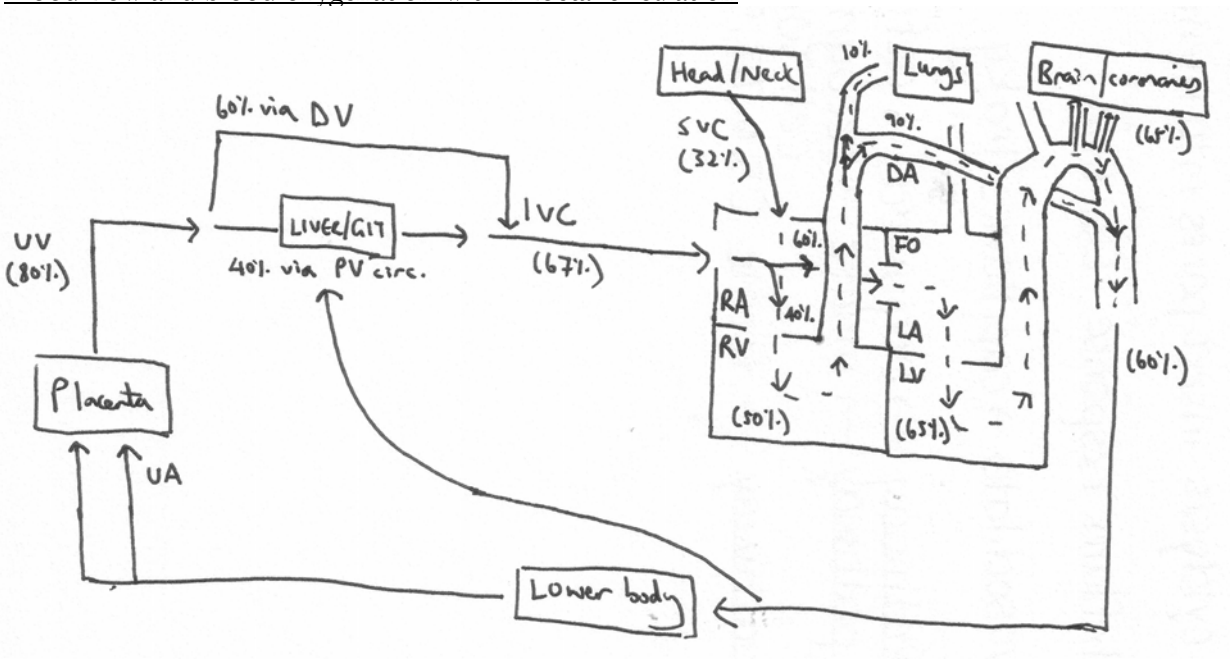
FOETAL AND NEONATAL PHYSIOLOGY

(a) ***To describe the foetal circulation.***

Overview of the foetal circulation:

- RV (pulmonary circulation) and LV (systemic circulation) work in "parallel" due to shunts (foramen ovale and ductus arteriosus)
- LV and RV are of equal size and wall thickness
- Foetal C.O. is dependent on HR (120-140 bpm) → thus, foetal distress (esp during labour) is indicated by HR < 100 bpm ("bradycardia" → foetal hypoxaemia) or > 180 bpm ("tachycardia" → foetal skull pressure)

Blood flow and blood oxygenation within foetal circulation:



- Oxygenated blood (PO_2 30 mmHg; SpO_2 80%) returns from placenta via 1x Umbilical vein → passes into L branch of Hepatic portal vein:
    - 60% of blood is shunted away from portal venous circulation into the IVC via "Ductus venosus"
    - 40% of blood mixes with the portal venous circulation of the GIT/liver
- Oxygenated blood shunted via the "ductus venosus" mixes with blood draining from the portal circulation within the IVC → IVC blood remains well oxygenated (SpO_2 67%)
- IVC blood then enters the RA:
    - 60% of this blood is directed across "Foramen ovale" to the LA by the "Crista terminalis" (muscular ridge in RA) → then passes into LV (PO_2 25 mmHg/SpO_2 65%) → then into the ascending aorta to supply the coronary arteries and brain with well oxygenated blood
    - 40% of this blood mixes with poorly oxygenated blood draining from the head/neck via the SVC (SpO_2 30%) → then passes into RV (SpO_2 50%) → then into pulmonary artery where:
        - 10% of blood enters the lungs (due to ↑ PVR 2° collapsed lungs)
        - 90% of blood is shunted across the "Ductus arteriosus" (wide muscular arterial channel b/t pulmonary artery and aorta) into the descending aorta → perfuses lower body (PO_2 20 mmHg/SpO_2 60%) and returns to placenta via 2x Umbilical arteries

Note – Venous return to the heart – 70% via IVC, 20% via SVC, 10% via lungs/coronary sinus

Note: - LV afterload → high resistance cerebral circulation and upper body circulation - RV afterload → low resistance ductus arteriosus and placenta, and high resistance pulmonary vasculature and lower body circulation

(b) ***To describe the circulatory and respiratory changes that occur at birth.***

(I) Circulatory changes at birth:

Overview of circulatory changes at birth:

- At birth, the circulatory system changes from a foetal system where the LV and RV function in "parallel" to an adult system where they function in "series" → this is initiated by Δs in resistances throughout the neonatal circulation, which produce haemodynamic changes that cause shunt closure

Key circulatory changes at birth:

- (1) Loss of low-resistance placental circulation
  - Due to clamping/closure of umbilical vessels
  - Causes – (i) ↑ SVR → ↑ LVEDP and ↑ LAP, and (ii) ↓ VR via IVC → ↓ RAP
- (2) Significant ↓ in resistance of pulmonary circulation
  - Due to (i) expansion of lung parenchyma initially (opens up extra-alveolar vessels), then (ii) removal of pulmonary HPV by ↑ PAO_2 later
  - Causes – (i) Significant ↓ PVR → ↓ PAP → ↓ RVEDP and ↓ RAP, (ii) Significant ↑ pulmonary blood flow 2° ↓ PVR, (iii) ↑ LAP 2° ↑ pulmonary BF
- (3) Closure of ductus venosus
  - Occurs few hrs post-delivery (?mechanism).
  - Causes ↓ VR via IVC → ↓ RAP
- (4) Shunt closures → reversion to adult circulation where LV/RV function in "series"
  - (a) Closure of foramen ovale → occurs when LAP > RAP. Permanently closes by fusion of septum secundum (4-6/52)
  - (b) Closure of ductus arteriosus → occurs within 10-15 hrs post-delivery (constricts in response to ↑ PaO_2 after the 1st breath, and ↓ [ ] of local/circulating PGE1/E2). Permanently closes by thrombosis/fibrosis (2-3/52)

(II) Respiratory changes at birth:

Overview of respiratory changes at birth:

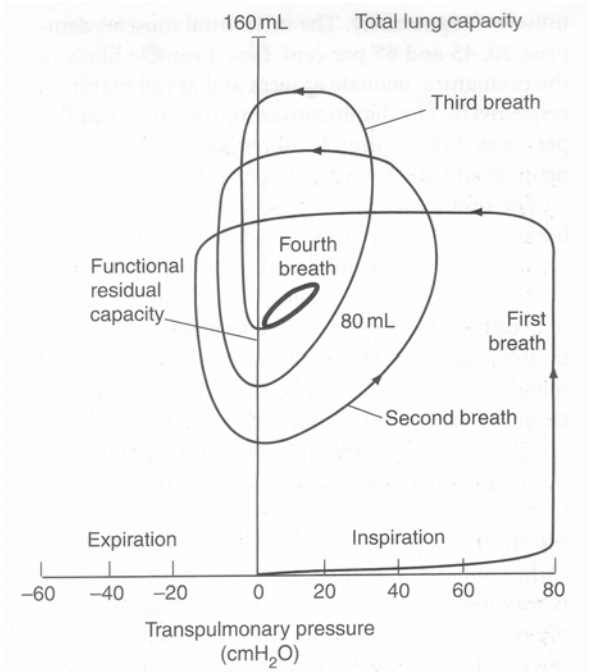
- (1) Loss of placental gas exchange → due to clamping/closure of umbilical vessels
- (2) Initiation of ventilation of newborn's lungs with the 1st few breaths → leading to (i) commencement of pulmonary gas exchange, and (ii) rapid establishment of FRC

Key respiratory changes at birth:

- (1) Foetal thorax is compressed during vaginal delivery (as the chest wall is very compliant due to a soft rib cage) → causes 35 mL of lung fluid to be squeezed out and reabsorbed into pulmonary circulation
- (2) Loss of placental gas exchange due to clamping/closure of umbilical vessels → causes hypoxaemia (PaO_2 ↓ from 30 to 15 mmHg), hypercapnoea ($PaCO_2$ ↑ to 60 mmHg) and acidaemia in newborn
- (3) Initiation of ventilation of newborn's lungs:
  - First few breaths are stimulated by various factors:
    - (i) Environmental sensory stimuli at birth (Eg. sound, touch, temperature, gravity) → afferent signals stimulate the reticular system → ↑ sensitivity of medullary respiratory centres
    - (ii) ↑ responsiveness and control over respiration of central and peripheral chemoreceptor (due to ↑ blood flow through them)
    - (iii) Central and peripheral chemoreceptors are stimulated by hypoxaemia, hypercapnoea and acidaemia caused by loss of placental circulation
  - First few breaths results in:

- (i) 1st breath requires a ↑ -ve $P_{INSPIRATORY}$ 70-100 cmH_2O → but magnitude of –ve $P_{INSPIRATORY}$ for subsequent breaths progressively ↓↓↓ due to (a) establishment of an air-liquid interface and (b) presence of surfactant (which ↓ ST at this interface)

Characteristic P-V loop profile:



- (ii) Rapid establishment of FRC → FRC ↑ to 20 mL/kg after a few minutes, then to 30 mL/kg (= adult FRC) within 1 hr
- (iii) Start of pulmonary gas exchange as lung is inflated
  - Newborn breathes with a TV 5 mL/kg (≈ 20 mL) and RR 30 breaths/min → MV 150 mL/kg/min
  - Rapid ↑ PaO_2, ↓ $PaCO_2$ and ↑ pH
  - Physiological DS ≈ 1.5-2 mL/kg
- (iv) Significant ↓ in resistance of pulmonary circulation (↓ PVR)
  - Due to (a) expansion of lung parenchyma initially (opens up extra-alveolar vessels), then (b) removal of pulmonary HPV by ↑ PAO_2
  - Causes → ↓ PAP/RVEDP/RAP, ↑ pulmonary BF and ↑ LAP → creates haemodynamics that favour closure of foramen ovale
- (v) Closure of ductus arteriosus (within 10-15 hrs post-birth) → due to VSMC contraction 2° ↑ PaO_2 a/w 1st breaths and ↓ [PGE1/2]

- (4) Foetal lung has 20 mL/kg of fluid at term → absorbed into pulmonary circulation:
  - During vaginal delivery → 35 mL absorbed 2° to thoracic compression
  - Post-delivery → remaining fluid is absorbed 2° to ↑ PBF a/w initiation of ventilation

Aside – Foetal respiratory system:
- Bronchial tree of foetal lung fully developed at 16/40
- Type II pneumocytes present in alveolar epithelium and produces surfactant at 24/40 (Nb. ↑ surfactant with (i) ↑ cortisol or thyroxine in mother (Ie. steroids), and (ii) ↑ lecithin in amniotic fluid)
- Preacinar pattern of foetal airway, and arteries/veins formed with capillaries in alveolar wall at 28/40
- Foetal breathing movements present → irregular initially, then later regular and rapid (60 breaths/min)

(c) ***To explain temperature regulation in the neonate and how this differs from the adult.***

Thermoneutral zone (TNZ) of neonate:

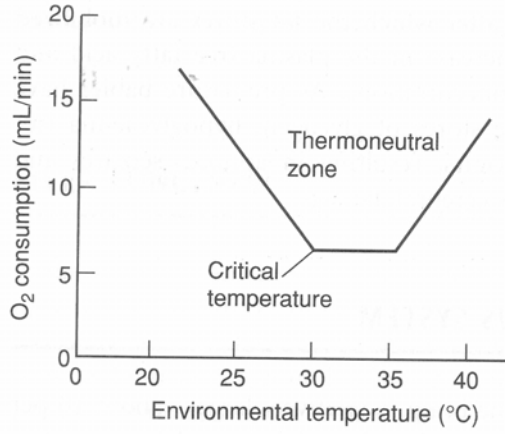
> Recall – TNZ is defined as the range of ambient temperatures in which core body temperature is maintained without an increase in metabolic rate and O_2 consumption (Ie. body heat production) above a resting level → within this zone, thermoregulation is performed only by mild changes in skin blood flow

TNZ of neonate vs adult:

- (i) Range of neonatal TNZ is higher and narrower cf. adult (see below)→ this is b/c they have ↑ evaporative heat losses requiring higher ambient temperatures to maintain core body temperatures without a significant ↑ in metabolic rate

Pre-term neonate:	35-36 °C
Full-term neonate:	32-34 °C (24-30 °C clothed)
Adult:	25-30 °C (20-22 °C clothed)

- (ii) "Critical temperature limits" of neonatal TNZ ↓ with ↑ maturity and body side (Ie. lower limit is 35 °C if preterm, 33°C at term, 32 °C after 2/52)



Note:
- Below the "lower critical temperature" of this zone → metabolic rate ↑ linearly as ambient temperature decreases to prevent ↓ in core body temperature
- Within the zone → metabolic rate remains constant as ambient temperature increases
- Above the "upper critical temperature" of this zone → metabolic rate ↑ linearly as ambient temperature increases to prevent ↑ in core body temperature

Neonatal thermoregulation:

The ability to maintain a stable core body temperature with Δs in ambient temperatures depends on the ability to balance heat production and heat loss → this balance is difficult for a neonate (due to the reasons below), resulting in ↑ risk of heat/cold stress with Δ in ambient temperatures:

- (1) Large SA:volume ratio (2-3x cf. adult) → ↑ environmental heat gain and losses
- (2) Thin subcutaneous tissues (50% cf. adult)→ ↓ insulating capacity and ↑ evaporative losses (esp when skin is wet) → ↑ environmental heat gain and losses
- (3) Higher TNZ (32-34 °C) → neonates have high evaporative heat losses and thus require a higher ambient temperature to maintain core body temperature without a significant rise in metabolic rate → this means they have ↑ environmental heat losses at lower ambient temperatures
- (4) Higher BMR (2x cf. adults) → significant heat loss is required to maintain thermal equilibrium (so TNZ is < body temperature) → so ↑ susceptible to heat stress (Ie. keeping a baby at 37 °C is a form of heat stress)
- (5) Limited sweating capacity (↑ susceptibility to heat stress), shivering response (↑ susceptibility to cold stress), and ability to exert direct control on environment

Mechanisms of neonatal thermoregulation:

- Within TNZ → temperature is maintained by changes in skin blood flow only → requires little ↑ in metabolic rate (or O_2 consumption)
- Cold stress → responses include:

    - (i) Behavioural changes (esp crying to signal attention)
    - (ii) Skin vasoconstriction
    - (iii) Non-shivering thermogenesis (involving brown fat)
    - (iv) ↑ muscular activity and shivering → these are NOT well developed cf. adults, and thus play a minor role
- Heat stress → responses include:
    - (i) Behavioural changes (Ie. crying, removing coverings)
    - (ii) Skin vasodilation
    - (iii) Sweating → limited role in neonates (33% effectiveness cf. adults), BUT sweating results in significant evaporative heat loss (↑ heat loss by 2x)

Aside – Non-shivering thermogenesis → SNS-mediated (β3 receptor) uncoupling of oxidative phosphorylation in brown fat and skeletal muscle → ↑ metabolic heat production without production of ATP or mechanical work

Brown fat:
- Found in newborns only (base of neck, interscapular areas, perinephric fat, around large abdominal vessels) → 2-6 % of total body weight of neonate
- Metabolically active fat tissue → contains many fat globules and mitochondria, highly vascular, and SNS-controlled (via β3 receptor) → responsible for metabolic heat production in neonates during cold stress (can ↑ metabolic rate by 2x)
- Mechanism – Uncouples mitochondrial oxidative phosphorylation so more heat is generated for a given amount of metabolism of metabolic fuels (esp FA oxidation):
    - (i) Metabolism of metabolic fuels → generates a H^+ gradient across the inner mitochondrial membrane → this leads to production of heat
    - (ii) Brown fat uncouples oxidative phosphorylation by inserting channels into this membrane → dissipates the H^+ gradient so no ATP is produced

Dangers of hypothermia in neonate are similar as in adults – but in neonates there is especially:
- (1) ↑ hypoxaemia due to (i) ↑ MRO_2/metabolism and (ii) ↑ respiratory distress 2° to ↓ surfactant synthesis
- (2) ↑ CVS instability (↓ C.O., BP and HR)
- (3) ↑ hypoglycaemia risk due to ↑ metabolism
- (4) ↑ delayed recovery from anaesthesia
- (5) ↑ coagulopathy
- (6) Significant alteration in PK of drugs

Dangers of hyperthermia in neonate:
- (1) ↑ evaporative water loss (due to ↑ SA:vol raito) → ↑ dehydration
- (2) ↑ apnoeic attacks

(d) ***To compare the physiological differences in organ function between neonate and adult.***

(e) ***To explain the control of body fluids in the neonate and how the control and composition differ from the adult.***

Overview of physiological differences in organ function between neonates and adults:

- Before birth → foetus relies on mother for O_2, nutrition, excretion, temperature regulation and homeostasis (via the placenta)
- After birth → placental functions are taken over by the neonate's organs → but these organs are not completely mature at birth → thus, they require continuous physiological adaptations such that they become "mature" at the end of the neonatal period

> Important to note → "Neonatal period" (first 28 days of life) vs "Infancy" (1-12 months post-birth)

Organ-specific physiological differences:

(1) Cardiovascular system:

C.O.	- C.O. very high at birth (280-430 mL/min/kg) → later ↓ to 150 mL/min/kg at 8/52 (cf. 70 mL/min/kg in adults) - ↑ distribution to VRG (Ie. heart, brain, liver, kidney; 50% vs 25% in adults) → to cope with ↑ MRO_2 of metabolically active organs - C.O. is dependent on HR → b/c SV is "fixed" due to a poorly compliant LV (which is a result of a ↑ % of non-contractile myocardial cells in the LV)
HR	↑ HR → 120-160 bpm at birth → gradually decreases to 100 bpm by 1 yr
BP	↓ BP → 70-90/40 mmHg at birth → ↑ gradually to 100/60-70 mmHg by 1 yr
Control of CVS	- SNS system is immature → results in ↑ hypotension and bradycardia with hypoxia, and ↓ efficient response to Δ in postural BP - Aortic chemoreceptors play a more vital role → prevents hypoxaemia-induced changes in haemodynamics (Ie. ↓ BP, vasoconstriction, and variable HR Δs) that is not properly compensated for by an immature SNS system - Circulation remains very labile → easily reverts back to foetal circulation if there is pulmonary vasoconstriction (triggered by hypoxaemia, hypercapnoea, acidaemia) causing ↑ PAP
Others	↑ physiological shunting (20% cf. 7% in adult)

(2) Respiratory system:

Anatomy	- Upper AW
	  o Large tongue and mandible angle (140° cf. 120° in adults)
	  o Narrow nasal passages (accounts for 50% of AWR)
	  o Obligate nasal breathing (cf. mouth breathing) → due to large tongue and mandible angle, and cephalad larynx → so nasal obstruction can precipitate respiratory distress!
	- Larynx
	  o Epiglottis is stiff, long, U-shaped and angled back 45° → so straight laryngoscope blade used for intubation
	  o Glottis is situated at C3/C4 level (cf. C6 in adults) and is angulated anteriorly → so backward pressure on larynx assists intubation
	  o Cricoid ring is the narrowest part of larynx → it enlarges during puberty so vocal cord in the narrowest part in adults
	- Lower AW
	  o Trachea is shorter (3-7 cm length) and smaller (6 mm diameter)
	  o Bronchi branch angle is similar to adults (30° R; 45° L) → risk of R endobronchial intubation remains

	o Small peripheral AWs (< 2 mm diameter) → account for remaining 50% of AWR (cf. 20% in adults) o ↓↓↓ bronchial muscle → so bronchospasms uncommon and bronchodilator drugs have minimal response - Chest wall o Ribs more horizontal → limited AP expansion (lose pump handle mechanism) and transverse expansion (lose bucket handle mechanism) → thus, minimal thoracic component to ventilation and ↑ reliance on diaphragmatic breathing o ↓ % type I muscle fibres (highly oxidative/slow contraction) in diaphragm (25% in neonate vs 55% in adults) and IC muscles (45% vs 65%) → ↑ risk of muscle fatigue
Lung volumes	- FRC (30 mL/kg) → same as adult (as FRC remains 40% of TLC) BUT ↓ stable and ↑ risk of atelectasis due to following reasons: o (i) Significant ↓ in outward recoil of CW (as rib is cartilaginous and contains very little respiratory muscles) o (ii) Mild ↓ inward recoil - TLC (75-80 mL/kg) → same as adult - VC (45 mL/kg) → lower cf. adult (60 mL/kg) - TV same as adult (7 mL/kg) - ↑ CC due to low elastic recoil of lungs → in fact, CC > FRC such that there is small AW closure during tidal ventilation → results in gas trapping and hypoxaemia
Minute ventilation	- MV = 140 mL/kg/min (2x adult) → required to cope with ↑ MRO_2 - ↑ MV generated by ↑↑ RR (30-40/min – cf. 12-15/min in adults) rather than ↑ TV (7 mL/kg – same as adult) → this minimises "work of breathing"
Lung mechanics	- Compliance o Lung – ↑ from 1.5 to 6 mL/cmH_2O within 24 hrs post-birth. Specific compliance similar as in adult (0.05/cmH_2O) o Chest wall – Very compliant due to soft rib cage (allows thorax compression to assist vaginal delivery) → BUT ↑ risk of respiratory failure due to sternal retraction and restricted diaphragm movement caused by AW obstruction - Airway resistance: o AWR ↓ from 90 cmH_2O/L/sec to 25 cmH_2O/L/min after 24 hrs post-birth o Resistance of nasal passages = 50% AWR - End-expiratory $P_{INTRAPLEURAL}$ ~ 0 (cf. –ve pressure in adults) - I:E ratio ~ 1 (cf. 1.5 in adults)
V/Q matching	- Significant V/Q mismatch (V/Q = 0.4) due to shunting caused by small AW closure/gas trapping during tidal ventilation → thus, neonate normally has a ↓ PaO_2 50-60 mmHg with A-a gradient of 30 mmHg - Dead space same as in adults (2.2 mL/kg), including physiological DS (V_D/V_T = 0.3)
Control of ventilation	- Respiratory control less developed (cf. adults) - Peripheral and central chemoreceptors are responsive: o CO_2 ventilatory response curve is shifted left cf. adult → so ventilation occurs at a ↓ level of $PaCO_2$ o O_2 ventilatory response → hypoxaemia causes a transient ↑ MV (2 mins only) post-birth → sustained ↑ MV response after 1 week o Nb. O_2/CO_2 ventilatory responses are depressed by hypothermia - Any ↑ in MV is achieved by ↑ TV (as RR is already ↑) - "Hering-Breuer reflex" (transient apnoea lasting 5 secs evoked by gradual lung inflation) and "Head's paradoxical inflation reflex" (↑ inspiratory

	effort evoked by partial inflation of lungs) are prominent - "Periodic respiration" is common and normal (pauses lasting 5-10 sec (up to 6 x per hr during sleep) → BUT "Apnoeic spells" are abnormal (pauses > 20 secs a/w bradycardia)
O_2 flux to tissues	↑ O_2 flux to tissues due to: - (i) ↑ O_2 carrying capacity of blood cf. adult (by 1.25x) → due to: o ↑ [Hb] → 170-180 g/L o HbF ($\alpha 2\gamma 2$) → left shift in Hb O_2 dissoc'n curve 2° inability to bind 2,3-DPG (lacks β subunits) → ↑ O_2 affinity (P_{50} = 19 mmHg) o ↑ MV → ↑ pO_2 - (ii) ↑ C.O. (esp ↑ % to VRG)
MRO_2	- ↑ resting MRO_2 (6-8 mL/kg/min → 2x adult resting MRO_2) due to ↑ metabolic rate → matched by ↑ O_2 flux to tissues - MRO_2 varies with ambient temperature → MRO_2 is lowest within "thermoneutral zone" → it ↑ 2x for every ↓ 2 °C
ABG	- Umbilical cord blood → combined respiratory and metabolic acidosis (pH 7.26, pO_2 20 mmHg, pCO_2 55 mmHg) - After birth → pH ↑ to 7.35 (within 2/52) then later to 7.40, pCO_2 ↓ to 32-36 mmHg initially then later ↑ to 40 mmHg, pO_2 ↑ to 50-60 mmHg

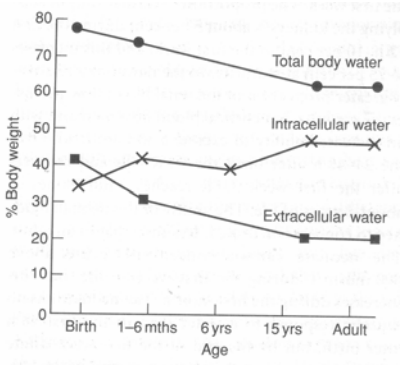
(3) Haematological system:

RBC	- Haemopoiesis – Starts in utero at (i) yolk sac (from 14 days gestation), then (ii) liver (from 14 days gestation until 1 week post-birth) and (iii) BM (from 5 months gestation) - Red cell survival – 30-40 days in utero → ↑ to 60-70 days at term - [Hb] – Foetal and neonatal Hb is 170-180 g/L at term → ↑ further 10-20 g/L in 1st few days post-birth (due to ECF excretion) but normalises after 1 week → ↓ steadily to 110-120 g/L by 1-2/12 post-birth (due to ↓ red cell mass) and remains low until puberty where it ↑ to adult levels - Hb type – In utero, HbF accounts for 90% of total Hb → this ↓ to 75% at birth → then ↓ gradually until it is replaced by HbA at 6/12 post-birth
Platelets	Same levels as adults, but transient and mild defect in function (due to ↓ 5-HT and adenine levels)
Coagulation	Vitamin K CF deficiency due to (i) ↓ liver synthesis (5-20% adult levels) and (ii) ↓ vitamin K stores

(4) Renal system:

Renal blood flow	- ↓ RBF (5% C.O. after birth → ↑ to 10% C.O. after 1/52) due to incomplete glomerular development and renal arteriolar vasoconstriction. - ↑ % RBF perfuses medulla → ↑ cortical blood flow when cortical nephrons develop
Glomerular function	Neonate has incomplete glomerular development → GFR is ↓ at birth → gradually rises such that it reaches adult values at 2 yrs
Tubular function	- Matures at different rates (distal tubules mature early → then proximal tubules → then loop of Henle) → this means in neonates have: o Impaired ability to secrete substances from proximal tubules o Impaired urine concentration ability (Ie. cannot concentrate urine > 600 mosm/L in 1st week post-birth) - Lack of diuretic response to H_2O load (esp in 1st 48 hrs post-birth)→ functional at end of 1st week (Ie. can make dilute urine)
Body fluid compartments	- Neonate has a TBWV 75% of body weight, ECFV 40% of body weight, ICFV 35% of body weight (↑ cf. adults due to ↑ ECFV) - Few days post-birth, excess ECF is excreted → continues until 4-6/12

	where ICFV = ECFV → then ICFV and ECFV continue to ↑ and ↓, respectively, until adult volumes achieved



(5) Hepatic system:
- Many liver functions are poorly developed (esp CHO metabolism and detoxification):
  - ↓ glycogen reserves (4 g/kg in neonate)
  - ↓ ability to conjugate drugs or bilirubin with glucuronide due to ↓ activity of hepatic UDP-glucuronyl transferase → enzyme activity reaches adult levels by 2/12
  - Immature liver enzyme systems → mature rapidly after birth such that they function at adult level by 3/12
  - ↓ albumin levels → synthesis starts in utero (at 12-16/40) and ↑ towards term

(6) Metabolic function:

Foetus	- Glucose is the main metabolic substrate → essential for foetal growth
	  - Mainly transferred from mother across placenta via "facilitated diffusion" (small amounts produced from a.a./fats in foetal liver)
	  - Foetal BGL ~ 70% of maternal BGL
	- In 3rd TM → glycogen stores and fat stores are laid down (Ie. liver and skeletal muscle glycogen stores ↑ from 9 g at 33/40 → 34 g at term)
	- MRO_2 = 4-5 mL/kg/min

Neonatal	- Immediate ↑ MR after birth:
	  - ↑ resting MRO_2 (6-8 mL/kg/min → 2x adult resting MRO_2) → matched by ↑ O_2 flux to tissues
	  - MRO_2 varies with ambient temperature → MRO_2 is lowest within "thermoneutral zone" → it ↑ 2x for every ↓ 2 °C
	- Energy source is 1°ly from glucose (BGL 2.7-3.3 mmol/L at term) → can also metabolise fat/proteins
	- Energy stores:
	  - ↓ glycogen stores cf adult (esp if pre-term) → easily exhausted within 3-4 hrs of starvation (cf. 12 hrs in adults) → thus, ↑ risk of hypoglycaemia (a/w apnoea, seizures and cerebral injury)
	  - Fat stores are important → need to mobilise them earlier during starvation cf. adults due to rapid depletion of glycogen

(7) Nervous and neuromuscular systems:

Brain	- Brain is large at term (10% total body weight) → weight ↑ 3x by 1 yr due to myelination and growth of dendrite processes - H_2O content ↓ by 1 yr (90 to 80%) - BBB is immature (this permits ↑ passage of drugs into brain) - ↑ levels of β-endorphins
NMJ	- End of 1st TM → peripheral muscles are innervated by motor nerves - From 28/40 → motor nerve endings differentiate to form MEPs, BUT there are lower [ ] of ACh within NMJ (this means delayed recovery from NMBD)