↓SVR, ↓BP little change in HR or CO
AS	↓gastric + small bowel motility Antiemetic: ↓sensitivity of CTZ	Min effect on GFR, or FF
Foetus	Crosses placenta	Little effect on renal or uteroplacental blood flow
Other	↓renovasc resistance ↓plasma catecholamine activity ↑BSL (alpha)	↓plasma renin
Toxicity/ SE	Drowsiness + dry mouth 50% CNS disturbance, fluid retention, constipation Rapid withdrawal → rebound HTN + ↑HR	CNS: sedation, depression, weakness, paraesthesia, dizziness CVS: Orthostatic hypotension, bradycardia, peripheral oedema GIT/ derm/ haem: ↓platelets, haemolytic anaemia, hepatic damage
Route/ dose	PO: 50-600microg 8hrly IV: 150-300microg	PO: 0.5-3g/day divided doses
Onset	IV: 10mins	
Duration	IV: 3-7hrs	
A	Bioavailability 100%	Variable absorption / Bioavailability 8-62%
D	Very lipid soluble: penetrates BBB / 20% PB Vd 2L/kg	50% PB Vd 0.2-0.3L/kg
M	50% liver to **inactive** metabolites	Conjugated to sulfate as crosses intestinal mucosa + liver
E	65% unchanged in urine 20% faeces elimination ½ life 6-23hrs	20-40% urine (2/3 unchanged) clearance 2-4ml/kg/min elimination ½ life 2.5hrs
Special points	↓MAC coadministered volatiles prolongs duration of LA when coadministered for neural blockade	Nasal congestion

	Nifedipine	**Hydralazine**	**Labetolol**	**Magnesium**
Chem	Dihydropyridine	Phthalazine derivative	Non-cardioselective	Divalent cation / inorganic sulfate
Class	CCB	Direct vasodilator	BB	Cation
Category	C	C	C	**D (changed from A)**
Uses	Antihypertensive + antianginal HTN / angina / Raynauds / coronary artery spasm	HTN/ acute severe HTN/ pre-eclampsia/ CCF	HTN Hypotensive anaesthesia Blunting SY response	Pre-eclampsia/ eclampsia / tocolytic HypoMg / asthma / barium poisoning AMI / Torsades / cardioplegic solutions Cerebral oedema/ autonomic hyperreflexia
Pres	Tablets: 5/10mg Slow release preparation	Tablets: 25/50mg Ampoules 20mg hydralazine hydrochloride White lyophilized powder reconstituted in water	Tablet: 100-800mg BD IV:	CCS 2.03mmol/ml ionic magnesium 50%
Action	**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 **1,4 Dihydropyridines**: prevent Ca2+ entry by extracellular allosteric modulation of L type Ca2+ channel	Peripheral vasodilation **MoA**: direct action on vascular smooth muscle: interfers with Ca2+ entry into cell or release of Ca2+ from intracellular stores → electromechanical decoupling + inhibition of contraction	**Selective antagonism of α1, β1, β2 adrenoceptors** (1:3 when PO and 1:7 when IV) Some intrinsic sympathomimetic activity at β2 adrenoceptors	Essential cofactor in >300 enzyme systems Essential for production of ATP, DNA, RNA, protein function **MoA**: dose dependent **presynaptic inhibition of ACh release at NMJ**
CNS	Slight ↑CBF 2° cerebral vasodilation	↑CBF	Crosses BBB	CNS depressant + anticonvulsant
CVS	peripheral + coronary artery vasodilator -ve inotrope ↓automaticity: ↓SA node activity → ↓HR ↓conduction velocity vascular smooth muscle dilation: ↓SVR, ↓PVR ↑CO (2o ↓afterload) ↑refractory period	Arteriolar vasodilation → ↓SVR Compensatory ↑HR → ↑CO	**α1 block** → ↓SVR/ SBP/ MAP/ ↓HR ↑Blood flow No reflex tachycardia	Peripheral vasodilation ↓BP ↓SA node; ↑SA conduction time, ↑PR interval, ↑AV nodal effective refractory period ↓vasoconstrictor + arrhythmogenic actions of adrenaline
Resp	Bronchodilator		Bronchospasm	Bronchodilator; ↓HPV
AS	↓GUT contractility ↓LES pressure			Osmotic laxative
Foetus	Relaxation of uterine muscle → may ↑risk PPH		**crosses placenta** – neonatal brady + hypoglycaemia rare **no ↓uteroplacental flow**	↓uterine tone + ↓contractility ↑placental perfusion **crosses placenta** → neonatal depression Cat D: neonatal bone demineralization + fractures associated with long-term in utero exposure
Other	No effect on renal blood flow ↑renin activity ↑catecholamines impaired platelet aggregation	↑RBF 2o ↑CO Na+ retention; ↑renin activity		Renal vasodilator + diuretic ↑clotting time, ↓TXA2
Toxicity/ SE	20%: flushing, dizziness, headache (vasodilation) oedema, gum hyperplasia	Headache, flushing, sweating, N+V May precipitate angina	↓HR, headache, nausea, scalp tingling	Warmth, flushing, nausea, headache, dizziness Somnolence, areflexia - Toxic effects reversed by Ca2+
Route/ dose	PO: 10-20mg 8hrly 100-200microg via coronary artery catheter over 2min	PO: 50-200mg/day divided IV: 5-20mg slowly	PO: 100-800mg BD IV: 5-20mg titrated	IV/ IM 10-20mmol over 20mins PO
Onset	PO: 20min	IV: 10mins / PO: 20-30min	IV: 2.5min / PO: 20-120min	IV: immediate / PO: 1hr
Duration	PO: 8hr (24hr SR)	IV: 1-4 hr / PO: 3-8hr	3hr	IV: 30min / PO: 6hr
A	Completely absorbed / Bioavailability 50-60%	Bioavailability 15-35%	Bioavailability 25%	PO 25-60% absorbed
D	95% protein bound Vd 1L/kg	90% protein bound Vd 4L/kg	50% protein bound Vd 3.5L/kg	30% protein bound
M	95% liver to 3 **inactive** metabolites	**Liver** Acetylation + oxidation → conjugation NB fast + slow acetylators / metabolisers	Liver: conjugation to glucuronide metabolites	>50% urine
E	90% urine; 10% faeces clearance 30-60L/hour elimination ½ life 1-10hr depending on route	50-90% urine (1-2% unchanged)/ 10% faeces clearance 1.4L/kg/hr elimination ½ life 0.7-3.6hours	½ life 6-8hr urine (60%); faeces via bile	

Explain the factors which influence the transfer of drugs across the placenta to the foetus

Methods of transfer of substances across placenta:

1. **Passive diffusion:**
   - **Fick's law:**
     - Rate of diffusion ∝ 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 ∝:
       - Thickness of placenta
       - MW:<500 Da cross easily, >1000 Da cross poorly

$$D = \frac{sol \times \Delta conc}{\sqrt{MW}} \times \frac{surf\ area}{thickness}$$

2. **Facilitated diffusion:** glucose via insulin independent glucose transport proteins GLUT-1 + GLUT-3. NB glucose transfer ∝ maternal BSL
3. **Active transport**: amino acids by Na dependent active transport
4. **Transcytosis**: IgG endocytosed by syncytiotrophoblast cells → 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 → **Fick's law:**

$$D = \frac{sol \times \Delta conc}{\sqrt{MW}} \times \frac{surf\ area}{thickness}$$

Factors that affect placental drug transfer

- **Drug factors:**
  - Rate of diffusion ∝ 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 ∝:
    - Thickness of placenta
    - MW:<500 Da cross easily, >1000 Da cross poorly
- **Maternal factors**
  - Maternal protein binding: ↑PB → ↓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 → ↓proteins available → ↑%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 → 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 → 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 → 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. ancencephaly
  - 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 timining 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

- Consider regional anaesthesia
- Use minimum effective dose
- Assess suitability for drug use based on risk/benefit

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 ↑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
  - No ↑ in malformation or other direct / indirect harmful effects on the human fetus
  - Studies in animals: **↑occurrence of fetal damage → significance uncertain** in humans.
- Category C
  - have caused / suspected of 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
- Benzos
  - ↑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 antiIIa 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 mild intake
  - Bioavailability of drug in infant
- Transfer highest with:
  - Low maternal PB
  - ↑lipid solubility
  - weakly basic drugs → become trapped in mild 2o to ionisation (pH of mild 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)
  - Dinfant (mg/kg/day) = Cmaternal (mg/L) x M/PAUC x Vinfant (L/kg/day)
- Arbitrary 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

NEONATAL PHYSIOLOGY

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

Foetal/ neonatal circulatory changes that occur at birth:

Birth: foetal circulation Δparallel → series circuit due to resistance changing throughout circulation

- **Removal of low resistance placenta**
  - clamping of cord → ↑SVR, ↑LVEDP, ↑LAP + loss of VR from umbilical vessels + closure of ductus
- **Inflation of the lungs**
  - Resp centre stimulation + ↑lung vol → ↓HPV → ↓PVR + ↑pulmonary blood flow
- **Closure of PDA**
  - ↑PaO2 + ↓prostaglandins (PGE1, PGE2) → constriction of ductus arteriosus in 10-15hrs
  - Permanent closure: 2-3weeks
  - COX inhibitors prevent complete closure in pt with CHD (rely on shunt from PDA for O2 supply)
  - Hypoxia in neonatal anaesthesia can trigger re-opening of PDA
- **Closure of foramen ovale**
  - ↑pulmonary blood flow, ↑LAP → LAP>RAP → closure of foramen ovale
  - permanent closure: 4-6weeks

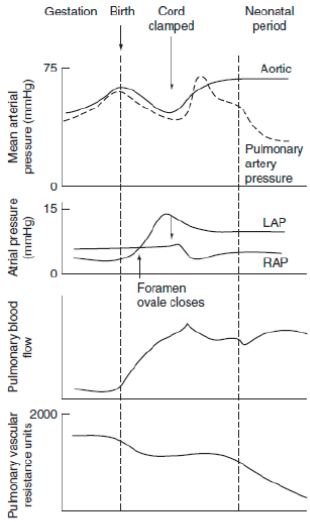


Figure 14.16 *Haemodynamic changes at birth. LAP, left atrial pressure; RAP, right atrial pressure.*

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 – 2° poor compliance of lungs)
  - subsequent breaths are easier due to establishment of air-liquid interface + surfactant ↓surface 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

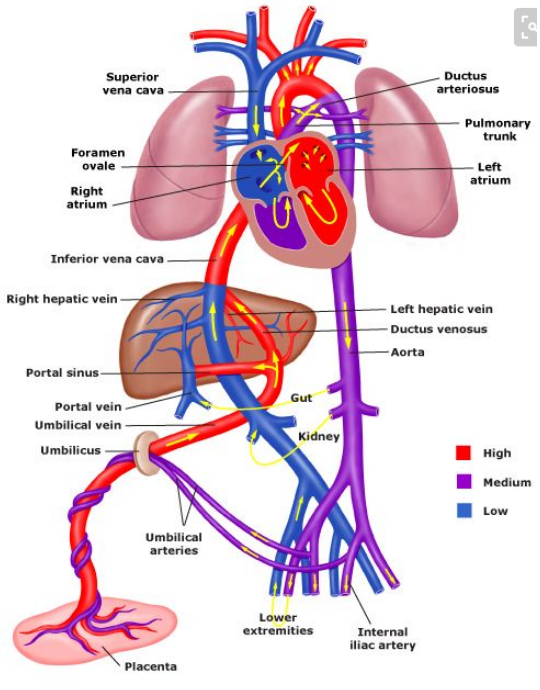
- not viable <24 weeks: inadequate surface area / surfactant / control
- Airway: jaw angle 140 degrees, high larynx (C3-4); long epiglottis; narrow cricoid; short trachea (4cm); large nasal airway
- Control:
  - High RR ↓WOB
  - ↑ response to ↑PCO2
  - unreliable response to hypoxia
  - Transient apnoea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

***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)

→ directed into RV → descending aorta by ductus arteriosus + ↑PVR
- arrangement has several features:
  - Patency of ductus arteriosus maintained by low PaO2 + vasodilating effects of prostaglandin E2
  - NB: ~10% CO passes through lungs → low O2 in lungs → vasoconstriction → ↑PVR
  - Blood with most O2 delivered to brain
  - Blood with least O2 delivered to umbi arteries for gas exchange
  - Both RV + LV eject to systemic circulations; similar size + wall thickness

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
- 1. ↑blood supply to placenta: uterine flow ↑x20 during pregnancy; not autoregulated and is pressure dependent
- 2. ↑foetal blood supply to placenta: umbilical arteries supply foetal deoxygenated blood to placenta; foetal CO is 1L/min (25-55% goes to placenta)
- 3. HbF: ↑affinity for O2 than HbA; HbF = 2α2γ; ↓affinity for 2,3,DPG → shifts HbF OHDC to L → HbF ↑affinity for O2 + ↑O2 loading in placenta; ↑saturation at given pO2 than adult Hb
- 4. [Hb]: ↑[HbF] → ↑O2 carrying capacity
- 5. Double Bohr effect: Bohr effect operative in both maternal and foetal circulations

Physiological principles

- **Bohr effect**: describes how ΔpCO2 and pH affect O2 transport
  - ↑pCO2 and ↓pH stabilises deoxy-Hb facilitating release of O2 → R shift in OHDC
  - ↓pCO2 and ↑pH → L shift OHDC
- **Double Bohr effect**: describes both effects happening on either side of placental gas exchange in mother + foetal circulations
  - ↑pCO2 in maternal intervillous sinuses assists O2 unloading → ↓pCO2 on foetal side assists O2 loading
  - Foetal blood flows from umbilical artery to umbilical vein → releases CO2 to mother and ↑O2 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

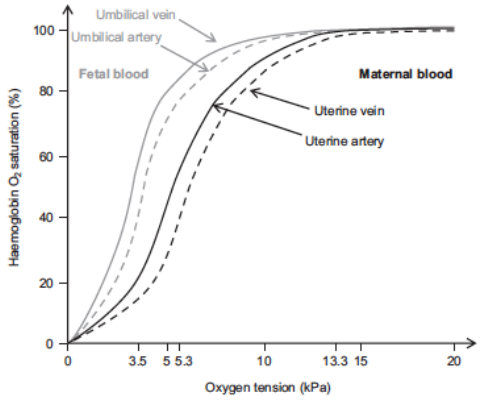
Approximate values:

	Umbilical vein	Umbilical artery	Maternal arterial
PO2	30mmHg	15	~100mmHg
pCO2	45	52	30
pH	7.2	7.3	7.4
%saturation Hb	30	70	100

Foetal O2 delivery

Foetal oxygenation is determined by:

- **delivery of O2 to placenta**
  - product of placental blood flow + 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 OHDC L shifted cf HbA curve
    - HbF has higher O2 binding affinity than maternal HbA → L shift HbF OHDC
    - Due to 2,3-DPG binding
    - Placenta produces 2,3-DPG → binds to b-globulin chains of HbA; cannot bind to y-globulin chains of HbF
    - 2,3-DPG shifts OHDC of maternal HbA to R → offloading additional O2 to HbF
  - Double Bohr effect
    - CO2 diffuses down conc gradient from foetus to mother
    - Bohr effect: ΔpCO2 and pH affect O2 transport
      - ↑pCO2 and ↓pH → R shift OHDC → release of O2
      - ↓pCO2 and ↑pH → L shift OHDC → ↑O2 binding capacity
    - Double Bohr effect:
      - effect on sides of placenta
      - 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
  - Foetal O2 carrying capacity
    - Foetus has ↑[Hb] than adults → ↑O2 carrying capacity



Transfer of CO2

- Haldane effect
  - Describes how ΔO2 saturation of Hb affect CO2 transport
  - **deoxyHb has ↑affinity for CO2 than oxyHb**
- Double Haldane effect
  - Haldane 1: placenta: placenta unloads O2 → ↓placental O2 → deoxyHbA has ↑affinity of CO2 → ↑placental CO2 uptake from foetus
  - Haldane 2: foetus: foetus takes up O2 → ↑HbF O2 → ↓HbF affinity for CO2 → ↑HbF 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
  - $D = \frac{sol \times \Delta conc}{\sqrt{MW}} \times \frac{surf\ area}{thickness}$
- Maternal placental flow ~600ml/min at term (2x foetal flow) → ↑diffusion by ↑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 γ subunits cf β→ prevent binding of 2,3-DPG → L shifted OHDC → favours O2 loading at ↓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 → ↑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
- CO2 diffusion
  - Foetal PaCO2 50mmHg; intervillous PCO2 37mmHg
  - CO2 offloading favoured in foetus by:
    - High foetal [Hb] ↑s amount of CO2 that can be carried as carbaminoHb
    - Double Haldane effect
      - Haldane effect: describes how ΔO2 sat of Hb affect CO2 transport: **deoxyHb has ↑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 → ↓placental O2 → deoxyHbA has ↑affinity of CO2 → ↑placental CO2 uptake from foetus
      - Haldane 2: foetus: foetus takes up O2 → ↑HbF O2 → ↓HbF affinity for CO2 → ↑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 → allows maternal abs to provide passive immunity to foetus
- Trophoblast cells lose many cell surface MHC molecules → making them less immunogenic; also cells cover themselves in mucoprotein which disguises them from maternal immunie 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

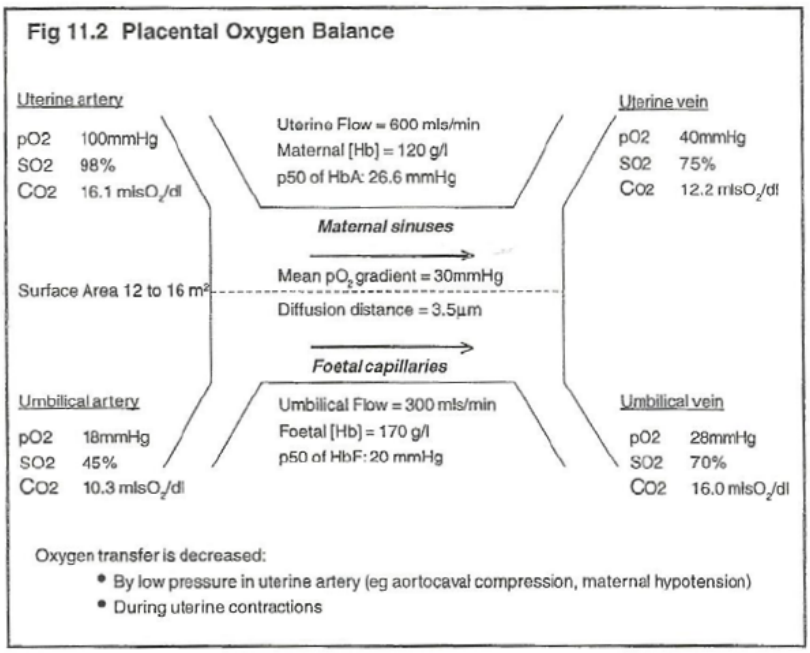
- synthesis of 4 main hormones:
  - bHCG
  - hPL: human placental lactogen (human chorionic somatomammotrophin)
  - Oestriol
  - Progesterone
- Synthesis of other hormones and growth factors
  - Placental corticotrophin
  - Human chorionic somatostatin
  - Human chorionic thyrotropin
  - Epidermal growth factor
  - Somatomedin

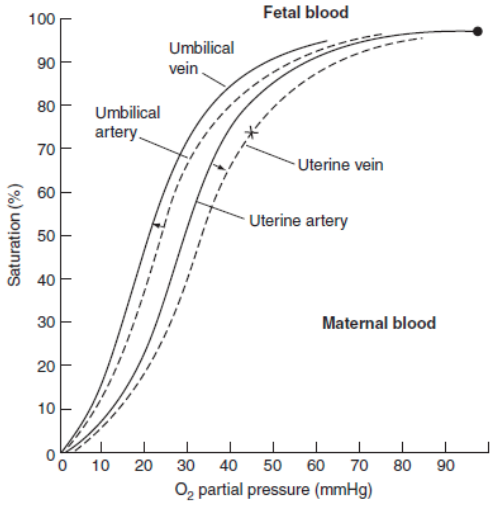
Describe the factors affecting the diffusion of gas at the placenta, including the Bohr and Haldane effects: PAST QUESTION 50%
Explain the Bohr and Haldane effects in trans-placental gas exchange: PAST QUESTION 42%

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





- Rate of diffusion governed by **Fick's law of diffusion**:

$$D = \frac{A}{t} \times \frac{sol}{\sqrt{MW}} \times \Delta conc$$

Where,

D = rate of diffusion
A = diffusional surface area
t = membrane thickness
sol = solubility of diffusate
MW = molecular weight of diffusate
Δconc = concentration gradient

- Placenta is much less efficient than the lung in terms of gas exchange because:
  - ↓area for diffusion (15m2 placenta vs. 80m2 lung)
  - ↑diffusion distance (3.5um placenta vs. 0.5um lung)

Concentration gradient across placenta

	Uterine A	Uterine V	Umbilical A	Umbilical V
Flow (mL/min)	600	600	300	300
pO_2 (mmHg)	100	40	18	28
pCO_2 (mmHg)	32	45	55	35

- 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, ↑temp, 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

- 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 Haldane effect**
  - Describes the Haldane effects happening across the placenta
  - Accounts for 45% of Co2 transfer between maternal and foetal circulation
  - Haldane 1: placenta: placenta unloads O2 → ↓placental O2 → deoxyHbA has ↑affinity of CO2 → ↑placental CO2 uptake from foetus
  - Haldane 2: foetus: foetus takes up O2 → ↑HbF O2 → ↓HbF affinity for CO2 → ↑HbF CO2 release to placenta
- Above is ↑via maternal hyperventilation → ↓maternal PaCO2 → ↑gradient for CO2 to diffuse from foetus to mother → ↑Bohr effect of foetus

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 – proro-porphyrin based ring with central ferrous (Fe2+) molecule bound to 4 globin chains
   - HbF = 2α2γ 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 ΔpCO2 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