PHYSIOLOGY OF PREGNANCY

Pregnancy is associated with major physiological changes:

1.- Hormonal changes

Progesterone changes during pregnancy:
- Smooth muscle relaxation.
- Generalised vasodilatation.
- Bronchodilatation.
- Dilatation within the renal tract.
- Slow gastrointestinal tract motility.
- Thermogenic.
- Nausea and vomiting.
- Decreases requirement of anaesthetics.

Hormonally mediated changes do not reverse immediately in the puerperium. Progesterone levels return to pre-pregnancy values 3–4 weeks after delivery.

2.- Mechanical changes

The uterus enlarges as pregnancy progresses.

The fundus is palpable:
- Abdominally at 2nd trimester
- At the umbilicus at 20 weeks
- At the xiphisternum at 36 weeks
- After delivery the uterus should not be palpable above the umbilicus.

Aortocaval compression

Aortocaval compression by the gravid uterus as a result of supine positioning reduces cardiac output and is associated with a decrease in systemic blood pressure. Supine hypotension is experienced by nearly 15% of women at term. From 13 weeks and maximal between 36-38 weeks gestation.

The severity of this effect is dependent on:
- Patient position.
- Weeks of Gestation.
- Systemic blood pressure.
- Presence of sympathetic block.

Moving from a supine to a lateral position reduces the femoral and IVC pressures.

3.- Cardiovascular changes

At the end of the first trimester, maternal cardiac output increases approximately 35% above pre-pregnancy values and increases up to 40-50% by the end of the 2nd and 3rd
This increased cardiac output is secondary to increases in both stroke volume (25% to 30%) and heart rate (15% to 25%).

Cardiac output returns toward pre-labor values approximately 24 hours postpartum, and reaches nonpregnant levels between 12 and 24 weeks after delivery.

Systolic, diastolic, and mean blood pressure may all decrease 5%-20% by 20 weeks gestational age and then gradually increase toward non-pregnant values as the pregnancy progresses.

**Labour cardiovascular changes**
Cardiac output ↑ further 25–50% in labour and ↑ additionally 15–30% during contractions.
Cardiac output ↑ even more at delivery because uteroplacental transfusion into the maternal intravascular volume, and increase in sympathetic nervous system activity. These changes are attenuated by epidural analgesia.

CVP also increases during contractions,
Partly due to sympathetic activity.
Partly from the transfer of up to 500 ml of blood from the intervillous space.

The implications of these changes for women with cardiac disease are significant.

**4.-Respiratory changes during Pregnancy**
Capillary engorgement of the mucosa of nasal cavity, pharynx and larynx begins early in the 1st trimester.
The thoracic cage ↑ in circumference by 5–7 cm because of the ↑ in both the anteroposterior and transverse diameters from flaring of the ribs.
The enlarging uterus displaces the diaphragm upwards in the later weeks of pregnancy, but the internal volume of the thoracic cavity remains unchanged.
Oxygen consumption and minute ventilation progressively increase during pregnancy.
Tidal volume, respiratory rate and inspiratory reserve volume also increase.

By term, both oxygen consumption and minute ventilation increase up to 50%. The combination of decreased FRC and increased oxygen consumption promotes rapid oxygen desaturation during periods of apnea.

PaCO₂ decreases to 28–32 mm Hg and significant respiratory alkalosis is prevented by a compensatory decrease in plasma bicarbonate concentration.

**Respiratory changes during the Puerperium**
FRC ↑ after delivery but remains below the prepregnant value for 1 to 2 weeks.
Oxygen consumption, tidal volume, and minute ventilation remain ↑ until at least 6 to 8 weeks after delivery. The alveolar and mixed venous PCO₂ increase slowly after delivery and are still slightly below prepregnant levels at 6 to 8 weeks postpartum.

**5.-Pregnancy Haematological and coagulation changes**
Plasma volume ↑ 15% in the 1st trimester and 50% by 32 weeks.
The RBC volume ↑ 20-30% so there is a reduction of about 15% in Hb and haematocrit: **physiological anaemia**
The blood WCC rises progressively
Pregnancy is associated with enhanced platelet turnover, clotting and fibrinolytic activity (increases PDF)
Coagulation factors
   I, VII–X and XII are increased
   XI and XIII are reduced.
   II and V remain the same
Total plasma protein concentration falls
   albumin is reduced
   globulin and fibrinogen levels are increased
The reductions in plasma proteins causes:
   Total colloid osmotic pressure is reduced by 5 mmHg.
   Drug-binding capacity of the plasma is altered, with consequent changes in pharmacokinetics and dynamics
   Plasma concentration of pseudocholinesterase is reduced by 20–25% at term.
Erythrocyte sedimentation rate and blood viscosity are increased.

**6.-Renal function changes**
Renal collecting system dilates from 1st trimester
Renal flow ↑ 30–50% at 30 weeks then ↓ gradually.
GFR ↑ about 150 ml /min in the 2nd trimester and falls towards term.
   ↓ plasma concentrations of urea and creatinine.
   decrease in plasma osmolality.
   Proteinuria (to 300mg/day) and glucosuria (1-10 g/day)

**7.-Gastrointestinal changes during pregnancy**
Cephalad displacement of stomach and intestines.
The intragastric pressure ↑ from 7-8 cmH$_2$O to 13-17cmH$_2$O in pregnancy.
Barrier pressure (lower oesophageal sphincter pressure minus gastric pressure) is reduced significantly.
LOS pressure appears to return to normal by 48 hours post delivery.
Pyrosis occurs in 55–80% of pregnant women and may occur at <20 weeks gestation.
This is thought to be due to gastro-oesophageal reflux that occurs when barrier pressure is reduced.
Approximately 50% of women in labour have ↑ gastrine production and gastric pH<2.5.
Gastric emptying is not delayed during pregnancy but becomes delayed during labour, particularly if opioids are administered.

**8.-Central nervous system changes during pregnancy**
Epidural space:
   Epidural veins are engorged
   Epidural pressure ↑
   ↑ abdominal pressure
↑ to 4-10 cmH₂O in labour and to 60 cmH₂O during bearing-down efforts

↑ Sympathetic tone
Less local anaesthetic is required to produce a given level of anaesthesia

9.-Musculoskeletal system changes during pregnancy
The mobility of the sacroiliac, sacroccocygeal, and pubic joints increases in preparation for passage of the foetus
relaxin hormone
Exaggerated lumbar lordosis

Physiology of labour
The first stage is defined by the onset of true labour and ends with complete cervical dilation.
The second stage begins with full cervical dilation, is characterized by foetal descent, and ends with complete delivery of the foetus.
The third stage extends from the birth of the baby to the delivery of the placenta.

Stages of Labor and Pain Pathways
1st stage of labor
'visceral pain’ transmitted by C and A-delta nerve fibers to the dorsal horn of spinal cord
involves T10 to L1 segments.

2nd stage
involves pudendal nerve to the S2-S4 dorsal root ganglia.
This pain can be localized to the perineum and is described as 'somatic'.

UTEROPLACENTAL PHYSIOLOGY

Placental flow
Uterine blood flow increases from 500 to 700 ml/min
10–12% of CO at term
>80% flow to the placenta.
Factors decrease uterine blood flow during pregnancy:
  - systemic hypotension
  - uterine vasoconstriction
  - uterine contractions.

Placental Exchange
1. Diffusion
2. Osmotic and hydrostatic pressure (bulk flow)
   Water moves across by osmotic and hydrostatic pressures.
3. Facilitated diffusion
   Glucose enters the foetal circulation down the concentration gradient (no energy is consumed) facilitated by a specific transporter molecule.
4. Active transport
Amino acids, vitamin B12, fatty acids, and some ions (calcium and phosphate) utilize this mechanism.

5. Vesicular transport
Large molecules, such as immunoglobulins, are transported by pinocytosis.
Iron enters the foetal circulation in this way, facilitated by ferritin and transferrin.

6. Breaks
Breaks in the placental membrane may permit mixing of maternal and foetal blood. This probably underlies Rh sensitization.

**Placental transfer of drugs**
Most drugs used in anaesthesia have molecular weights well under 1000 and consequently can readily diffuse across the placenta.
Virtually all transfer of drugs across the placenta occurs by simple diffusion; its rate of transfer is determined by Fick’s law of diffusion, which states that:
\[ Q = k A (C_m - C_f) / D \]
- **Q** = rate of diffusion
- **A** = area
- **C** = concentration drug
- **D** = thickness membrane

**Factors affecting placental drug transfer**

**Lipid solubility**
Lipophilic molecules diffuse readily lipid membranes.

**Degree of ionisation**
Only the non-ionized fraction of a drug crosses the placental membrane (most anaesthetics).

**Protein binding**
The diffusibility of a protein-bound drug is negligible compared with that of free drug.

**Molecular weight of drug**
Drugs with MW of 600 Daltons or less readily diffuse across the placenta (most anaesthetic drugs)

**Maternal-foetal pH**
Changes in maternal or foetal pH alter the degree of ionization of a drug and protein binding. This effect is dependent on the pKa of the drug.
If the pKa is near the pH of blood small changes in blood pH produce large changes in drug ionisation.

**Ion trapping:**
Acidotic foetus ↑ ionisation of the drug, which is then unable to equilibrate with the maternal circulation by diffusion back across the placenta.
Drug accumulation in the foetus relevant for local anaesthetics.
Drug transfer occurs down a concentration gradient

Maternal drug concentration
Depends on the route of administration, total maternal dose, volume of distribution and drug clearance and metabolism.
- highest after intravenous administration
- epidural and intramuscular similar maternal blood concentrations.
- systemic drug absorption will be greater from more vascular tissues,

Foetal drug concentration
The foetus eliminates drugs less effectively
- less plasma protein binding capacity
- less mature enzyme systems than the mother
- some transfer of drugs occurs back across the placenta to the mother if the maternal concentration falls below that in the foetus.

Placental transport of substances
Oxygen
Crosses the placenta by simple diffusion depends on:
- difference between the oxygen tension
- shape of the foetal oxyhaemoglobin dissociation curve
- Bohr effect.
The foetal oxyhaemoglobin dissociation curve lies to the left of the maternal curve.
Favours transfer of oxygen from the mother to the foetus.
P50 foetal blood is 19 to 21 mm Hg
P50 adult blood equals 27 mm Hg
This difference is largely a result of the high concentration of Hb F in foetal blood (75% to 84%).

Oxygen: Bohr effect
A rise or fall in CO₂ (↑ or ↓ pH) leads to right or left shift in the oxyHb dissociation curve.
At the gas exchange interface:
- foetal blood gives up CO₂, becomes more alkaline (left shift) and develops a greater affinity for O₂.
- maternal blood takes up CO₂, becomes more acidic (right shift) and releases O₂.

Double Bohr effect accounts for 2–8% of the transplacental transfer of oxygen.
Carbon dioxide
It is present in blood
dissolved CO$_2$ (8%): crosses the placenta by simple diffusion
bicarbonate ion (62%)
carbamino haemoglobin (30%)
The placental membrane is highly permeable to CO$_2$, which is 20 times more diffusible
than oxygen.
A rise or fall in O$_2$ tension leads to a ↓ or ↑ affinity for CO$_2$ (Haldane effect) and this affects the transport of CO$_2$.
The materno-foetal transfer of oxygen produces de-oxyhaemoglobin in the maternal
blood that has a greater affinity for CO$_2$ than oxyhaemoglobin. As the fetal blood takes
up oxygen, it enhances CO$_2$ release.
This is known as the double Haldane effect and it may account for as much as 46% of
the transplacental transfer of CO$_2$.

Placental transfer of individual drugs
Muscle relaxants
Muscle relaxants are highly ionized, and therefore poorly lipid-soluble, their transfer is
almost negligible.
Anticholinergics
Atropine is detected in umbilical circulation within 1–2 minutes of maternal IV
injection.
Glycopyrrolate is poorly transferred.
Opioids:
All opioids cross the placenta in significant amounts
Local anaesthetic agents
Local anaesthetic agents cross the placenta by simple diffusion.
Commonly used local anaesthetics have MW from 234 Daltons (lidocaine) to 288
(bupivacaine).
Weak bases and have relatively low degrees of ionisation and high lipid solubility at
normal pH
‘ion trapping’.
Drugs that are highly plasma protein-bound (bupivacaine, etidocaine) will have
reduced placental transfer and lower F/M ratios compared with those with
lower plasma protein binding (lidocaine, mepivicaine)
Transfer to the foetus is also affected by other factors, which include:
dose: higher doses result generally in higher maternal and foetal blood
concentrations
effects of adjuvants such as epinephrine
The vascularity of the site of injection will determine the rate of absorption of
the drug.
absorption from the paracervical injection is greater than from epidural
injection.
ANAESTHETIC IMPLICATIONS OF PREGNANCY

Endotracheal intubation
- Smaller endotracheal tube required
- ↑ risk of trauma with nasotracheal intubation
- ↑ risk of failed intubation
- ↑ risk of pulmonary aspiration of gastric contents

Maternal oxygenation
- ↑ physiologic shunt when supine
- ↑ rate of denitrogenation
- fast decline of PaO₂ during apnea
- ↑ oxygen consumption:
  - Decreased FRC (store of oxygen)

Maternal ventilation
- ↑ minute ventilation required
  - PaCO₂ under 20 mmHg can alter blood flow to the placenta

Regional anesthesia: pregnancy implications

Technical considerations
- Lumbar lordosis increased
- Head-down tilt when in lateral position
- Aortocaval compression
- CSF return unaltered
- Reduced sensitivity of “hanging drop” technique