Obstetric anaesthesia 1: physiological changes in pregnancy

Maternal physiology undergoes adaptations across most organ systems from the first trimester, driven by a combination of progesterone release from the placenta and the increased metabolic demands associated with pregnancy. Such changes are vital evolutionary adaptations to accommodate the growing fetus and prepare the parturient for delivery. From the second trimester onwards, physiological changes are compounded by the mechanical effects of the gravid uterus. This article gives an overview of the physiological adaptations during pregnancy, including implications for drug metabolism and administration. It is the first of a series of three – subsequent articles will cover anaesthetic conduct for labour and operative delivery.

Cardiovascular changes

Changes in the cardiovascular system begin as early as 8 weeks of pregnancy. As mean arterial pressure is a product of cardiac output and systemic vascular resistance, the obstetric patient is vulnerable to significant changes in blood pressure because of alterations in both cardiac output and systemic vascular resistance. Progesterone drives peripheral vasodilatation leading to a drop in systemic vascular resistance (25–30%) and a compensatory increase in cardiac output by around 40% or more during labour and delivery.

Increases in both stroke volume and heart rate account for this increase in cardiac output. Stroke volume is increased via early increases in cardiac ventricular wall muscle mass and end diastolic volume. Both left ventricular hypertrophy and dilatation reverse after pregnancy, but can result in electrocardiogram changes of left axis deviation, depressed ST segments and inversion or flattening of the T-wave in lead III. Maternal intravascular fluid volume begins to increase in the first trimester of pregnancy as a result of increased stimulation of the renin–angiotensin–aldosterone axis, which promotes sodium reabsorption and subsequent water retention.

Pulmonary vascular resistance, like systemic vascular resistance, decreases significantly in normal pregnancy. The colloid osmotic pressure is reduced by about 30%, making pregnant women particularly susceptible to pulmonary oedema. These physiological adaptations lead to findings on cardiovascular examination that may be misinterpreted as pathological (*Table 1*).

After 20 weeks' gestation (or earlier with a larger gravid uterus or polyhydramnios), the mother being in a recumbent position can lead to supine hypotension, with secondary effects on placental and fetal hypoperfusion. Evidence from indirect measurements of perfusion such as differential blood pressure, but also angiography, shows that the gravid uterus exerts external pressure on the inferior vena cava, causing a reduction in venous return to the heart and potentially catastrophic falls in stroke volume and cardiac output (Howard et al, 1953). The abdominal aorta may also compress in the supine position, decreasing uterine artery blood flow (Bieniarz et al, 1966). Avoidance of aortacaval compression has led to the use of left lateral tilt or positioning particularly during periods of fetal distress or operative delivery to provide optimal physiological conditions for maintenance of cardiac output.

Although studies have challenged confidence in the capacity to mitigate against supine haemodynamic changes with a more practically achievable lateral tilt to 15° than 20° (Cluver et al, 2013; Higuchi et al, 2015), displacement of the gravid uterus remains an important early compensatory intervention in the face of maternal hypotension (Bieniarz et al, 1966). However, during maternal cardiac arrest, manual uterine displacement is preferable as it interferes less with cardiac compression than left lateral tilt.

Respiratory changes

Changes in the respiratory system start as early as the 4th week of gestation. Total lung capacity decreases as a result of encroachment of the diaphragm by the gravid uterus. Additionally, the functional residual capacity, residual volume and expiratory reserve volume all decrease by term. At term the gravid uterus can increase diaphragmatic

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Table 1. Cardiovascular findings which can be considered non-pathological in pregnancy

Physical examination	Bounding or collapsing pulse
	Ejection systolic murmur (Soam-Pillay et al, 2016)
Electrocardiogram changes (may be the result of changes in position of the heart)	Atrial and ventricular ectopics
	Q wave (small) and inverted T wave in lead III
	ST segment depression and T-wave inversion in the inferior and lateral leads
	Left axis shift of QRS, shortened PR interval

> Blood flow to the liver remains unchanged, but the percentage of cardiac output to the liver is reduced, which may impair clearance of substances requiring extensive hepatic metabolism

elevation by 4 cm. However, inspiratory capacity and inspiratory reserve volume are increased as a result of compensatory relaxation of ligaments across the chest wall to increase thoracic transverse and antero-posterior diameters.

Breathing becomes relatively more dependent upon diaphragm displacement at term, which is advantageous when placing parturients in a supine position for operative delivery. Unfortunately the fall in functional residual capacity means that supine positioning causes distal alveoli collapse in at least 50% of term women; as a consequence pre-oxygenation ahead of general anaesthesia is less effective (Hill and Pickinpaugh, 2008). There is no change in vital capacity (Bieniarz et al, 1966; Hill and Pickinpaugh, 2008), peak expiratory flow rate or forced expiratory volume in 1 second (Soma-Pillay and Pattinson, 2016).

There is a significant increase in oxygen demand during normal pregnancy because of the metabolic demands of the mother and fetus. The mother's basal metabolic rate increases by 15% and there is a 20% increased consumption of oxygen. There is a 40–50% increase in minute ventilation, mostly as a result of an increase in tidal volume rather than in the respiratory rate, although increased progesterone levels can increase the sensitivity of the medullary respiratory centre to carbon dioxide (Shagana et al, 2018). Maternal hyperventilation causes arterial partial pressure of oxygen (PaO_2) to increase and arterial partial pressure of carbon dioxide ($PaCO_2$) to fall, with a compensatory fall in serum bicarbonate to 18–22 mmol/litre. A mild fully compensated respiratory alkalosis is therefore normal in pregnancy (arterial pH 7.44) (Soma-Pillay and Pattinson, 2016).

Haematological changes

Plasma volume increases progressively throughout pregnancy and in proportion with fetal growth, beginning at 6 weeks gestation and reaching a maximal increase of approximately 45–50% by term (Whittaker et al, 1996). White and red blood cell counts increase but with no change in mean corpuscular volume or mean corpuscular haemoglobin concentration (Peck and Arias, 1979). Plasma volume increases relatively more than blood cell volume, leading to a dilution of haemoglobin, termed physiological anaemia of pregnancy. As a result, concentrations of haemoglobin may fall at term to 110–150 g/litre, yet overall oxygen-carrying capacity of the blood is increased. The additional blood volume rises in accordance with a need to convey extra oxygen to organs with very large increases in metabolic demand, including the placenta, but also provides a residual to compensate for potential blood loss at delivery.

Another evolutionary adaptation in preparation for delivery of the fetus, and potential blood loss that may occur concurrently, is an increase in blood coagulability as gestation progresses. There is an increase in levels of fibrinogen and factor VIII and slower increases in levels of factors VII, IX, X and XII. The platelet titres tend to fall slightly as a result of the relative dilution by plasma, yet overall circulating platelet cell volume is increased. Fibrinolytic activity is diminished during pregnancy by unknown mechanisms. These changes increase the risk of thromboembolic events and last until approximately 8 weeks post-partum (Muallem and Rubeiz, 2006). Thromboprophylaxis is therefore an important discussion following delivery, requiring an individualised, risk-adaptive approach.

Renal changes

Increased renal plasma flow (driven by changes in the cardiovascular system and increases in renin secretion) directly increases the glomerular filtration rate by 50% during the second trimester and until 3 months postpartum, predictably causing decreases in plasma concentrations of urea, creatinine and nitrogen (Davison and Dunlop, 1980). There is reduced absorption of glucose and amino acids, potentially causing glucosuria and aminoaciduria in normal pregnancies.

Serum concentrations of highly protein-bound drugs are lower during pregnancy because of a combination of expanded blood volume and increased glomerular filtration rate (Chapman et al, 1997). After the 12th week of gestation, the enlarging uterus can compress the ureters as they cross the pelvic brim and cause ureteral dilatation by obstructing flow. These changes return to normal by the 6th week postpartum (Shagana et al, 2018).

Gastrointestinal changes

Progesterone also drives changes in the gastrointestinal systems, decreasing gastrointestinal motility, oesophageal pressure and food absorption (Baron et al, 1993). Conversely, intragastric pressure increases as the stomach is displaced by the gravid uterus leading to symptomatic gastro-oesophageal reflux in 80% of patients (Yentis et al, 2013). The gastric emptying time of solid and liquid material is slowed during labour and hence there is a risk of Mendelson's syndrome (pneumonitis from aspiration of gastric contents), particularly if general anaesthesia is required.

Liver changes

Pregnancy-related changes in sex hormones directly affect biliary smooth muscle contractility, but these changes are asymptomatic in normal pregnancy (Egan et al, 2012). In pathological cases, hormone-induced changes in biliary transport and metabolism can lead to symptomatic obstetric cholestasis.

Abnormalities in hepatic enzymes and proteins in the context of normal pregnancy are limited to an increase of alkaline phosphatase level (placental and bone origin) (Baron et al, 1993) and a decrease in albumin level (as a result of haemodilution) and are not indicative of pathology unless markedly abnormal or accompanied by other hepatic abnormalities (Kia and Rinella, 2013). Blood flow to the liver remains unchanged, but the percentage of cardiac output to the liver is reduced, which may impair clearance of substances requiring extensive hepatic metabolism (Robson et al, 1990).

Dilution of plasma cholinesterase at term by up to 25% and for a further 3 days postpartum may prolong neuromuscular blockade after the administration of suxamethonium, although this is rarely clinically significant.

The physiological changes discussed above are summarized in *Table 2*.

Pharmacological changes in pregnancy

Physiological alterations during pregnancy can affect both the pharmacokinetic and the pharmacodynamic profile of drugs.

Bioavailability

Gastric absorption is unchanged during pregnancy (Wong et al, 2002, 2007) but the nociceptive stimulus of labour, anxiety, or the administration of opioids (including neuraxial opioids) causes decreased gastric emptying and delayed intestinal absorption of drugs. The changes in liver enzyme activity can alter activation of prodrugs (and therefore the time course of drug onset), as well as absorption, metabolism and clearance of drugs (Wong et al, 2007; Ansari et al, 2016).

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Distribution

Increased plasma volume results in reduction in maternal plasma protein concentration and therefore drug-binding ability is 70–80% of normal values at the time of delivery (Dean et al, 1980). This is particularly relevant for drugs that are water soluble and highly protein bound, with increased free fraction of highly protein-bound drugs such as midazolam, digoxin, phenytoin and valproic acid.

Increased plasma volume increases the volume of distribution for water-soluble drugs, so pregnancy may be associated with lower peak and steady-state drug concentrations if the dosing regimen is unchanged (Krauer and Krauer, 1977).

Obstetric patients who remain on these agents during pregnancy (especially for arrhythmia or seizure control) need cautious dose monitoring and possible adjustment.

Table 2. Physiological changes during pregnancy

System	Physiological changes
Cardiovascular	Heart rate ↑ peaking at 28–32 weeks
	Stroke volume ↑ by 30%
	Cardiac output ↑ 40% by term
	↓ systemic vascular resistance
Respiratory	↑ tidal volume and 50% ↑ in minute volume
	↑ oxygen consumption approximately 20% by third trimester
	↓ functional residual capacity from 20 weeks
	↓ $PaCO_2$ to 4 kPa by 12 weeks
Haematological	↑ intravascular volume; 50% plasma and 20% red cell expansion causing physiological anaemia (haemoglobin ~100 g/litre at term)
	Constant ↑ white cell count, peaking after delivery
	↑ in all clotting factors excluding XI and XIII (therefore ↑ risk of venous thromboembolism)
	Small ↓ in platelets
	↓ fibrinolytic activity
Renal	↑ renal blood flow, glomerular filtration rate and renin–angiotensin system activation
	↑ sodium and water retention
	↓ plasma creatinine and urea
Gastrointestinal	Normal gastric emptying time and acidity, but prolonged during labour
	↓ lower oesophageal tone, normal by possibly 36 hours post-partum
	↑ incidence of gastro-oesophageal reflux disease
Endocrine	↑ peripheral insulin resistance causing ↑ risk of gestational diabetes mellitus

adapted from Yentis et al (2018)

Placenta drug transfer

The utero-placental unit acts as another compartment in terms of drug distribution for agents that can cross the placenta. Teratogenic agents which are specifically avoided in the first trimester because of the risks of fetal abnormalities include warfarin, phenytoin and sodium valproate. Non-steroidal anti-inflammatory agents should especially be avoided after 28 weeks' gestation because of the risk of premature ductus arteriosus closure (Nejdlova and Johnson, 2012).

Owing to the lower pH environment in the fetal sac, drugs such as opioid compounds become more ionized, essentially causing 'ion trapping' (H+ ions bind to the non-ionized form, trapping the drug in the fetal circulation) and increased concentrations in the fetal circulation that are not able to be cleared efficiently by the maternal system. This is particularly crucial during labour and delivery and guides decision making towards prescribing shorter-acting opioids.

Clearance

Drug metabolism and excretion rely on the liver and kidney blood flow and function. Alteration in renal function can significantly increase the clearance of renally excreted drugs such as heparin (Ansari et al, 2016). *Table 3* gives examples of changes in metabolic liver enzymes. The clearance determines the concentration of the drug during steady state.

Half life

The half life of an agent (the time taken for the plasma concentration of the agent to reduce to half) is unpredictable in pregnancy as both volume of distribution and clearance increase throughout pregnancy. The volume of distribution is important to determine the loading dose of a drug needed to achieve therapeutic concentrations (Feghali et al, 2015). The half life determines how often

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the drug must be given to maintain adequate drug levels. In the absence of pharmacokinetic studies, the half life is considered unchanged in pregnancy, so drugs should be dosed with the same frequency in pregnant and non-pregnant women (Ansari et al, 2016).

Conclusions

Surgery during pregnancy brings the additional challenge of balancing the needs of both mother and baby, each with separate but inter-related physiological considerations. Careful consideration must be given to anaesthetic technique for obstetric and non-obstetric surgery in coincidentally pregnant patients, considering the factors listed in *Table 4*.

Unpicking the evidence for detrimental effects of surgery and anaesthesia on pregnancy outcomes is challenging, owing to a lack of appropriate controls and outdated data when assessing risk in most observational studies. Hence concerns regarding potential risk of miscarriage and fetal loss during non-obstetric surgery are common, but probably disproportionate (Tolcher et al, 2018) with safe anaesthesia and surgery demonstrating excellent outcomes for a wide range of non-obstetric procedures during pregnancy.

All general anaesthetic drugs, and many supplementary drugs given during anaesthesia, cross the placental barrier. Although there are no randomized controlled trials to provide clear evidence of mortality and morbidity benefit to regional anaesthesia over general anaesthesia, a neuraxial technique is preferable when possible to minimize fetal drug exposure, avoid airway and respiratory disturbance, and provide optimal postoperative analgesia.

The next articles in this series will look at anaesthetic conduct for labour and operative delivery. **BJHM**

Conflict of interest: none.

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Table 3. Alterations to metabolic activity of hepatic metabolic enzymes during pregnancy and clinical consequences

Enzyme	Substrate	Effect of pregnancy on enzyme activity	Clinical effect
CYP2D6	Codeine	Induced	Decreased availability of codeine
CYP3A4, CYP2B6, CYP2C9 and uridine 5'-diphosphate	CYP2B6: propofol, ketamine; CYP2C9: celecoxib, ibuprofen, flurbiprofen, warfarin and phenytoin; CYP3A4: acetaminophen, codeine, ciclosporin, diazepam, erythromycin	Induced	Decreased availability of these drugs
CYP1A2	Caffeine	Reduced	Increased plasma concentration especially by third trimester

Table 4. Important maternal adaptations and implication for anaesthetic practice

Obstetric factor	Potential risk	Anaesthetic conduct	Comment
Gastro-oesophageal reflux disease	Mendelson's syndrome	Preoperative proton pump inhibitor and prokinetic	Increased risk from 20 weeks' gestation
Weight gain, larger breasts and vascularised airway tissue	Difficult airway	Difficult airway equipment	Consider smaller endotracheal tube of size 6.5–7.0 mm
Reduced functional residual capacity	Quicker time to hypoxia	Head-up tilt position, consider nasal oxygenation in addition to mask, consider ventilation (<20 cmH_20)	
Aortocaval compression	Maternal hypotension and resultant fetal distress	Left lateral tilt when supine or manual displacement of uterus	Can also adopt lateral positions
Sensitivity to anaesthetic volatile agents	Maternal hypotension and reduction in uterine tone	Mindful reduction in minimum alveolar concentration, but close depth of anaesthesia monitoring for risk of awareness, e.g. bispectral index monitoring, entropy	Fetus exposed to volatile anaesthetic gases as well
Unclear effect of nitrous oxide	Possible teratogenic link in fetus	Avoid in first trimester	Owing to possible effects on B-methionine synthesis

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KEY POINTS

- Cardiac output increases by 40% during pregnancy. At term the gravid uterus can impede blood flow by compression of major vessels.
- Fall in functional residual capacity during pregnancy results in less effective pre-oxygenation ahead of general anaesthesia. This, together with the significant increase in oxygen consumption during pregnancy, can cause rapid desaturation during a period of apnoea and airway manipulation or instrumentation.
- The increase in blood coagulability as gestation progresses increases the risk of thromboembolic events until approximately 8 weeks post-partum.
- Gastric emptying times are slowed during labour, hence the increased risk of pneumonitis from aspiration of gastric contents.
- The percentage of cardiac output to the liver is reduced, which may impair clearance of substances requiring extensive hepatic metabolism.
- Teratogenic agents (including warfarin, phenytoin and sodium valproate) are specifically avoided in the first trimester because the risk of fetal abnormalities.