Fundamentals of Anaesthesia and Acute Medicine

Anaesthesia for Obstetrics and Gynaecology

Edited by
Robin Russell
Consultant Anaesthetist and Honorary Senior Clinical Lecturer, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford

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BMJ Books

First published in 2000
by the BMJ Publishing Group, BMA House, Tavistock Square,
London WC1H 9JR

www.bmjbooks.com

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0-7279-1276-3

Typeset by Phoenix Photosetting, Chatham, Kent
Printed and bound by J W Arrowsmith Ltd, Bristol

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Foreword

The Fundamentals of Anaesthesia and Acute Medicine series

The pace of change within the biological sciences continues to increase and nowhere is this more apparent than in the specialties of anaesthesia, acute medicine, and intensive care. Although many practitioners continue to rely on comprehensive but bulky texts for reference, the accelerating rate of biomedical advances makes this source of information increasingly likely to be dated, even if the latest edition is used. The series *Fundamentals of Anaesthesia and Acute Medicine* aims to bring to the reader up-to-date and authoritative reviews of the principal clinical topics which make up the specialties. Each volume will cover the fundamentals of the topic in a comprehensive manner but will also emphasise recent developments of controversial issues.

International differences in the practice of anaesthesia and intensive care are now much less than in the past and the editors of each volume have commissioned chapters from acknowledged authorities throughout the world to assemble contributions of the highest possible calibre. Three volumes will appear annually and, as the pace and extent of clinically significant advances vary among the individual topics, new editions will be commissioned to ensure that practitioners will be in a position to keep abreast of the important developments within the specialties.

Not only does the pace of advance in biomedical science serve to justify the appearance of an international series of this nature but the current awareness of the need for more formal continuing education also underlines the timeliness of its appearance. The editors would welcome feedback from readers about the series, which is aimed at both established practitioners and trainees preparing for degrees and diplomas in anaesthesia and intensive care.

RONALD M JONES
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Preface

Obstetric anaesthesia continues to increase in popularity whilst advances in gynaecological surgery have implications for anaesthetic practice. This book is possibly the first text dedicated to both these aspects of women's anaesthesia.

Obstetric anaesthesia is rewarding in nature but appropriate training of correct technique can only increase the safety of both mother and baby during childbirth and is perhaps of greater significance. For those involved in the anaesthetic care of women undergoing gynaecological procedures there is now an increasing amount of laparoscopic work and an expansion in outpatient surgery. This book is aimed primarily at anaesthetists in training, with individual authors attempting to provide a thorough grounding of principles and practice of anaesthetic management based on current evidence. Due to its size the book is not a comprehensive review of all aspects of women's anaesthesia, but it should offer readers a helpful foundation on which to base their clinical practice.

ROBIN RUSSELL

1: Maternal changes in pregnancy

JAMES ELDRIDGE

During pregnancy a woman's physiology and anatomy change more rapidly than in any other stage of healthy adult life. What is normal in a non-pregnant woman may be abnormal during pregnancy and equally, what is abnormal when not pregnant may be normal in pregnancy. Optimal anaesthesia requires knowledge of how a woman's body adapts during pregnancy, labour, and delivery. This chapter reviews the changes of which the anaesthetist needs to be aware and examines the important issues when anaesthesia is to be provided for women who require non-obstetric surgery during pregnancy.

Physiological changes

Cardiovascular system

Haemodynamic studies in pregnancy are notoriously difficult to interpret. Many of the earlier studies reported that cardiac output and blood pressure fell in the third trimester but unfortunately, no precautions were taken to avoid aortocaval compression. Other investigations have used early postpartum values of cardiovascular variables as controls for pregnant values. These are unsuitable because some haemodynamic changes persist for several months into the postpartum period, especially in breastfeeding mothers. The most informative studies have followed mothers serially from before conception and then throughout pregnancy, avoiding the supine position during all assessments. Various techniques have been used to assess cardiac output during pregnancy, including the Fick method, thoracic impedance (which has proven unreliable), thermodilution (which requires invasive instrumentation), and echocardiography. Even though echocardiography is not as accurate as thermodilution, because it is not invasive, women find that serial measurements through pregnancy are acceptable.

Echocardiography has revealed that left ventricular mass increases during

pregnancy, just as it increases in athletes starting an exercise training programme. In this respect, pregnancy appears to be comparable to a prolonged period of moderate exercise. Cardiac output starts to increase early in the first trimester, probably under a hormonal influence. By the eighth gestational week, output has risen by over 20%[1] and it peaks at approximately 50% above the non-pregnant state by the end of the second trimester. Cardiac output then changes little until term. The earliest rise in cardiac output is a result of an elevated heart rate but by the end of the first trimester, the increased stroke volume is the predominant cause. Although in the third trimester, stroke volume may fall a little, cardiac output is maintained by the heart rate, which continues to increase slightly[2] (Fig 1.1).

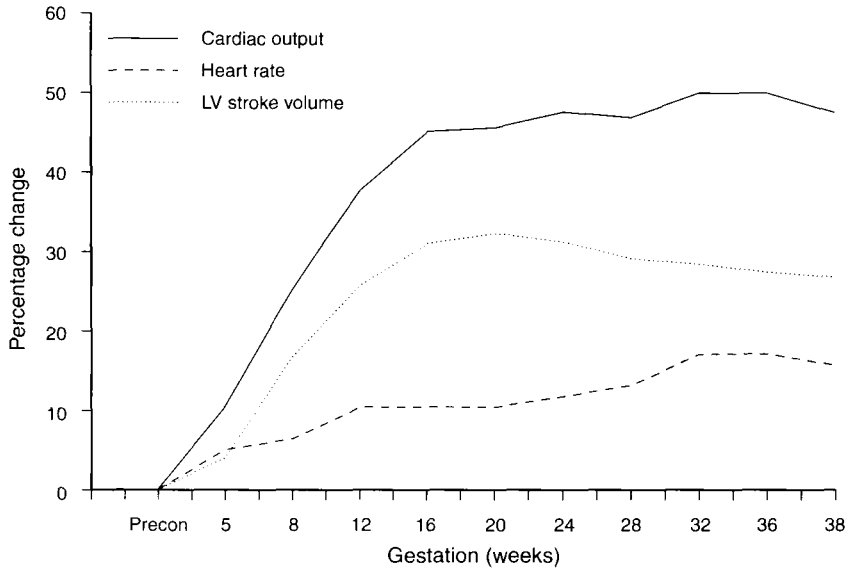

Fig 1.1 Changes in cardiac output, left ventricular stroke volume and heart rate during pregnancy expressed as a percentage of the preconceptual value (from Robson *et al.*[2] with permission)

Despite an elevated cardiac output, blood pressure falls in early pregnancy. Diastolic pressure reaches its nadir by midgestation, reflecting a 35% decline in the peripheral vascular resistance.[2] By term, the diastolic pressure returns to pre-pregnant levels although the peripheral vascular resistance remains 20% below its pre-pregnant value. The fall in peripheral vascular resistance is predominantly due to the low resistance of the placental intervillous space, although progesterone, prostacyclin, and oestrogens also promote systemic vasodilation.

The aortic area increases by about 14% during a woman's first pregnancy and this appears to be a permanent change. Aortic compliance also

increases, producing a marginal fall in systolic pressure during the second trimester but, in normal pregnancy, systolic pressure will have returned to pre-pregnant values by term.[2]

Pulmonary vascular resistance falls during pregnancy, so that pulmonary blood pressure does not change despite the increased cardiac output.[3] Pulmonary capillary wedge pressure is unchanged but as colloid oncotic pressure falls, the gradient in pulmonary transcapillary pressure is reduced. By term the transcapillary pressure has fallen by nearly 30%, suggesting a greater propensity for pulmonary oedema.[3]

Despite an increase in blood volume, central venous pressure is unaltered because of an increase in venous capacitance.

Cardiovascular changes in labour

Cardiovascular activity is increased further by labour. Women with cardiovascular disease are at particular risk during the peripartum period because of rapid changes in cardiac output, preload and afterload.

In labour, sympathetic activity increases, particularly in women who do not receive regional analgesia.[4] Between contractions, the heart rate may not alter but stroke volume, cardiac output, and blood pressure steadily rise. When the cervix has dilated to 8 cm, stroke volume is elevated by nearly 30%.[5]

With each contraction, direct compression of the intervillous space occurs and blood is forced out of the placental unit, producing an autotransfusion. The central venous pressure rises,[6] stroke volume is augmented, and cardiac output increases.[5,7] If the pain of labour is well controlled with a regional block, the heart rate may fall during a contraction but cardiac output still climbs by 10–15%.[7] Without regional analgesia, the increase in cardiac output is greater and the heart rate increases rather than falls.[8]

At delivery, the intervillous space is eliminated and there is an immediate reduction in venous capacity. The associated autotransfusion usually exceeds blood loss and so there is a rapid rise in central venous pressure and cardiac output to approximately 25% above prelabouring values.[5] Over the succeeding hours this declines slowly, returning to prelabouring values on the second postpartum day. Cardiac output remains above pre-pregnancy values for 12–24 weeks.

Aortocaval occlusion

Between 1932 and 1935, Ahltorp published three papers describing how pregnant women who were positioned supine became nauseated, hypotensive, and cyanotic and even lost consciousness. He found that the symptoms could be produced in some women even when they were prone if the uterus was lifted and pushed posteriorly. He correctly hypothesised that the symptoms might be due to inferior vena cava compression.[9] These

symptoms are now referred to as the supine hypotensive syndrome. All pregnant women are at risk of developing the supine hypotensive syndrome because the posterior aspect of the enlarging uterus is in close proximity to the great vessels of the abdomen. Angiography reveals that inferior vena caval compression is commonplace.[10] If venous return to the right atrium is significantly impaired, cardiac output falls and this may be followed by hypotension. However, in many women the collateral circulation through the epidural and azygous veins is sufficient to maintain an adequate cardiac output. Even so, vena caval occlusion can still be detected by a rise in femoral venous pressures.

Elevated femoral venous pressures have been demonstrated in the supine position as early as the 16th week of gestation,[11] but it is very unusual for women to develop supine hypotension before 20 weeks. If a woman at term is placed in a supine position, femoral venous pressures rise to twice their normal value[11] and complete occlusion of the inferior vena cava occurs in over 90% of individuals.[10] Only 60% of women, however, become symptomatic when supine because collateral venous circulation and compensatory systemic vasoconstriction are sufficient to maintain blood pressure. Even at term, less than 10% of women actually develop overt supine hypotensive syndrome.[12] If symptoms do occur, they usually become apparent within 3–10 minutes of adopting a supine position, although occasionally symptoms may take up to 30 minutes to appear.

Inferior vena caval occlusion not only causes femoral venous pressures to rise but also causes elevated pressures in uterine veins which may compromise placental perfusion. This is less likely if the placenta has implanted in the fundus of the uterus because ovarian veins, which usually drain into the inferior vena cava above the site of compression, commonly provide sufficient collateral circulation to prevent engorgement of the placental bed.[13]

Placental blood flow may also be compromised by aortic compression. Complete occlusion is rare but partial occlusion is common at term. The site of compression is usually at the pelvic brim and occurs most frequently during contractions in early labour. Partial occlusion of the aorta may not affect brachial artery blood pressure but systemic vascular resistance rises and cardiac output may fall. Pressure in the femoral arteries falls and, more importantly, the pressure in the uterine arteries is reduced because the origin of the uterine vessels is usually below the site of aortic compression. This, in combination with elevated venous pressure, compromises placental perfusion and hence fetal oxygenation. Kauppila and colleagues found that intervillous blood flow was reduced by 20% when pregnant women were turned from a left lateral to a supine position.[14] During labour, as the fetal head descends into the pelvis, the severity of aortic occlusion is reduced.[15]

Various maternal positions have been suggested to reduce the incidence of aortocaval occlusion. Techniques such as adopting a semirecumbent

position or flexion of the hips have been suggested but these are not as effective as tilting the mother laterally.[15] To reduce the pressure of the uterus on the inferior vena cava, the left lateral wedge is most commonly employed. Over 90% of women find that a left wedge alleviates symptoms more effectively than a right wedge. Classically, a 15° tilt is recommended, although partial vena caval occlusion may be present even in the full lateral position. It is only in the prone position, with the uterus hanging freely, that caval compression does not occur. Aortic compression is also known to be present even with a tilt of over 30° and is only relieved in the full lateral position.[15] If a 15° tilt does not relieve symptoms of supine hypotension, then the tilt should be increased until symptoms abate.

Respiratory system

As the pregnant uterus enlarges into the abdominal cavity, the diaphragm becomes elevated and the transverse diameter of the thoracic cage increases. By term the thoracic cage is nearly fully expanded and inspiration is almost exclusively produced by diaphragmatic descent. Although total lung capacity is slightly reduced during pregnancy, vital capacity hardly changes.[16,17] Tidal volume increases and by term reaches 30% greater than pre-pregnant values with half of the increase occurring in the first trimester.[18] Early in pregnancy the increase in tidal volume is accommodated by a reduced inspiratory reserve volume. In the third trimester, it is the expiratory reserve volume that is reduced, while the inspiratory reserve volume actually increases. By term, expiratory reserve volume has fallen by 25% and residual volume is also reduced by 15%. The combination of these changes produces a 20% fall in functional residual capacity (FRC) (Fig 1.2).[16] The reduction in FRC occurs predominantly in the third trimester and, not surprisingly, is dependent on maternal posture with a much greater reduction in FRC occurring when women are supine. Even though the closing volume is unchanged by pregnancy,[17] the fall in FRC causes airway closure in 50% of supine women at term, making them vulnerable to hypoxia.[19]

The reduced FRC and increased oxygen demand make pregnant women prone to desaturate more rapidly than non-pregnant women during periods of apnoea. Archer and Marx found that after intubation and ventilation with 97% oxygen for four minutes followed by 60 seconds of apnoea, arterial oxygen tension fell by 7.8 kPa in non-pregnant women, while in pregnant women the fall was 21 kPa.[20] This reinforces the importance of preoxygenation before induction of anaesthesia in pregnant women.

Gas flow through the airways is little changed by pregnancy. Although the hypocapnia of pregnancy would tend to cause bronchconstriction, the large airways dilate (probably under the influence of progesterone), maintaining the conductance of the airways. Flow volume loops, forced

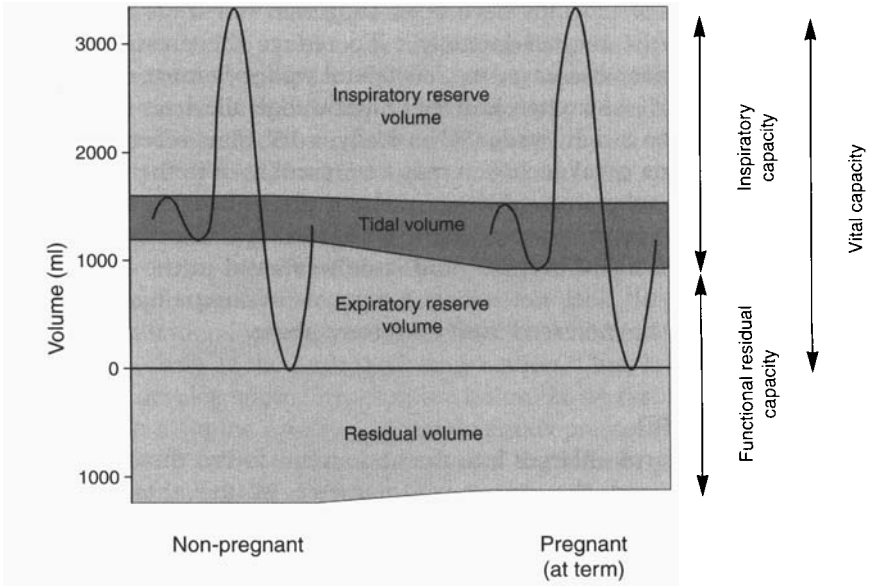

Fig 1.2 Changes in respiratory volumes and capacities in the non-pregnant and pregnant states

expiratory volume in one second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) are all unchanged.[17]

Oxygen consumption increases by nearly 60% during pregnancy.[18] The increased demand is predominantly due to fetal requirements but maternal cardiac, respiratory, renal, and uterine consumption also contribute. Carbon dioxide production mirrors this increase.[18] The respiratory rate is only marginally increased by pregnancy but the combination of an increased tidal volume and a reduction in physiological dead space[21] nearly doubles the alveolar ventilation. The reduced physiological dead space is probably caused by improved perfusion of ventilated alveoli. The change in alveolar ventilation is under hormonal control as the supply of oxygen and the excretion of carbon dioxide are in excess of requirements.[22] The controlling agent is, once again, most likely to be progesterone as the arterial partial pressure of carbon dioxide is inversely related to the progesterone concentration.[23] Progesterone increases the sensitivity of the respiratory centre to carbon dioxide and acts as a direct respiratory stimulant.[24]

The hyperventilation of pregnancy decreases arterial carbon dioxide partial pressure to approximately 4.0 kPa. This fall occurs by the end of the first trimester and is maintained thereafter.[18] The gradient between endtidal and arterial carbon dioxide partial pressure is also reduced during pregnancy. In non-pregnant women this gradient is usually 0.5–0.8 kPa. At the end of the first trimester the gradient is often negligible and by term the

gradient occasionally reverses. Therefore in pregnant women, the endtidal carbon dioxide partial pressure can usually be assumed to correlate closely with the arterial carbon dioxide partial pressure.

Arterial oxygen partial pressure increases marginally during pregnancy provided the supine position is avoided. This increase is most marked in the first trimester and declines towards pre-pregnant values by term.[25] The fall in physiological dead space contributes to improved oxygenation, as does a change in arteriovenous oxygen difference. The arteriovenous oxygen difference is reduced in pregnancy, because oxygen supply is increased more than oxygen demand.

Renal compensation for respiratory alkalosis occurs with serum bicarbonate falling from 24 to 20 mmol/l, although arterial pH remains slightly raised.[26] Despite maternal alkalosis, the P_{50} of the oxyhaemoglobin dissociation curve increases steadily throughout pregnancy,[27] most probably because of an elevated 2,3 diphosphoglycerate concentration (although not all studies have found raised 2,3 diphosphoglycerate levels). Elevation of the P_{50} increases the delivery of oxygen from maternal haemoglobin to fetal haemoglobin as well as to maternal tissues.

During labour, painful contractions cause further hyperventilation and arterial pH values in excess of 7.50 are not uncommon. This reduces respiratory drive and may cause periods of apnoea and maternal hypoxia between contractions, particularly if systemic opiates are given for pain relief. Indeed, Deckardt found that primiparous women in labour who received epidural analgesia with local anaesthetics alone had a mean oxyhaemoglobin saturation of 94.3% while those given systemic opiate had a mean saturation of 88.8%.[28] However, epidural opiates may also cause hypoxic episodes. Porter and colleagues found that women given epidural analgesia with an infusion of 0.0625% bupivacaine plus 2.5 μg/ml fentanyl have significantly more periods of desaturation below 95% than women receiving an epidural infusion of plain 0.125% bupivacaine.[29]

Gastrointestinal system

Over 70% of pregnant women suffer from heartburn.[30] Anatomical changes and hormonal effects on smooth muscle tone promote reflux of gastric contents into the oesophagus. During pregnancy, the stomach is shifted cephalad and the intra-abdominal portion of the oesophagus is often displaced into the thoracic cavity[30] which reduces the efficiency of the lower oesophageal sphincter. (The lower oesophageal sphincter is sometimes referred to as the lower oesophageal high pressure zone, as no true anatomical sphincter exists in the lower oesophagus.) Moreover, the pressure which the lower oesophageal sphincter can exert is reduced in pregnancy by the smooth muscle relaxant action of progesterone. While the competence of the lower oesophageal sphincter is reduced, the intragastric pressure rises

because the enlarging uterus compresses the intra-abdominal contents. The barrier pressure is the difference between the intragastric pressure and the lower oesophageal sphincter pressure. Reduction in barrier pressure is associated with heartburn in women in their first trimester,[31] although at what stage in gestation an asymptomatic woman is at increased risk of regurgitation remains a matter of debate. The hormonal influence on lower oesophageal tone starts in early pregnancy but compression of intra-abdominal structures by the uterus is insignificant before the 20th week of pregnancy. Vanner studied 100 women undergoing termination of pregnancy, 50 during the first trimester and 50 in the second.[32] He found that the incidence of gastro-oesophageal reflux into the lower oesophagus was not significantly different between groups. Potentially more serious was that reflux into the upper oesophagus occurred in two women, one in each trimester. However, this was no more frequent than would be expected in the non-pregnant population.

Should regurgitation occur, the consequences are determined, at least in part, by the volume and acidity of the intragastric contents. Serial studies of acid production throughout pregnancy have proved difficult to perform because women are understandably reluctant to swallow nasogastric tubes repeatedly. Gastrin has been used as a surrogate marker for gastric secretion. It is a polypeptide hormone secreted by the antrum of the stomach and induces copious gastric secretions. Maternal plasma gastrin concentration rises steadily through the second and third trimesters of pregnancy.[33] However, to conclude that this indicates a steadily rising level of gastric secretion may be wrong, as direct measurements of gastric volume in cohorts of women in each trimester of pregnancy suggest that both the basal and histamine-augmented gastric secretion and acidity are unchanged in the first and third trimesters and are actually marginally reduced in the second.[34]

Gastric emptying also affects the residual volume in the stomach. Over the years, various methods have been used to assess gastric emptying, including gastric aspiration, realtime ultrasound, epigastric impedance, applied potential tomography, X-ray studies and radioisotope techniques. Most studies, however, have used the paracetamol absorption technique because of its simplicity and ready acceptance by pregnant women. The technique correlates closely to the rate of clearance of liquid from the stomach. The majority of recent studies suggest that there is little change in gastric emptying times between non-pregnant controls and women in the first, second or third trimesters.[34] Even in early labour gastric emptying is rarely prolonged[35] but some delay does occur in women near to delivery.[36] Gastric emptying is dramatically slowed if systemic opiates are given for pain relief in labour.[35,37] In contrast, pain relief with an epidural infusion of local anaesthetic and fentanyl at up to 20 μg/h does not alter gastric emptying,[38] although large boluses of epidural opiates may have some effect.

The risk of regurgitation in the postpartum period decreases rapidly. Reduction in intra-abdominal pressure occurs immediately on delivery and, 20 hours postdelivery, the acidity and volume of gastric contents are the same as in non-pregnant controls. Lower oesophageal sphincter tone may take longer to return to pre-pregnant strength. In a study of 25 conscious women between 24 and 80 hours postpartum who were placed in four positions including lithotomy, five regurgitated. However, this was a lower proportion than in non-pregnant controls and considerably lower than the 17 of 25 in whom reflux was observed before delivery.[39] In the same study, reflux did not occur in any woman more than 48 hours post delivery. These data suggest that by 48 hours postpartum, women do not routinely require intubation providing there are no other specific indications.[40]

Haematology

Both red cell mass and plasma volume increase during pregnancy. However, the increase in plasma volume is proportionally greater and this results in the well-known physiological anaemia of pregnancy. Plasma volume starts to increase in the first trimester and expands rapidly in the second, with a small further increment in the third trimester. Early studies suggested that plasma volume actually decreased in the third trimester but this was probably the result of women being placed supine when measurements were made. By term plasma volume has expanded by nearly 50% (1500 ml).[41,42] This expansion is under hormonal control.[43] Progesterone increases aldosterone production and oestrogens increase renin activity, promoting salt and water retention. The increase in total body water varies markedly between women but is about 6000 ml by the later part of the third trimester.

The haematocrit falls during pregnancy by nearly 15%,[42] although the red cell mass actually increases. Studies on the red cell mass before the 12th week of gestation are contradictory but from the end of the first trimester, it is clear that the red cell mass increases steadily, reaching 30% above the pre-pregnant level by term.[42,44] The increase in red cell mass parallels, and is probably caused by, an increase in erythropoietin. The source of erythropoietin is not established but is likely to be predominantly renal, although some placental or fetal production may contribute.[45]

The physiological anaemia of pregnancy may be important in preventing placental infarcts. Koller noted that haemoglobin concentrations above the norm for any particular stage of gestation were associated with intrauterine growth retardation and placental infarcts while anaemia in pregnancy led to placental enlargement.[46] He hypothesised that the higher viscosity produced by increased haemoglobin concentration was a causative factor for placental infarcts.

Platelet count is unaltered between the second and third trimesters but platelet turnover changes. Platelet distribution width is an indicator of

thrombocytopoietic activity in the bone marrow. During pregnancy, distribution width increases, implying an increased production of platelets. As the platelet count is unaltered, platelet consumption must also be increased. Several studies have suggested that platelet half-life is reduced in pregnancy, although this is only marked in pre-eclamptic women.[47] Not only is platelet activity increased but platelet function is also changed, as bleeding time is reduced during pregnancy. In the peripartum period platelet activation is, not surprisingly, increased further. Platelet factor 4 and β-thromboglobulin are indicators of platelet activation and both are increased during labour, peaking during delivery itself.[48]

Reduced prothrombin and partial thromboplastin times in addition to changes in thromboelastography all indicate that a hypercoagulable state exists during pregnancy. Although partly caused by the change in platelet function, the clotting cascade and fibrinolytic system are also modified. Most, but not all of the clotting factors are increased. Plasma concentrations of factors I, VII, VIII, IX, X, and XII are all elevated, while those of factors II and V are unaltered.[49,50] Furthermore, the concentration of antithrombin III, an inhibitor of the clotting cascade, is reduced by term. The fibrinolytic system is activated during pregnancy. Fibrin degradation products are significantly elevated at term, implying a state of accelerated coagulation and fibrinolysis.[51] Although fibrinolytic activity is depressed during labour itself, it rises within 15 minutes of delivery and within one hour fibrin degradation products are increased. Plasma fibrinogen decreases rapidly with placental separation.[50]

Blood loss at delivery varies widely. Following vaginal delivery, average blood loss is approximately 600 ml, while at caesarean section it may be up to 1000 ml.[52] During the first five postpartum days, the haematocrit continues to fall. The haematocrit on the second postpartum day correlates most closely with the haematocrit six weeks postpartum.[53] Blood volume decreases over the first seven days, returning to near pre-pregnant levels by nine weeks postdelivery.

Hepatic function

The gross anatomy of the liver is little changed by pregnancy although it is displaced laterally and cephalad in the third trimester. The elevated cardiac output of pregnancy is not reflected by any change in liver blood flow. However, physiological function of the liver is altered. A proliferation of smooth endoplasmic reticulum occurs, with a steady increase in hepatic microsomal activity. Progesterone in particular induces this increased hepatic activity. At the same time progesterone also competitively inhibits oxidative reactions. In contrast, conjugative reactions are unaffected.

Total body albumin is increased in pregnancy, although serum albumin concentration falls by 25%. The ratio of albumin to globulin is also

reduced.[54] Serum concentrations of some specific carrier proteins, such as thyroid-binding globulin, may rise during pregnancy.[55]

Many liver enzymes are increased to the upper limits of their normal range including aspartate transaminase, alanine transferase, lactate dehydrogenase, and γ-glutamyl transpeptidase.[54] Although alkaline phosphatase increases by up to 400%, this is predominantly caused by placental production of the enzyme.

Certain signs of liver disease, including palmar erythema and spider naevi, are common during pregnancy but are rarely indicators of significant pathology. However, pregnant women are more prone to gallstone production. Bravermann demonstrated that, following a test meal, gallbladder emptying is prolonged in early pregnancy and is both prolonged and incomplete during the third trimester.[56]

Renal function

During pregnancy the kidneys increase in length by about 1 cm[57] and both the ureters and the pelvicalyceal system dilate. Ureteric dilation is produced by increased smooth muscle mass during the first trimester. This is enhanced in the second trimester by the enlarging uterus compressing the ureters at the pelvic brim, producing partial ureteric obstruction.[58] Both the ureters and the pelvicalyceal systems return to pre-pregnant dimensions by 12 weeks postpartum.

Renal blood flow increases early in the first trimester, reaching about 75% above pre-pregnant levels by term.[59] The increase in renal blood flow is associated with a 50% rise in glomerular filtration rate (GFR). Early studies demonstrated a fall in both renal blood flow and GFR in the third trimester but this only occurs when estimates are made with women in a supine position.

Although production of urea and creatinine is little altered during pregnancy, the increase in GFR reduces the plasma concentrations of both. These reach a nadir by the end of the first trimester and are maintained near this level until term. During pregnancy estimates of renal function should always be compared with values that have been established as being "normal" for the particular gestation. Such is the case for uric acid, the concentration of which has become one of the standard markers of renal function in pre-eclampsia. Normal renal handling of serum uric acid is complex, involving free filtration by the glomeruli, then almost complete reabsorption in the proximal tubule with a small proportion being resecreted back into the tubular lumen before a further phase of reabsorption. Altogether, only 10% of the filtered load is excreted. During pregnancy, although there is little change in purine metabolism, uric acid levels fall in the first trimester but then gradually increase to near pre-pregnancy levels at the time of delivery.[60]

The increase in GFR presents more glucose to the distal tubules. As pregnant women do not increase their tubular reabsorption of glucose in parallel with the increase in GFR, glucosuria is not uncommon. During pregnancy glucosuria does not necessarily indicate either renal disease or diabetes mellitus and usually resolves within a week of delivery.

Osmoregulation is also altered by pregnancy with a fall of approximately 10 mOsm/kg during gestation. This is not compensated by an increased water excretion, indicating a change in antidiuretic hormone secretion. However, total body sodium does increase by 500–900 mmol.[58] Although progesterone promotes sodium excretion, its effects are more than counterbalanced by the elevated levels of aldosterone, renin, angiotensin, and oestrogens, all of which promote sodium reabsorption.

Renal compensation for the respiratory alkalosis of pregnancy occurs (see above), with the serum bicarbonate falling from 24 to 20 mmol/l. However, capacity for renal bicarbonate reabsorption remains unaltered during pregnancy.

Immune function

Pregnancy produces a unique immunological state in which the host tolerates the presence of foreign tissue. The survival of the human species is dependent on this tolerance but the precise mechanism by which it occurs remains to be determined.

The immune system can be divided into two distinct components: cell-mediated immunity and humoral immunity. These interact to protect the host from both pathogenic and neoplastic invasion. Cell-mediated immunity is produced by phagocytes, which activate a non-specific response, and by T-lymphocytes which confer specific immunity. Between 50% and 70% of phagocytes are neutrophils. Natural killer cells form a subpopulation of phagocytes, making up 5–10% of monocytes, and provide resistance to viral infections and suppression of neoplastic cells. Humoral immunity is composed of the antibody and the complement systems. Antibodies are produced by modified B-lymphocytes called plasma cells and the complement system is made up of a series of proteins, which, when activated, culminate in the formation of a membrane attack complex.

Even in the non-pregnant individual, immune activity varies with time, which complicates comparative studies between the pregnant and non-pregnant state because the control level of activity is difficult to assess. However, although studies are contradictory, most indicate that pregnancy is associated with only minor changes in overall function of the immune system.[61] While T-cell activity and quantity appear to be unaltered,[62] the effectiveness of the natural killer cells is diminished although their number is maintained.[63] The leucocyte count increases only marginally through pregnancy but in labour it rises rapidly to approximately 11 000 mm^{-3} and

peaks on the first postpartum day at 15 000 mm ^{3}. This rise is predominantly due to increased numbers of neutrophils. The leucocyte count returns to normal by the sixth postpartum week.

The concentrations of immunoglobulins A, G, and M and *in vitro* antibody function are unchanged by pregnancy,[55] although specific humoral antibody titres may alter. In the immediate postpartum period the B-lymphocyte population may decrease, although it is constant during pregnancy itself. The concentration of complement proteins and their activity are either maintained or increased during pregnancy.[64]

Most epidemiological studies of infections during pregnancy also suggest an immune system that is functioning normally,[61] although some infections are more common. In particular, viral infections with polio, hepatitis A and B, and cytomegalovirus are more prevalent and pathological. Protozoal infections with malaria, toxoplasmosis, amoebiasis, giardiasis, and trypanosomiasis are also more common. Autoimmune diseases, however, may improve during pregnancy.

Despite apparently normal function, the immune system adapts in ways not fully understood, allowing a pregnant woman to carry her fetus. Whilst the exact mechanism remains to be determined, some factors have been established.[61] On a cell surface, the human leucocyte antigen (HLA) determinants are one of the major sites for assessing antigenicity. HLA determinants are usually polymorphic structures but on trophoblast cells they are monomorphic and other antigenic markers appear to be missing. This low density of immunogens may limit a pregnant woman's ability to respond to trophoblast cells. In addition, although the T-lymphocyte's response to a systemic challenge of fetal cells is normal, local response at the placental site appears suppressed. Even when cytotoxic T-lymphocytes are present, they appear unable to kill trophoblast cells.[65] This is probably due to a local release of immunosuppressive agents from placental tissues.

Central nervous system

There is little evidence of major change in central nervous system (CNS) activity during pregnancy but minor changes in pain threshold, susceptibility to general and local anaesthetics, and alterations in sympathetic activity all occur.

In animal experiments, pain threshold during pregnancy has been found to increase. The mechanism is probably mediated through opiate receptors, as intrathecal or systemic opiate antagonists reverse the change in pain threshold.[66] These receptors may be stimulated by an increased concentration of endorphins. In human pregnancy, the plasma concentration of β-endorphin has been variously reported as either unchanged or elevated but during labour the concentration increases significantly.[67] The source of the endorphins is not clear. The placenta may contribute and the fetal unit may

also produce endorphins, as the umbilical arterial concentration of endorphins is higher than the umbilical venous concentration. However, endorphins do not readily cross the blood–brain barrier and in humans the concentration of β-endorphin is not increased in cerebrospinal fluid, even in labour,[67] so the exact site of analgesic action of β-endorphin remains to be determined.

As pregnancy progresses, there is a steady rise in the activity of the sympathetic nervous system. In particular, sympathetic tone of venous capacitance beds in the legs is increased,[68] suggesting a susceptibility to sympatholytic events such as epidural anaesthesia.

The pharmacodynamic responses to general and local anaesthetics are altered by pregnancy. The minimum alveolar concentration (MAC) of halogenated inhalational agents in ewes is reduced by 25–40%.[69] This is probably caused by the increased progesterone concentration, although changes in serotonin[70] and endorphin levels may also have a role.

In pregnancy the rise in progesterone concentration also reduces the amount of local anaesthetic required to block nerve conduction. Interestingly, acute exposure to progesterone does not alter the sensitivity of nerves to local anaesthetic agents,[71] but prolonged exposure does.[72] This suggests that progesterone induces a mediator that actually produces the alteration in neuronal function. During pregnancy a given dose of either intrathecal or epidural local anaesthetic blocks more dermatomes than in non-pregnant controls, the effect starting in the first trimester. This may be due to increased susceptibility of the nerve fibres to the local anaesthetic but the anatomical changes in the epidural space that occur during pregnancy also contribute.

Anatomical changes

The vertebral canal

During pregnancy the lumbar lordosis of the vertebral column is often more prominent. This alters the relationship of the iliac crest to the lumbar spine. At term, the line between the crests is at the height of the L3–4 interspace while in non-pregnant women, it is more commonly at the L4–5 interspace.

Location of the epidural space may be more exacting for several reasons. Subcutaneous deposition of adipose tissue and interstial oedema may make palpation of the vertebral spines difficult whilst the lumbar lordosis reduces the distance between adjacent lumbar spines. In addition, the presence of a gravid uterus at term may prevent a women from adequately flexing her back. The ligaments are softened by the change in the hormonal milieu during pregnancy and this alters the feel of the ligamentum flavum. Finally, the epidural veins become engorged, especially during uterine contractions, and so are more likely to be punctured during insertion of an epidural

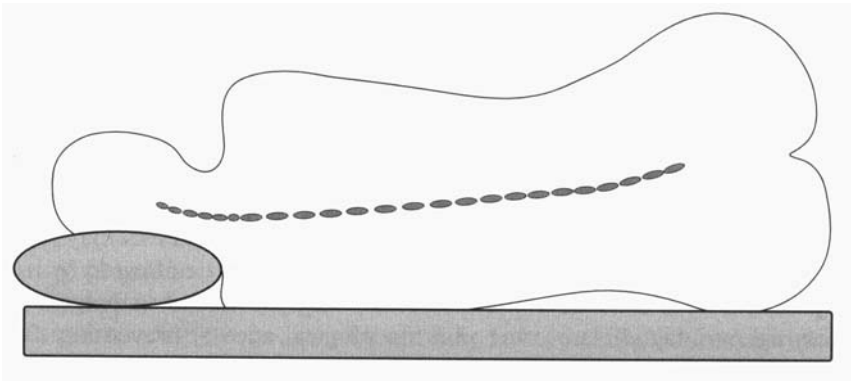

Fig 1.3 When lying laterally, a pregnant woman's hips are usually broader than her shoulders. The spinal canal is therefore tilted head down and this may increase the cephalad spread of hyperbaric intrathecal solutions

catheter. Distension of epidural veins may increase the spread of local anaesthetic within the spinal canal. Rostral movement of intrathecal local anaesthetic is also increased in pregnancy as engorged epidural veins compress the dural sac. This is enhanced in a lateral position because, at term, maternal hips are usually significantly wider than shoulders and therefore the vertebral column is tilted slightly head down (Fig 1.3).

Airway changes

The increase in interstitial fluid that occurs in pregnancy, combined with capillary engorgement, results in mucosal oedema and hyperaemia. This often causes nasal stuffiness and nose bleeds are common.[73] The false cords and arytenoids may be swollen and occasionally vocal cord oedema can cause life-threatening airway obstruction.[74] Airway management may also be hindered by enlargement of breast tissue, making insertion of a laryngoscope into the mouth awkward. Below the vocal cords the bronchi are usually slightly dilated during pregnancy and although the physiological dead space is reduced, the anatomical dead space is unchanged. The upward displacement of the diaphragm causes a widening of the bronchial angle and the lateral diameter of the chest is increased.[73]

Pharmacological changes

Pharmacokinetics

Maternal pharmacokinetics are altered by the physiological changes of pregnancy. Uptake, distribution, metabolism, and elimination of drugs are all affected and the overall effect on free plasma concentration of agents may be unpredictable.

Although gastric emptying during pregnancy is little changed, the reduced intestinal motility alters uptake of oral drugs. Drugs that are slowly absorbed in the small bowel, such as digoxin, may have increased bioavailability.[75] More dramatically, if systemic opiates are given during labour and gastric emptying arrested, any subsequent orally administered drug has little effect unless it is absorbed in the stomach. In the immediate postpartum period, when gastric emptying returns to normal, the reverse is true. A large dose of drug may be presented to the small bowel and this may result in an excessive plasma concentration. Oral uptake may be affected by iron supplements and antacids which are commonly prescribed in pregnancy. These agents may chelate other pharmacological agents, preventing their absorption.[75]

Uptake of inhalational agents is affected by respiratory and cardiovascular changes of pregnancy. Both gestational hyperventilation and reduction in functional residual capacity produce a more rapid equilibration of inhaled, alveolar and hence arterial partial pressure of agents. This effect is counteracted by the increased cardiac output of pregnancy but respiratory effects predominate.

The volume of distribution of most agents is increased. This particularly affects polar water-soluble drugs, which are predominantly dispersed across the extracellular space. This increases by as much as 5 l during pregnancy. Lipid-soluble drugs also have an increased volume of distribution but the proportional increase is rather smaller. The activity of these drugs is usually more affected by changes in protein binding.

Albumin concentration falls by about 25% at term.[55] Acidic drugs, such as salicylates and most anti-epileptic agents, and some neutral drugs, such as warfarin, are primarily bound to albumin. The fall in albumin concentration increases the free drug fraction of these agents. This effect is enhanced by the increase in the fatty acid concentration that occurs in pregnancy as fatty acids competitively reduce the number of binding sites on each albumin molecule. With fewer binding sites available, free drug fraction of an agent increases. The increase in free drug fraction counteracts the fall in total drug concentration produced by expansion of the volume of distribution so that, despite an apparent decrease in total drug concentration, free drug concentration may actually rise.[76]

Basic drugs such as local anaesthetics are bound to α_1-acid glycoprotein, the concentration of which changes little during pregnancy. However, α_1-acid glycoprotein is an acute-phase protein and serum concentration may increase by 50% in the peripartum period.[77] The clinical significance of this increase has not been addressed. The concentration of some binding proteins such as thyroxine-binding globulin, caeruloplasmin, and transferrin also increases during pregnancy.[55]

Most drugs are eliminated either through the renal system or by hepatic metabolism or both. Renal excretion predominates for many water-soluble

agents. The increase in renal blood flow, glomerular filtration rate, and creatinine clearance that occurs during pregnancy is accompanied by an increase in excretion of water-soluble drugs such as pancuronium. Lipid-soluble agents are more commonly metabolised in the liver before excretion.

Drugs with a high first-pass hepatic extraction, such as lignocaine, are relatively unaffected by changes in liver enzyme activity. Although they would be affected by changes in liver blood flow, this actually alters little during pregnancy and so metabolism of these agents is not significantly changed. In contrast, drugs with a low first-pass metabolism are relatively immune to changes in liver blood flow but are affected by changes in enzyme activity. Progesterone is a potent inducer of hepatic enzymes and this results in an increase in hepatic extraction of drugs such as phenytoin, paracetamol, and some β-blockers.[75]

Plasma cholinesterase concentration falls by about 25% by term and in the immediate postpartum period it falls by a further 35%.[78] Agents that are eliminated by plasma cholinesterase, such as suxamethonium, mivacurium, and remifentanil, might be expected to have a prolonged duration of action. The effect of reduced plasma cholinesterase concentration on suxamethonium, however, is offset by an increase in volume of distribution and consequently the duration of action of suxamethonium is actually unchanged at term. In contrast, in the immediate postpartum period, as volume of distribution falls rapidly, the duration of action of suxamethonium is prolonged by about three minutes.[79]

In general, during pregnancy the half-life of polar drugs is reduced whereas, for more lipid-soluble agents, it is increased. However, it is not always possible to predict the changes that actually occur because of the multiple factors that influence the pharmacokinetic properties of an agent.

Anaesthesia for non-obstetric surgery during pregnancy

Between 0.75% and 2.2% of pregnant women undergo non-obstetric operations during their pregnancy.[80,81] A wide variety of surgical procedures are performed. Of 5405 non-obstetric operations carried out on pregnant women in Sweden between 1973 and 1981, 25% were classified as abdominal surgery, 19% genitourinary and gynaecological, and an additional 10% were classified as laparoscopic surgery. Almost all the laparoscopic surgery was performed in the first trimester.[80]

Although some diagnostic or surgical procedures have the potential to harm the fetus, important treatments should not be denied to pregnant women as the fetus is inescapably dependent on maternal health for continued survival. However, where possible, elective surgery should be postponed until after delivery.

When surgery is required, anaesthetists need to consider the effect of pregnancy on the mother and how anaesthetic technique can affect a developing fetus. The association between non-obstetric surgery and fetal outcome has been the focus of several investigations. Shnider found an 8.8% spontaneous abortion rate when he reviewed 147 women who underwent surgery during pregnancy.[82] Similarly, Brodsky found a fetal loss of 8.0% when surgery was performed in the first trimester and 6.9% in the second trimester compared to control rates of 5.1% and 1.4% respectively.[81] In the largest series reported so far, Mazze reviewed 720 000 births in Sweden.[80] He identified 5405 operations performed for non-obstetric reasons. In the group of women who underwent surgery, the incidence of premature delivery increased to 7.47% compared with a control rate of 5.13% (a 46% increase), with an associated increase in the number of neonates with very low birth weight. The predominant reason for fetal loss and premature delivery is probably the underlying medical condition rather than exposure to anaesthetic agents.

However, anaesthetic mishaps producing maternal hypoxia and hypotension are a threat to the fetus and even relatively small changes in maternal physiology may significantly compromise fetal health. To prevent fetal asphyxia, uterine blood flow and maternal oxygenation must be maintained. Studies in the pregnant ewe demonstrate that when uterine blood flow is reduced by 65%, fetal arterial oxygen tension falls by over 1 kPa and fetal acidosis follows within 10 minutes.[83] As uterine blood flow is not autoregulated, arterial hypotension or elevated venous pressure results in reduced uterine blood flow. Aortocaval compression must be avoided as it causes both. Furthermore, anaesthesia may be associated with hypocapnia, alkalosis or catecholamine release, all of which may lead to uterine arterial vasoconstriction.

In premature neonates, high fetal oxygen tensions may cause retrolental fibroplasia and promote closure of the ductus arteriosus. *In utero*, however, the fetus is protected from these potentially harmful effects because placental oxygen consumption and inequalities in distribution of placental blood flow prevent the fetus from achieving an arterial oxygen tension much above 9 kPa even when maternal arterial partial pressure of oxygen is above 85 kPa.[84] Thus, while maternal inspired oxygen concentrations above 50% have little benefit for the fetus, they cause it no harm and so higher maternal inspired oxygen concentrations can be safely used if required.

Teratogenicity may be defined as any significant postnatal change in form or function in an offspring after prenatal treatment. The risk of exposing a fetus to a teratogen varies with the gestational age of the fetus. Within two weeks of conception, teratogenic changes are unlikely as fetal loss is the more probable outcome for an affected fetus. Fetal abnormalities are more likely if exposure to a teratogen occurs between the fourth and 11th gestational week as this is the period of organogenesis. Some organs continue to

develop after this period and so exposure to teratogens may still be harmful but changes are more likely to be minor morphological or functional changes. Causes of teratogenicity are diverse and include infection, pyrexia, hypoxia, and acidosis as well as the more well-recognised hazard of ionising radiation.

The association of drugs with teratogenicity is an emotive issue. Whilst evidence is often contradictory, few drugs are actually proven teratogens and none of these is routinely used in anaesthesia. Many drugs have, however, been implicated as possible teratogens. Most of the evidence giving rise to this concern has come from either epidemiological studies or animal experiments. As effects are usually rare, epidemiological studies must assess very large numbers of patients to establish a causative effect. Few prospective studies have been performed and none of them are large, but retrospective studies have been reported. Between 1963 and 1989 seven epidemiological studies were published that reviewed fetal deformities in women who had received an anaesthetic during pregnancy. A total of over 9100 patients were analysed. In all seven of these studies, the incidence of fetal deformities was no different from the matched control rate in women who did not undergo surgery. Unfortunately, these reports included a mixture of anaesthetic and surgical techniques and not all series specified in which trimester surgery took place.[80,85] By including patients who had a low risk of teratogenicity, such as those in the second or third trimester, a change in fetal deformity rate may have been masked. The group thought to be at greatest risk are those who undergo general anaesthesia in the first trimester. Of 2252 women identified by Mazze and Kallen who had surgery in the first trimester, more than 60% received general anaesthesia and a further 25% were given an unknown anaesthetic. Even in this high-risk group, the number of neonates with congenital abnormalities was almost identical to the expected number (44 vs 42.6) with the observed/expected ratio of 1.0 (confidence intervals of 0.8–1.4).[80] This would suggest that the risk of anaesthesia causing teratogenic changes is very small.

Despite reassuring information from these studies, there is still concern over particular agents, often because of information derived from animal studies. Extrapolation from animal studies to humans, however, must be treated cautiously especially as the duration and dosage of exposure to agents during the animal experiments often do not match those used clinically.

Premedication

Although several epidemiological studies suggested a link between chronic exposure to diazepam in the first trimester and subsequent cleft lip formation, this has not been supported by more recent studies.[86] No study has suggested that a single dose, as might be used for premedication, is associated with teratogenicity. Long-term administration may lead to neonatal

withdrawal symptoms following delivery and exposure just before delivery may cause neonatal drowsiness and hypotonia.

Ranitidine and cimetidine are not known to be harmful but caution is advised with chronic exposure to cimetidine because of known androgenic effects in adults.

Induction agents

Thiopentone has been used for many years and does not appear to be associated with fetal abnormalities although formal studies have not been conducted. Chronic exposure to barbiturates may be associated with fetal anomalies although evidence is contradictory.

Reproductive studies in animals have suggested that propofol may lead to delayed or abnormal ossification. However, the effect of administering propofol to humans during early pregnancy has not been investigated and its use is therefore controversial. Studies using propofol during caesarean section at term suggest it is a safe agent to use in the third trimester although neonatal depression has been reported.

Animal studies of etomidate suggest that this agent is not teratogenic. Nevertheless, it is a potent inhibitor of cortisol synthesis and neonates have lower cortisol concentrations when women are given etomidate for induction of anaesthesia for caesarean section.[87]

Ketamine in early pregnancy increases intrauterine pressure, which may cause fetal asphyxia even though blood pressure is maintained. In the third trimester this increase in intrauterine pressure does not occur.

Inhalational agents

Halothane and isoflurane have been extensively used during pregnancy, suggesting that these are safe agents. Some animal data, however, give cause for concern. Several investigators have reported increased fetal loss and teratogenicity in animals following gestational exposure to halothane but these findings have not been reproduced by others.[88,89,90] One animal study suggested that isoflurane in high concentration might be toxic to the fetus, but this was not confirmed when lower doses were used.[91]

In humans the use of twice the minimum alveolar concentrations of halogenated vapours causes a significant reduction in maternal blood pressure and cardiac output with an associated fall in uterine blood flow, despite uterine vasodilation. Such high concentrations should therefore be avoided. Lower concentrations may also cause a fall in blood pressure but this appears to be compensated by uterine vasodilation. The halogenated vapours also cause uterine relaxation, which may be beneficial for surgery during pregnancy as premature labour may be prevented.

Nitrous oxide has been extensively investigated. It oxidises the cobalt in vitamin B_{12} from cob(I)alamin to cob(II)alamin. This inactivates the action of vitamin B_{12} as a coenzyme for methionine synthetase. Methionine syn-

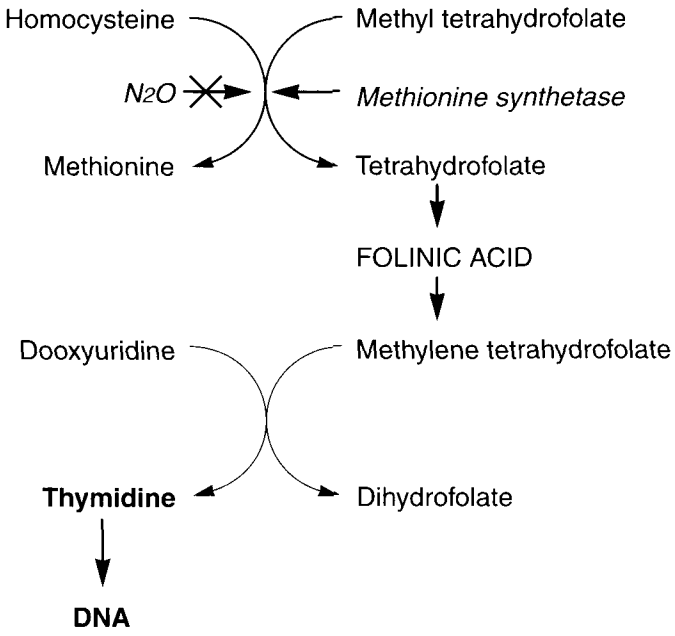

Fig 1.4 Nitrous oxide inhibits methionine synthetase, blocking the production of methionine and ultimately thymidine and DNA

thetase is required for the formation of methionine as well as thymidine, one of the subunits of DNA (Fig 1.4). The consequences of its inhibition are complex. Interference with DNA synthesis obviously gives rise to concern for teratogenic effects and animal studies have lent some support to this. Nitrous oxide has consistently been found to have teratogenic effects on Sprague-Dawley rats, although these effects only appear when the animals are exposed to 50–75% nitrous oxide for 24 hours on days 8 or 9 of their gestation, which is the period of greatest vulnerability. Confusingly, although folinic acid restores the ability to synthesise DNA, it does not prevent the teratogenic effects of nitrous oxide whilst simultaneous exposure to halothane does prevent these effects,[91] suggesting that the teratogenic mechanism may not simply involve methionine synthetase inhibition.

In humans, several epidemiological studies of occupational exposure to nitrous oxide during pregnancy have suggested an association between exposure and an increased incidence of teratogenicity and spontaneous abortion. Tannenbaum and Goldberg, however, reviewed 14 studies and concluded that despite the consistently positive results, the number of methodological errors was such that they could not accept the conclusion that occupational exposure to nitrous oxide caused adverse effects.[92] The American Society of Anesthesiology commissioned a similar report, which

also failed to demonstrate any significant increase in congenital abnormalities or spontaneous abortion with occupational exposure to nitrous oxide.[93]

Muscle relaxants

Because muscle relaxants only cross the placenta in very small quantities, fetal exposure to these agents is limited. Animal data using doses of pancuronium, vecuronium, atracurium, and tubocurare nearly 300 times higher than the concentration of normal fetal exposure suggested that morphological changes may occur.[94] However, there are no data associating the commonly used depolarising or non-depolarising muscle relaxants with teratogenicity in concentrations comparable with those that a fetus is likely to be exposed to during clinical practice.

Anticholinesterase inhibitors

These agents are highly ionised and so, like muscle relaxants, do not readily cross the placenta. There is no evidence to suggest teratogenicity, although pyridostigmine, when used chronically to treat myasthenia gravis, may cause premature labour.

Analgesics

Although the opiates readily cross the placenta, brief exposure is safe. Long-term exposure will cause symptoms of withdrawal when the fetus is delivered. Animal studies have not demonstrated any teratogenic changes associated with exposure to morphine, fentanyl or alfentanil, providing the side-effects of hypoventilation and impaired feeding are eliminated. Use of any opiate near the time of delivery may cause neonatal depression.

Non-steroidal anti-inflammatory agents act through the inhibition of prostaglandin synthesis and their use in early pregnancy may cause bleeding and fetal loss. Case reports have also suggested that chronic exposure in the third trimester may cause premature closure of the ductus arteriosus and persistent pulmonary hypertension of the newborn.

Bupivacaine and lignocaine have a very good safety record. However, at nearly 10 times the maximum dose recommended for use in humans, bupivacaine has embryocidal effects in rats. When used at delivery, bupivacaine has no significant neonatal neurobehavioural effects, while lignocaine may have a mild effect.[95] Cocaine abuse during pregnancy may increase the incidence of fetal abnormalities in the genitourinary and gastrointestinal tracts.

Anaesthesia during the first trimester

When a pregnant woman is anaesthetised, the fetus is exposed to the anaesthetic agents. However, as already discussed, the direct risks from this are low. Of greater importance are the indirect effects on the fetus that may

occur when anaesthesia alters maternal physiology. Periods of maternal hypoxia, hypotension, hyper- or hypocarbia must be avoided and uterine perfusion needs to be optimised. Haemorrhage causing significant maternal anaemia may also cause fetal hypoxia. Every effort must be made to maintain maternal physiological parameters in the range appropriate for gestational age throughout the perioperative period. Although each trimester has slightly different anaesthetic implications, these general principles should be observed at every stage of gestation.

The most common surgical procedure in the first trimester is laparoscopy but cervical cerclage is also common in the latter part of the first and early in the second trimester. Even when the initial expectation is that fetal loss is inevitable, anaesthesia should be performed with the assumption that the fetus will survive. To reduce the risks of teratogenicity and fetal loss, semi-urgent surgery should be delayed from the first to the second trimester whenever possible.

There are insufficient data to conclude whether regional or general anaesthesia is the safer option for either mother or fetus. However, many obstetric anaesthetists would argue that, when possible, regional anaesthesia should be used. In part, this is because drug exposure is minimal, especially when intrathecal local anaesthetics are used, and in part because regional anaesthesia allows the mother to continue to protect her own airway. Airway management in the first and early second trimester is a controversial subject. Within the first few weeks of pregnancy, the lower oesophageal barrier pressure falls. Because of this, some anaesthetists would recommend a rapid-sequence induction whenever general anaesthesia is administered to pregnant women, no matter what gestation. However, gastric emptying time is little changed by pregnancy.[34] Vanner and colleagues demonstrated that significant reflux is not increased in asymptomatic women during the first trimester.[32] Although aspiration is an important cause of maternal mortality, when Atrash reviewed maternal mortality in the United States between 1979 and 1986, none of the 21 deaths that were due to aspiration were attributed to surgery associated with medical abortion or hydatidiform mole.[96] These were the two procedures that were most likely to be performed without intubation. Furthermore, rapid-sequence induction is not completely devoid of risk. It is associated with a higher incidence of failed intubation,[97] which may promote loss of airway control. Suxamethonium, the most commonly used muscle relaxant for a rapid-sequence induction, is associated with potentially fatal side-effects. Anaphylactic reactions occur in between one in 5000 and one in 20 000 administrations and bradycardias, hyperkalaemia, and malignant hyperpyrexia may also occur with its use.

The overall balance of risk between intubation and mask anaesthesia for asymptomatic women during the first and early second trimester remains difficult to assess. While the issue remains unresolved, the majority of

anaesthetists are happy not to intubate the trachea of otherwise uncomplicated pregnant women at 12 weeks gestation, while most would intubate pregnant women undergoing surgery after 20 weeks gestation.

Anaesthesia during the second trimester

From midgestation, some pregnant women become vulnerable to aortocaval occlusion. Although collateral circulation may be sufficient to prevent overt supine hypotension, uterine perfusion may still be compromised. Therefore all women after 20 weeks gestation should be tilted or wedged to the left during surgery.

During this trimester perioperative fetal monitoring becomes possible. From the 16th week of gestation the fetal heart can be detected with Doppler techniques and from around the 20th week, baseline variability of the fetal heart rate becomes apparent. At this point information about fetal well-being can be derived. This is only advantageous if the monitoring does not interfere with the surgery and if a useful intervention can be made to correct a detected abnormality. The value of fetal monitoring remains to be demonstrated but case reports of modification of anaesthetic technique and suppression of premature labour suggest that there are benefits to the fetus.[98] It should be realised, however, that interpretation of fetal heart rate during anaesthesia may be difficult. Loss of variability is to be expected with exposure to anaesthetic agents and mild fetal bradycardia is also common, especially if maternal hypothermia occurs. While a normal fetal heart rate is reassuring, abnormal fetal heart rates by themselves do not necessarily indicate fetal distress. Nevertheless, an advantage of monitoring is that if an abnormal fetal heart rate is detected, the anaesthetic technique can be reviewed to confirm that optimal conditions are being maintained.

Monitoring uterine activity postoperatively may offer the greatest benefit, as premature labour is a significant risk after surgery. Once the uterus has reached the umbilicus, an external pressure transducer can detect uterine contractions. If regular uterine contractions occur either pre- or postoperatively, appropriate tocolytic therapy can be instituted. Routine fetal and uterine monitoring of all pregnant women undergoing surgery has been recommended.[98]

Anaesthesia during the third trimester

In the third trimester the anaesthetic considerations are very similar to those of caesarean section at term except that uterine relaxation is advantageous and fetal depression is to be expected. As the fetus is viable, detection of fetal compromise becomes increasingly important because the baby may be delivered if necessary. While general anaesthesia is required for many surgical procedures, most obstetric anaesthetists would recommend

regional anaesthesia whenever possible because at term regional anaesthesia has a 16-fold lower mortality rate than general anaesthesia.[99]

During the third trimester women become particularly vulnerable to hypoxia because of the combination of increased oxygen consumption and the reduced FRC, especially in the supine position. Adequate preoxygenation and denitrogenation are crucial. A rapid-sequence induction should always be used and, as in the second trimester, pregnant women must always be tilted or wedged to the left. Although excessive doses of volatile agents should be avoided, adequate doses must be maintained to avoid awareness. MAC is reduced during pregnancy but inadequate anaesthesia is associated with increased catecholamine release, which reduces placental blood flow. For the same reason postoperative analgesia must be effective. Although opiates can be used, they may result in maternal hypercarbia; regional analgesia with local anaesthetic agents may be advantageous.

In the third trimester every effort should be made to monitor the fetal heart rate and uterine activity as far as possible both during and after surgery. If severe fetal distress is detected and cannot be rapidly corrected, the baby should be delivered.

Surgical procedures during pregnancy

Intracranial haemorrhage causes almost 5% of maternal deaths.[100,101] Because intracranial pathology is relatively common during pregnancy, neurosurgery is actually performed surprisingly frequently. In Mazze's study of surgery during pregnancy, over 6% of operations were neurosurgical.[80]

Neuroanaesthetists often use mild hyperventilation to control intracranial pressure. Because a pregnant woman is already hypocapnic, arterial carbon dioxide partial pressure has to be reduced further to reduce intracranial pressure. Such hyperventilation impairs uterine blood flow, shifts the oxyhaemoglobin dissociation curve to the left and reduces fetal oxygenation. While the benefits of hypocapnia must be assessed carefully before use, in practice the fetus can usually tolerate a period of hypocapnia. Some centres also use deliberate mild hypothermia for neurosurgery, which the baby usually tolerates although fetal heart rate variability is lost and mild bradycardia is common. Osmotic diuretics (mannitol) are sometimes requested during neurosurgery but these can cause fetal dehydration and should be avoided if possible. Deliberate hypotension should only be employed if absolutely necessary as a sustained fall in blood pressure causes fetal hypoxia and acidaemia.

The incidence of cardiac surgery during pregnancy is probably rising. Pregnancy does not seem to increase the maternal mortality associated with the surgery, but fetal loss as high as 25% is to be expected with such operations. If cardiopulmonary bypass is required, the fetus appears to tolerate

mild hypothermia well, although fetal heart rate patterns may become very abnormal. Whenever possible, blood pressure should be maintained above 60 mmHg, even during bypass. Fetal heart rate monitoring should be used and if the trace is unexpectedly abnormal, a remedial cause should be sought. Careful consideration should be given to the effect on the uterine circulation of the vasoactive drugs used. When possible, α-agonists should be avoided. However, maternal well-being should remain paramount.

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