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Physiological Changes Associated with Pregnancy

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Summary

Physiological and anatomical alterations develop in many organ systems during the course of pregnancy and delivery. Early changes are due, in part, to the metabolic demands brought on by the fetus, placenta and uterus and to the increasing levels of pregnancy hormones. Later changes, starting in mid-pregnancy, are anatomical in nature and are caused by mechanical pressure from the expanding uterus. These alterations create unique requirements for the anaesthetic management of the pregnant woman.

CARDIOVASCULAR SYSTEM

The pregnancy induced changes in the cardiovascular system develop primarily to meet the increased metabolic demands of the mother and fetus.

Blood volume

Blood volume increases progressively from 6-8 weeks gestation (pregnancy) and reaches a maximum at approximately 32-34 weeks with little change thereafter. Most of the added volume of blood is accounted for by an increased capacity of the uterine, breast, renal, striated muscle and cutaneous vascular systems, with no evidence of circulatory overload in the healthy pregnant woman. The increase in plasma volume (40-50%) is relatively greater than that of red cell mass (20-30%) resulting in haemodilution and a decrease in haemoglobin concentration. Intake of supplemental iron and folic acid is necessary to restore haemoglobin levels to normal ($12g.dl^{-1}$). The increased blood volume serves two purposes. First, it facilitates maternal and fetal exchanges of respiratory gases, nutrients and metabolites. Second, it reduces the impact of maternal blood loss at delivery. Typical losses of 300-500ml for vaginal births and 750-1000ml for caesarean sections are thus compensated with the so-called 'autotransfusion' of blood from the contracting uterus.

Blood constituents

As mentioned above, red cell mass is increased 20-30%. Leukocyte counts are variable during gestation, but usually remain within the upper limits of normal. Marked elevations, however, develop during and after parturition (delivery). Fibrinogen, as well as total body and plasma levels of factors VII, V11, IX, and X increase markedly. The number of platelets also rises, yet not above the upper limits of normal and this is combined with a decrease in fibrinolytic activity. All these changes tend to make pregnancy a relatively hypercoagulable state. This prevents excessive bleeding at delivery but increases the risk of thrombo-embolic complications. At delivery there is an increase in fibrinolytic activity, especially the third stage, and a high concentration of plasminogen activators in the uterus, both of which may activate disseminated intravascular coagulopathy.

Cardiac output

Cardiac output increases to a similar degree as the blood volume. During the first trimester cardiac output is 30-40% higher than in the non-pregnant state. Steady rises are shown on Doppler echocardiography, from an average of $6.7l.min^{-1}$ at 8-11weeks to about $8.7l.min^{-1}$ flow at 36-39weeks; they are due, primarily, to an increase in stroke volume (35%) and, to a lesser extent, to a more rapid heart rate (15%). There is a steady reduction in systemic vascular resistance (SVR) which contributes towards the hyperdynamic circulation observed in pregnancy.

During labour further increases are seen with pain in response to increased catecholamine secretion; this increase can be blunted with the institution of labour analgesia. Also during labour, there is an increase in intravascular volume by 300-500ml of blood from the contracting uterus to the venous system.

Following delivery this autotransfusion compensates for the blood losses and tends to further increase cardiac output by 50% of pre-delivery values. At this point, stroke volume is increased while heart rate is slowed. The left ventricular work of the heart is increased by 40%. This represents a high risk period for parturients with cardiac disease.

Cardiac size, position and the ECG

There are both size and position changes which can lead to changes in ECG appearance. The heart is enlarged by both chamber dilation and hypertrophy. Dilation across the tricuspid valve can initiate mild regurgitant flow causing a normal grade I or II systolic murmur. Upward displacement of the diaphragm by the enlarging uterus causes the heart to shift to the left and anteriorly, so that the apex beat is moved outward and upward. These changes lead to common ECG findings of left axis deviation, sagging ST segments and frequently inversion or flattening of the T wave in lead III.

Blood pressure

Systemic arterial pressure is never increased during normal gestation. In fact, by mid-pregnancy, a slight decrease in diastolic pressure can be recognized. Pulmonary arterial pressure also maintains a constant

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level. However, vascular tone is more dependent upon sympathetic control than in the non-pregnant state, so that hypotension develops more readily and more markedly consequent to sympathetic blockade following spinal or extradural (epidural) anaesthesia. Central venous and brachial venous pressures remain unchanged during pregnancy, but femoral venous pressure is progressively increased due to mechanical factors. There is also a reduction in afterload and an increase in preload which, together with the increase in blood volume, may produce functional murmurs.

Aorto-caval compression

From mid-pregnancy, the enlarged uterus compresses both the inferior vena cava and the lower aorta when the patient lies supine. Obstruction of the inferior vena cava reduces venous return to the heart leading to a fall in cardiac output by as much as 24% towards term. This occurs with all women in the third trimester in the supine position to some extent. This can be concealed, such as in the unanaesthetised state when most women are capable of compensating for the resultant decrease in stroke volume by increasing systemic vascular resistance and heart rate, or revealed during anaesthesia when these compensatory mechanisms are reduced or abolished so that significant hypotension may rapidly develop.

The main consequence of aorto-caval compression is a reduction in venous return and subsequently cardiac output and blood pressure. As well as leading to maternal hypoxia it also causes impaired uteroplacental flow which leads to fetal hypoxia and acidosis. Obstruction of the lower aorta and its branches also causes diminished blood flow to kidneys, and lower extremities. During the last trimester, maternal renal function is markedly lower in the supine than in the lateral position. There are alternative venous pathways (the paravertebral and azygos systems), through which venous return is diverted.

Venous distension

Venous caliber increases to approximately 150% during the course of gestation and the venous ends of capillaries become dilated, causing reduced blood flow. These vascular changes contribute to delayed absorption of subcutaneously or intramuscularly injected substances. Distension of the extradural veins heightens the risk of vascular damage during institution of a regional block. The increased venous volume within the rigid spinal canal reduces the volume or capacity of the extradural and intrathecal spaces for local anaesthetic solutions. This will therefore increase the spread of injected drugs. During labour, venous pressure increases by 4-6cmH_2O in the first stage and by up to 50cmH_2O in the second stage during contractions.

Clinical implications

Despite the increased workload of the heart during gestation and labour, the healthy woman has no impairment of cardiac reserve. In contrast, for the gravida with heart disease and low cardiac reserve, the increase in the work of the heart may cause ventricular failure and pulmonary oedema. In these women, further increases in cardiac workload during labour must be prevented by effective pain relief, optimally provided by extradural or spinal analgesia. Since cardiac output is highest in the immediate postpartum period, sympathetic blockade should be maintained for several hours after delivery and then weaned off slowly.

Teaching point

There is a 30% reduction in volume of local anaesthetic solution required at term when compared to the non-pregnant woman, to achieve the same block.

Aorto-caval compression and its sequelae must be avoided. No woman in late pregnancy should lie supine without manipulating the uterus off the great abdomino-pelvic vessels. During labour, the parturient should rest on her side, left or right.

During Caesarean section and for other indications demanding the supine position, the uterus should be displaced, usually to the left, by placing a rigid wedge under the right hip and/or tilting the table left side down.

RESPIRATORY SYSTEM

Changes within the respiratory system are of great significance to the anaesthetist.

Respiratory tract

Hormonal changes to the mucosal vasculature of the respiratory tract lead to capillary engorgement and swelling of the lining in the nose, oropharynx, larynx, and trachea. Symptoms of nasal congestion, voice change and upper respiratory tract infection may prevail throughout gestation. These symptoms can be exacerbated by fluid overload or oedema associated with pregnancy-induced hypertension (PIH) or pre-eclampsia. In such cases, manipulation of the airway can result in profuse bleeding from the nose ororopharynx. Endotracheal intubation can be difficult and a smaller than usual endotracheal tube may be required to fit through the larynx. Airway resistance is reduced, probably due to the progesterone-mediated relaxation of the bronchial musculature.

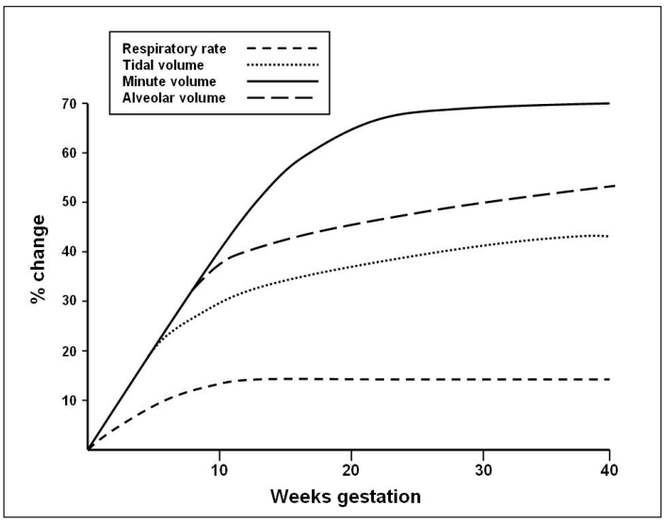

Figure 1. *Respiratory changes in pregnancy*

Lung volumes

Upward displacement by the gravid uterus causes a 4cm elevation of the diaphragm, but total lung capacity decreases only slightly because of compensatory increases in the transverse and antero-posterior diameters of the chest by as much as 5-7cm, as well as flaring of the ribs. These changes are brought about by hormonal

effects that loosen ligaments. Despite the upward displacement, the diaphragm moves with greater excursions during breathing in the pregnant than in the non-pregnant state. In fact, breathing is more diaphragmatic than thoracic during gestation, an advantage during supine positioning and high regional blockade.

From the middle of the second trimester, expiratory reserve volume, residual volume and functional residual volume are progressively decreased, by approximately 20% at term. Lung compliance is relatively unaffected, but chest wall compliance is reduced, especially in the lithotomy position.

Ventilation and respiratory gases

A progressive increase in minute ventilation starts soon after conception and peaks at 50% above normal levels around the second trimester. This increase is effected by a 40% rise in tidal volume and a 15% rise in respiratory rate (2-3breaths.min^{-1}). Since deadspace remains unchanged, alveolar ventilation is about 70% higher at the end of gestation. Arterial and alveolar carbon dioxide tensions are decreased by the increased ventilation. An average $PaCO_2$ of 4.3kPa (32mmHg) and arterial oxygen tension of 13.7kPa (105mmHg) persist during most of gestation. The development of alkalosis is forestalled by compensatory decreases in serum bicarbonate. Only carbon dioxide tensions below 3.7kPa (28mmHg) lead to a respiratory alkalosis.

During labour ventilation may be further accentuated, either voluntarily (Lamaze method of pain control and relaxation) or involuntarily in response to pain and anxiety. Such excessive hyperventilation results in marked hypocarbia and severe alkalosis, which can lead to cerebral and uteroplacental vasoconstricton and a left shift of the oxygen dissociation curve. This reduces the release of oxygen from haemoglobin, with consequent decreased maternal tissue oxygenation as well as reduced oxygen transfer to the fetus. Furthermore, episodes of hyperventilation may be followed by periods of hypoventilation as the blood carbon dioxide tension ($PaCO_2$) returns to normal. This may lead to both maternal and fetal hypoxia.

Oxygen consumption increases gradually in response to the needs of the growing fetus, culminating in a rise of at least 20% at term. During labour, oxygen consumption is further increased (up to and over 60%) as a result of the exaggerated cardiac and respiratory work load. This remains high after delivery to pay off the oxygen debt and correct the levels.

Clinical implications

The changes in respiratory function have clinical relevance for the anaesthesiologist. General anaesthesia is not the routine choice of anaesthetic for caesarian section because of the airway problems associated with pregnancy. These problems result from anatomical changes such as enlarged breasts and oedema of the airway, that make intubation more difficult. The failed intubation rate increases to 1 in 250 and is worse in the obese and those suffering from pre-eclampsia. There is also an increased risk of aspiration because of the gastrointestinal changes, and, most importantly, the increased oxygen consumption and the decreased reserve due to the reduced functional residual capacity, can result in a rapid fall in arterial oxygen tension during apnoea. This occurs despite careful maternal positioning and preoxygenation. The increased minute ventilation combined with decreased functional residual capacity hastens inhalation induction or changes in depth of anaesthesia when breathing spontaneously.

GASTROINTESTINAL SYSTEM

Since aspiration of gastric contents is an important cause of maternal morbidity and mortality in association with anesthesia, an examination of the controversy surrounding gastrointestinal changes in pregnancy is justified. The intragastric pressure is normally 7-8cmH_2O, this increases to 13-17cmH_2O in pregnancy and can increase to 40cmH_2O with twins and in the obese.

Mechanical changes

The enlarging uterus causes a gradual cephalad displacement of stomach and intestines. At term the stomach has attained a vertical position rather than its normal horizontal one. These mechanical forces lead to increased intragastric pressures as well as a change in the angle of the gastroesophageal junction, which in turn tends toward greater oesophageal reflux.

Physiological changes

The hormonal effects on the gastrointestinal tract are an issue of debate among anaesthetists. Relaxation of the lower oesophageal sphincter has been described, but there have been differing views about the effect on motility of the gastrointestinal tract and the times at which it is most prominent. Many believe that there is also retardation of gastrointestinal motility and gastric emptying, producing increased gastric volume with decreased pH, beginning as early as 8-10weeks of gestation. Recent studies, however, have shed a different light on the subject. Measuring peak plasma concentrations of drugs absorbed exclusively in the duodenum in both non-pregnant and pregnant volunteers, at different times of gestation, it was shown that peak absorption occurred at the same interval in all women with the exception those in labour. This suggests that gastric emptying is delayed only at the time of delivery.

Thus, the raised risk of aspiration is due to an increase of oesophageal reflux and decreased pH of gastric contents. The heightened incidence of difficult endotracheal intubations worsens the situation.

> **Teaching point**
> The pregnant woman should be considered to be a 'full stomach' patient with increased risk of aspiration during most of gestation.

Pulmonary aspiration of gastric contents can occur either following vomiting (active) or regurgitation (passive). Aspiration of solid material causes atelectasis, obstructive pneumonitis or lung abscess, while aspiration of acidic gastric contents results in chemical pneumonitis (Mendelson's syndrome). The most serious consequences follow aspiration of acidic materials containing particulate matter as may follow swallowing certain antacids such as magnesium trisilicate. Clear antacids such as sodium citrate (0.3mol) or bicarbonate should be used. While the incidence of pulmonary aspiration of solid food has decreased due to patient education, that of gastric acid has remained constant.

Clinical implications

The danger of aspiration is almost eliminated when regional anaesthesia or inhalational analgesia is used. During general anaesthesia airway protection by means of a cuffed endotracheal tube is mandatory. Although awake intubation is safest, discomfort and the lack of patient cooperation and discomfort prevent it being the routine method for securing the airway. The endotracheal tube is placed immediately following loss of consciousness after induction of general anesthesia.

Teaching point

Special precautions should be heeded, even when induction to intubation time is expected to be brief, to prevent the regurgitation:

1. Supine position with lateral tilt to minimise any increase in intragastric pressure.
2. Preoxygenation prior to induction then no positive pressure ventilation prior to insertion of the endotracheal tube to prevent distention of the stomach with gas (rapid sequence induction).
3. Cricoid pressure (Sellick's maneouvre) during induction which is maintained until endotracheal tube placement in the trachea has been confimed. Cricoid pressure should be applied to the cricoid cartilage whilst supporting the back of the neck. This occludes the oesophagus, thus obstructing the path of regurgitation.

The acidity and volume of gastric contents can be reduced by pharmacologic interventions which may prove invaluable. Most importantly, a nonparticulate oral antacid, 30ml of sodium 0.3molar citrate or bicarbonate, should be given immediately prior to induction of general anesthesia to all women. In addition, histamine H_2-receptor antagonist the night before and the morning of delivery may reduce secretion of hydrochloric acid (ranitidine 150mg orally).

METABOLISM

All metabolic functions are increased during pregnancy to provide for the demands of fetus, placenta and uterus as well as for the gravida's increased basal metabolic rate and oxygen consumption. Protein metabolism is enhanced to supply substrate for maternal and fetal growth. Fat metabolism increases as evidenced by elevation in all lipid fractions in the blood. Carbohydrate metabolism, however, demonstrates the most dramatic changes. Hormones such as human placental lactogen, progesterone, prolactin and cortisol, together with reduced liver enzyme activity of glucokinase and phosphofructokinase, result in an insulin resistant state. Normal women counteract this by increasing their production of insulin, however women with gestational diabetes are unable to do this. As early as 15 weeks of gestation, maternal blood glucose levels after an overnight fast are considerably lower than in the nongravid state, this is due to altered hormonal balance, expanded maternal blood volume, increased placental transfer of glucose and loss through the kidneys because of a low renal threshold.

RENAL PHYSIOLOGY

Renal plasma flow and glomerular filtration rate begin to increase progressively during the first trimester. At term, both are 50-60% higher than in the non-pregnant state. This parallels the increases in blood volume and cardiac output. The elevations in plasma flow and glomerular filtration result in an elevation in creatinine clearance. Blood urea and serum creatinine are reduced by 40%. The increase in glomerular filtration may overwhelm the ability of the renal tubules to reabsorb leading to glucose and protein losses in the urine. Thus, mild glycosuria (1-10g.day^{-1}) and/or proteinuria (to 300mg.day^{-1}) can occur in normal pregnancy. There is also an increase in filtered sodium, but tubular absorption is increased by an increase in aldosterone secretion, via the renin-angiotensin mechanism. There is also a decrease in plasma osmolality. This is a measure of the osmotic activity of a substance in solution and is defined as the number of osmoles in a kilogram of solvent. In practice it indicates that the plasma concentrations of electrolytes, glucose and urea fall if, for example, more water than sodiumis retained. Over the whole period of gestation there is retention of 7.5l of water and 900mmol of sodium.

After the 12th week of gestation, progesterone can induce dilation and atony of the renal calyses and ureters. With advancing gestation, the enlarging uterus can compress the ureters as they cross the pelvic brim and cause further dilatation by obstructing flow. These changes may contribute to the frequency of urinary tract infections during pregnancy. The effect of postural compression of the aortic branches perfusing the kidneys has been discussed.

DRUG RESPONSES

The response to anaesthetic and adjuvant drugs is modified during pregnancy and the early puerperium. The most pertinent alteration is a reduced drug requirement, manifest in both regional and general anaesthesia.

Regional anaesthesia

From the late first trimester to the early puerperium, a smaller dose of local anaesthetic is required to obtain the desired level of spinal or extradural blockade. During the last months of gestation, approximately two-thirds of the normal dose is adequate. This altered response, which is due to CSF and hormonal changes and an increase in volume of the epidural veins, subsides progressively in the early postpartum period.

General anaesthesia

Induction and changes in depth of inhalation anaesthesia occur with greater rapidity in pregnant women than in non-pregnant subjects. Pregnancy enhances anaesthetic uptake in two ways. The increase in resting ventilation delivers more agent into the alveoli per unit time, while the reduction in functional residual capacity favors rapid replacement of lung gas with the inspired agent. In addition, there is a reduction in anaesthetic requirements, with a fall in the minimum alveolar concentrations (MAC) of halogenated vapors. When measured in sheep MAC was 25-40% lower in gravid as compared with non-pregnant animals.

The decreased functional residual capacity has a further effect on the management of general anaesthesia. As referred to earlier, the resultant reduction in oxygen storage capacity, together with the elevated oxygen consumption, leads to an unusually rapid decline in arterial oxygen tension in the apnoeic anaesthetised gravida.

There are also alterations in the response to intravenous agents, in particular prolongation of their elimination halflives consequent to the greater distribution volume (resulting from the pregnancy-induced increase in plasma volume). Thus, the mean elimination half-life for thiopentone in gravid women is more than doubled in comparison with that in non-gravid young patients.

Serum cholinesterase. Serum cholinesterase levels fall by 24-28% during the first trimester without a marked change for the remainder of gestation. However, even lower levels (about 33% reduction) develop during the first seven postpartum days. The decreased levels of the enzyme are still sufficient for normal hydrolysis of clinical doses of suxamethonium or chloroprocaine during gestation. Postpartum, however, approximately 10% of women will be at risk of a prolonged reaction to suxamethonium.

Clinical implications

These altered drug responses must be taken into consideration whenever a patient is pregnant or in the early puerperium.

CONCLUSION

A good understanding of the physiological changes in pregnancy is essential in the management of both the well woman, but also in those women who have a pre-existing medical condition. Anticipation of these problems should be part of routine ante-natal care and referral to a tertiary centre should be made if it is felt serious. This has been highlighted in *Saving Mother's Lives*, the UK's triannual report into maternal morbidity and mortality 2003-2005 (available at www.cemach.org.uk).