

Medical Diseases Complicating Pregnancy

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In the most recent Report on Confidential Enquiries into Maternal Deaths in the UK covering 1994–1996, the leading causes of direct maternal deaths are thromboembolic disease (46 patients), hypertension (20), early pregnancy loss (14), haemorrhage (12), amniotic fluid embolism (17), genital tract sepsis (14) and death from anaesthesia (1). This pattern shows little change from the previous triennium. Heart disease (28) is a major cause of indirect death. Other causes of indirect death include epilepsy (19) and asthma (3).

Thromboembolic disease

In the UK, thromboembolic disease remains the leading cause of maternal mortality, accounting for 36% of direct deaths. The rate was 2.1 deaths per 100,000 maternities in 1994–1996 and is increasing. Thromboembolic disease may occur at any gestation, and healthcare professionals should have a low threshold for investigating leg or chest symptoms in pregnant women.

A thromboembolic event occurs in 1/1500 pregnancies. Antenatal deep vein thrombosis (DVT) occurs in 0.06–0.09% of pregnancies, being twice as common in women over 35 years. In the puerperium DVT is also related to maternal age and mode of delivery. Pulmonary emboli are more common in the puerperium, especially following caesarean section.

Physiological changes of the coagulation system in pregnancy: the risk of thromboembolic disease is increased six-fold in pregnancy. There is an increase in coagulation factors I (fibrinogen), V, VII, VIII, IX, X, XII, von Willebrand factor antigen and ristocetin cofactor activity and a decrease in

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some endogenous anticoagulants (antithrombin, protein S and activated protein C ratio) which is most marked near term and following delivery. Fibrinolysis is impaired during pregnancy.

Peripheral vasodilatation occurs in normal pregnancy, resulting in a marked fall in velocity of blood flow. This fall is most marked in women undergoing caesarean section. It also occurs to a greater extent in the left femoral vein compared with the right. This is secondary to compression of the left iliac vein by the right iliac artery and the ovarian artery, which cross the vein only on the left side, leading to the predominance of left-sided (85%) DVTs in pregnancy.

Management

Ante-partum: every pregnant woman's risk of thromboembolic disease should be assessed at booking, by establishing whether she has a personal or family history. In addition, every pregnant woman who enters a high-risk situation should have her risk re-evaluated. Prophylactic treatment for thromboembolic disease should be offered to women at high risk. Women who have experienced a thrombosis during pregnancy should be closely followed up, preferably by a doctor with an interest in the management of thrombosis in pregnancy.

Previous thromboembolic event – women who have had a single previous thromboembolic event, have no family history and a negative thrombophilia screen should take aspirin, 75 mg/day, throughout pregnancy and low molecular weight heparin (LMWH) at a thromboprophylactic dose (e.g. dalteparin

sodium, 5000 U/day subcutaneously) from the onset of labour until 6 weeks post-partum. Women who have had more than one thromboembolic event or who have had a single event but have a positive family history or thrombophilia screen should take prophylactic LMWH from early pregnancy until 6 weeks after delivery.

Positive thrombophilia screen – increasingly, women discover they have a thrombophilia when a family member is screened. The risk of thrombosis in the presence of thrombophilia is lower in those with a family rather than a personal history of thromboembolic disease. It may be appropriate to give low dose aspirin antenatally. Thromboprophylaxis should be determined on an individual basis, but these women require LMWH if they undergo caesarean section.

High-risk obstetric guidelines – in 1995, the Royal College of Obstetricians and Gynaecologists issued guidelines relating to thromboprophylaxis in pregnancy, including treatment following caesarean section (Figure 1). Each unit should have a locally agreed policy, based on these guidelines, which is strictly adhered to. Many hospitals give thromboprophylaxis to most, if not all, women undergoing caesarean section.

Acute episodes – it is essential to confirm or exclude a diagnosis of thrombosis with objective testing. Data from non-pregnant individuals suggest that 16% of patients with untreated DVT develop pulmonary embolus, and 13% of these die, though anticoagulation reduces the risk. Thus, a positive diagnosis of thrombosis requires immediate management, but because the

Thromboprophylaxis at caesarean section

Definition

Low risk

- Elective caesarean section
- Uncomplicated pregnancy
- No other risk factors

Moderate risk

- Emergency caesarean section in labour
- Age (> 35 years)
- Obese (> 80 kg)
- Gross varicose veins
- Current infection
- Pre-eclampsia
- Immobilization before caesarean section for more than 4 days
- Major current illness (e.g. heart or lung disease, inflammatory bowel disease, nephrotic syndrome, diabetes)

High risk

- Three or more moderate risk factors
- Extended abdominal or pelvic surgery (e.g. caesarean hysterectomy)
- Personal or family history of thromboembolic disease
- Positive thrombophilia
- Paralysis of lower limbs

Management

Early mobilization
Good hydration

Prophylactic stockings for thromboembolic disease or subcutaneous heparin

Prophylactic stockings for thromboembolic disease plus subcutaneous heparin (commencing during caesarean section and continuing for 5 days)

Source: Royal College of Obstetricians and Gynaecologists. Report of the RCOG Working Party on Prophylaxis against Thromboembolism in Gynaecology and Obstetrics. London: Chameleon Press, 1995.

treatment is not without risk, it is vital that the diagnosis is confirmed.

Chest radiography seldom diagnoses pulmonary embolism but may reveal other causes of dyspnoea or chest pain. It should not be withheld solely because of the pregnancy, and can be performed with the knowledge that the amount of radiation is negligible (Figure 2).

Arterial blood gas analysis should be performed in the sitting or left lateral position because in the supine position, inferior vena caval compression by the gravid uterus and functional reduction in pulmonary residual capacity and closing volume may give a false impression of hypoxia. In uncomplicated pregnancy, the partial pressure of oxygen is unchanged or increased, compared with the non-pregnant situation, but falls by about 2 kPa (17 mm Hg) when lying supine. The partial pressure of carbon dioxide in normal pregnancy falls from 5 kPa (35–40 mm Hg) to 4 kPa (30 mm Hg).

ECG lacks specificity, but shows a sinus tachycardia if pulmonary embolism is present. D dimers may be elevated in pregnancy as a result of the prothrombotic changes that occur and are therefore unreliable. There should be a low threshold for performing Doppler ultrasound of the femoral veins or lung ventilation and perfusion scanning (Figure 2).

If a DVT or pulmonary embolus is diagnosed (or strongly suspected), anticoagulation with heparin should be commenced. Warfarin should not be used in the first-line management of thromboembolic disease in pregnant women: it is teratogenic in the first trimester, increases the risk of miscarriage and stillbirth, anticoagulates the fetus and increases the risk of spontaneous haemorrhage (especially intracerebral) *in utero*. Both, heparin and warfarin are safe during lactation.

When an intravenous infusion of unfractionated heparin is used for acute treatment, chronic-phase treatment is commenced after 5–7 days. This is given traditionally as unfractionated heparin 10,000 U b.d. subcutaneously, because

the standard non-pregnant dose of 5000 b.d. is insufficient. LMWH is effective and safe in pregnancy, and it is used for treatment and prophylaxis. If used for treatment, it is continued in therapeutic doses to complete 6–12 weeks of therapy depending on individual circumstances and local policy. It is then replaced by a once daily prophylactic dose of LMWH (e.g. enoxaparin, 40 mg, dalteparin sodium, 5000 U, tinzaparin, 50 U/kg) which is continued until 6 weeks postnatally. For pulmonary embolism or extensive iliofemoral DVT, intravenous unfractionated heparin may be used as first-line treatment in the acute phase until there is enough evidence for the efficacy of LMWH in pregnancy in these circumstances.

Intra-partum: it is important to have a clear delivery plan including every possible emergency situation. The plan should be clearly documented in the patient's notes and agreed by the woman, obstetrician, anaesthetist and haematologist/obstetric physician.

Most obstetric anaesthetists are willing to perform a regional blockade 12 hours following the last LMWH dose. It is important to remember that removal of the epidural catheter has a higher incidence of LMWH-related complications than insertion and this should be delayed until at least 12 hours post LMWH dose. For women with antithrombin deficiency, depending on the titre in the weeks leading up to delivery, an antithrombin infusion may be required before and/or during labour.

Thrombolysis – in non-pregnant patients, there is no clear evidence that thrombolysis improves the clinical outcome of thromboembolic disease, and most physicians reserve its use for critically ill patients. Experience of thrombolytic treatment in pregnancy is even more limited. There is a significant risk of bleeding and it is recommended for use only in life-threatening circumstances.

Estimated radiation to the fetus and increased risk of childhood cancer following common diagnostic procedures¹

Investigation	Estimated radiation to the fetus (mGy)	Probability of fatal cancer to age 15 years
Conventional radiograph		
• Chest	0.01	< 1/1,000,000
• Pelvis	1.1	1/300,000
• Skull	0.01	< 1/1,000,000
• Spine	1.7	1/20,000
CT		
• Chest (including spiral CT)	0.06	1/560,000
• Pelvimetry	0.2	1/170,000
Nuclear medicine		
• Lung perfusion (technetium 99m)	0.2	1/170,000
• Lung ventilation (technetium 99m)	0.3	1/110,000

¹The baseline UK national risk for cancer in the first 15 years of life is about 1/650, of which 50% is fatal.

Post-partum: for women who had thromboembolic disease during pregnancy, a thrombophilia screen should be performed after discontinuation of anticoagulation treatment at least 6 weeks postnatally to assess the risk of recurrence, and to plan management during future pregnancies. Warfarin does not pass into breast milk, therefore women injecting heparin may wish to change to warfarin after delivery, once the risk of post-partum haemorrhage has passed (up to day 5). However, they will have to attend regularly for measurement of their prothrombin time. Contraception should also be discussed. The oestrogen-containing combined oral contraceptive pill is contraindicated in women who have had a thrombosis, but other forms of contraception (hormonal and non-hormonal) are permissible.

Cardiac disease

In the UK, cardiac disease is the second most common cause of maternal death. The physiological haemodynamic adaptation to pregnancy and delivery may place the woman with cardiac disease at serious risk. In the most recent Report on Confidential Enquiries into Maternal Deaths, 29% of the indirect deaths were a result of cardiac disease, of which 26% were congenital, 21% ischaemic and 53% acquired. The incidence of congenital heart disease in pregnancy is increasing, reflecting advances in corrective surgery for severe defects. It is important to consider the woman's risk of ventricular failure (particularly when the right ventricle is acting as the systemic pumping chamber) and any residual pulmonary hypertension. Paradoxical embolism through a right-to-left shunt may cause cerebrovascular accidents in uncorrected Fallot's tetralogy and atrial septal defects. The incidence of rheumatic fever has declined, but rheumatic heart disease, most commonly mitral stenosis, may present for the first time in pregnancy, especially in immigrants.

Whatever the underlying cardiac problem, the ability to tolerate pregnancy and delivery is related to the presence of cyanosis and pulmonary hypertension, the haemodynamic significance of any lesion and the functional state (Figure 3). Cyanosis alone may not be as important in predicting poor outcome as the association of cyanosis with Eisenmenger's syndrome, poor functional class, or both. Poor pregnancy outcome is more likely if the woman is in a poor functional status (NYHA class III or IV) regardless of the specific lesion. Conversely, those in functional classes I or II are likely to do well in pregnancy. Each case must be assessed individually, but women with certain conditions must always be treated as high risk. These include pulmonary hypertension and Eisenmenger's syndrome, severe aortic or mitral stenosis, Marfan's syndrome or cyanotic congenital heart disease.

Management

New York Heart Association (NYHA) functional classification

- Grade I No breathlessness
- Grade II Breathlessness on severe exertion
- Grade III Breathlessness on mild exertion
- Grade IV Breathlessness at rest

Ante-partum: women with cardiac disease should be assessed before pregnancy. Counselling regarding possible fetal and maternal risks and, in some women, the need to avoid pregnancy, may be appropriate. Detailed assessment by an obstetrician, cardiologist and obstetric anaesthetist with an agreed plan for delivery is crucial. Women with congenital heart disease should be referred for a detailed fetal cardiac ultrasound scan because the risk of a congenital heart defect (2–5%) is more than double that of the general population. Some women require elective admission for bed rest to maximize oxygen saturation. Maternal cyanosis and hypoxaemia may adversely affect the fetus increasing the risks of intrauterine growth restriction, miscarriage and spontaneous and iatrogenic prematurity. Serial assessment of fetal growth and well-being is appropriate. If antidysrhythmics are required there is most experience in pregnancy with digoxin and β -blockers. Verapamil, adenosine and DC cardioversion are safe, and flecainide is safe in the second and third trimesters.

Intra-partum: antibiotic prophylaxis to cover delivery is advocated for women with structural heart defects. The exceptions are those with a repaired patent ductus arteriosus, those with an isolated ostium secundum atrial septal defect, and those with mitral valve prolapse without regurgitation. Prophylaxis is mandatory for women with artificial heart valves and those who have had endocarditis.

Women should be nursed in the left or right lateral position. The supine and lithotomy positions should be avoided to minimize the risk of pulmonary oedema. If the mother has to be kept on her back, the pelvis should be rotated so that the uterus drops forward, and cardiac output as well as uteroplacental blood flow are optimized. Continuous ECG and oxygen saturation monitoring, and for certain patients, more invasive monitoring with central venous and arterial cannulation, is required. Full resuscitation facilities must be available.

Epidural anaesthesia and analgesia using incremental doses and with judicious pre-loading are well tolerated in most conditions. Nevertheless, extreme caution is needed in cases of limited stroke volume and left ventricular outflow tract obstruction (e.g. aortic stenosis, hypertrophic cardiomyopathy). If a pudendal block is required lidocaine (lignocaine) without adrenaline (epinephrine) should be used. Oxytocin without ergometrine is recommended for management of the third stage. If there are concerns regarding the need to avoid vasodilatation, this can be administered by small increments of a dilute solution. Women should sit up as soon as possible after delivery. Close and regular observation is required for at least 24 hours after delivery, and transfer to a high-dependency or intensive care ward may be appropriate.

Post-partum: if the mother is well, breast-feeding is not contraindicated. Contraception should be discussed together with the safety of future pregnancies.

Pulmonary hypertension

Pulmonary hypertension may be the result of lung disease (e.g. cystic fibrosis), primary pulmonary hypertension, pulmonary veno-occlusive disease, or Eisenmenger's syndrome. The fall

in systemic vascular resistance in pregnancy combined with the fixed pulmonary vascular resistance (which usually falls in pregnancy) means that there is an increase in right-to-left shunting and these women cannot increase pulmonary blood flow to match the increased cardiac output.

Maternal mortality is 30–50% in Eisenmenger's syndrome, and pregnancy is contraindicated. If a woman with significant pulmonary hypertension becomes pregnant, termination should be offered. If this is declined, prophylactic heparin should be given and bed rest and oxygen therapy instituted if hypoxia develops. Any systemic hypotension or vasodilatation (such as intra-partum or post-partum haemorrhage or related to anaesthesia) may lead to shunt reversal or increased right-to-left shunting, and should be avoided by immediate volume replacement. Opinion varies as to whether these patients should be delivered by elective caesarean section and whether regional anaesthesia is safe. They should be managed in an ICU by anaesthetists, cardiologists and obstetricians with expertise in the care of complicated heart disease. Any drug given to reduce pulmonary artery pressure (other than inhaled nitric oxide) will also reduce systemic pressures and the temptation to manipulate pulmonary artery pressure with vasodilators should be resisted. For this reason, monitoring with arterial and central venous lines with attention to adequate filling is recommended in preference to Swan–Ganz catheterization. Most women with Eisenmenger's syndrome who die as a result of their pregnancy, do so after delivery.

Aortic stenosis

Aortic stenosis is unlikely to cause problems unless the gradient is severe (over 100 mm Hg in the non-pregnant state). The risks are angina, hypertension, heart failure and sudden death. Symptoms (e.g. angina, dyspnoea, syncope) as well as hypertension may be controlled with β -blockers, provided left ventricular function is good. The development of resting tachycardia may indicate a failing left ventricle, unable to maintain the increased stroke volume of pregnancy. Balloon valvotomy may allow relief of severe stenosis and continuation of the pregnancy in severe cases. During delivery, the main complications are pulmonary oedema secondary to left ventricular failure and low cardiac output from decreased venous return. Venocaval compression and hypovolaemia must therefore be avoided.

Mitral stenosis

The increased blood volume, heart rate, and cardiac output accompanying normal pregnancy increase left atrial pressure and may cause pulmonary congestion and pulmonary oedema. Tachycardia is particularly dangerous in mitral stenosis, because diastolic filling of the left ventricle (which is slowed in mitral stenosis) is further decreased, and there is a consequent fall in stroke volume and a rise in left atrial pressure, precipitating pulmonary oedema. Even if a woman is asymptomatic at the beginning of pregnancy, she may deteriorate rapidly and develop exertional dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea due to pulmonary oedema later in gestation. This may be precipitated by a rise in the resting heart rate as a result of a failure to increase stroke volume adequately. If tachycardia develops, β -blockers should be given to slow the heart rate and allow time for left atrial emptying. If atrial fibrillation occurs, this should be converted to

sinus rhythm with digitalization, or DC cardioversion. The risk of pulmonary oedema is greatest immediately after delivery, owing to the increase in wedge pressure accompanying the rise in blood volume. For this reason, cautious reduction in pre-load is desirable before delivery. Generally, fluid restriction and the fluid losses accompanying labour are adequate to produce a wedge of 14 mm Hg or less. If the pre-load is decreased too much, cardiac output will fall. Decreases in systemic vascular resistance lead to tachycardia and should be avoided. Epidural anaesthesia is desirable for vaginal and abdominal delivery. Pulmonary oedema should be treated promptly if it occurs.

Marfan's syndrome

The cardiovascular features of Marfan's syndrome include mitral valve prolapse, mitral regurgitation, aortic root dilation and aortic incompetence. Marfan's syndrome is inherited as an autosomal dominant condition and those with cardiac lesions tend to have offspring with cardiac abnormalities. Women should be advised that pregnancy carries a significant risk if the aortic root diameter is greater than 4–4.5 cm, or if there has been a steady increase in the aortic root dimension over preceding visits. Pregnancy increases the risk of aortic dissection and aortic rupture, particularly in those with pre-existing aortic dilatation. This risk is related to the family history, and is increased if relatives with the syndrome have suffered aortic rupture. There is a significant risk even in the absence of preconceptual cardiovascular abnormality and though aortic root dilatation may be a predictor of risk, dissection may occur without significant dilatation or hypertension.

Regular echocardiography assessments should be performed throughout pregnancy. β -blockers have been shown to reduce the rate of aortic dilatation and the risk of complications. They should be continued or started in pregnant patients with aortic dilatation or hypertension. For women with stable aortic measurements less than 4 cm, a vaginal delivery under epidural anaesthesia is recommended, unless there are obstetric indications for caesarean section. Epidural anaesthesia helps to limit the rise in systolic and diastolic blood pressure occurring with the pain and anxiety accompanying uterine contraction. Elective caesarean section with regional anaesthesia is recommended for those with aortic root dimensions greater than 4 cm or with increases in aortic root diameter during pregnancy, in order to avoid the rise in cardiac output associated with labour.

Peri-partum cardiomyopathy

Peri-partum cardiomyopathy is a rare condition specific to pregnancy that usually presents peri-partum or in the first month after delivery. There is a dilated cardiomyopathy and congestive cardiac failure with markedly reduced left ventricular function. There is a significant risk of pulmonary, cerebral and systemic embolization. Peri-partum cardiomyopathy is more common in multiple pregnancy, pregnancy complicated by hypertension, and in multiparous and older women. Management includes anticoagulants and conventional treatment for heart failure including bed rest, diuretics, digoxin, after-load reduction and inotropes. Elective delivery should be undertaken if the

condition presents antenatally. Thromboprophylaxis should be continued intra-partum and post-partum. Angiotensin-converting inhibitors may be used to treat cardiac failure after delivery. About 50% of patients make a spontaneous and full recovery. Women should be counselled regarding the high risk of recurrence in future pregnancies especially if cardiac size does not return to normal.

Ischaemic heart disease

The incidence of myocardial infarction in pregnancy is increasing as older women who smoke are becoming pregnant. The risk is highest in the third trimester and overall maternal mortality is about 20%. Myocardial infarction in pregnancy has been successfully managed with thrombolysis, balloon angioplasty and coronary artery bypass grafting. Low-dose aspirin, 75–150 mg/day, is safe in pregnancy and should be continued or commenced for primary and secondary prophylaxis or in the acute management of myocardial infarction. Anti-anginal medication including nitrates and heparin may also be used safely.

Asthma

The prevalence of asthma in women of childbearing age is increasing. Asthma is the most common pre-existing medical disorder encountered in pregnancy. Management during pregnancy should include reassurance regarding the safety of medications used to control asthma. The biggest danger to the mother and fetus comes from poorly controlled or undertreated disease.

Changes in respiratory function during pregnancy: normal pregnancy is associated with a 20% increase in oxygen consumption and a 15% increase in the maternal metabolic rate. This extra demand is achieved by a 40–50% increase in resting minute ventilation, resulting mainly from a rise in tidal volume rather than respiratory rate. This hyperventilation causes the partial pressure of oxygen in the arteries to increase and that of carbon dioxide to fall, with a compensatory fall in serum bicarbonate to 18–22 mmol/litre. A mild respiratory alkalosis is normal in pregnancy (arterial pH 7.44). Up to 75% of women experience a subjective feeling of breathlessness at some time during pregnancy, possibly because of an increased awareness of physiological hyperventilation. This is most common in the third trimester and may lead to diagnostic confusion. In late pregnancy, the diaphragmatic elevation caused by the enlarging uterus leads to a decrease in functional residual capacity (FRC), but diaphragm excursion is unaffected and therefore vital capacity is unchanged. There is no change in peak expiratory flow rate or forced expiratory volume in 1 second in pregnancy. However, the fall in FRC may exacerbate hypoxaemia because of premature airway closure when acute asthma complicates pregnancy.

The effect of pregnancy on asthma in an individual woman is unpredictable. Women with mild disease are unlikely to experience problems, whereas those with severe asthma are at greater risk of deterioration, particularly late in pregnancy. Physiological changes during pregnancy that may improve asthma include progesterone-mediated bronchodilation and increased serum free cortisol. Those that may explain deterioration include increased stress and increased gastro-oesophageal reflux. Many asthmatic

experience worsening of their symptoms during pregnancy because they stop or reduce medication, due to unfounded fears (either their own or their medical advisers’) about its safety.

The effect of asthma on pregnancy in most women is negligible. However, severe, poorly controlled asthma may have an adverse effect on fetal outcome as a result of chronic or intermittent maternal hypoxaemia. Some studies have suggested an increase in the risk of premature labour and low birth weight, though two prospective case-control studies have not confirmed these findings. Similarly, higher rates of pregnancy-induced hypertension or pre-eclampsia, and caesarean section have been reported, but this may be a consequence of increased surveillance of asthmatic pregnancies, rather than a result of maternal asthma. Corticosteroid use may act as a confounder. The magnitude of any adverse effect on perinatal outcome is small and related to the degree of control of the asthma.

Management

Management of asthma in pregnancy does not differ from management outside pregnancy. The priority should be effective control of the disease process, with the aim being total freedom from symptoms both day and night. The medications used to treat asthma are safe in pregnancy. Great attention must be given to reassuring women about the safety of the drugs used to treat asthma in pregnancy and during lactation. Asthma should be treated as aggressively in pregnant women as in non-pregnant women. Pregnancy, because of the increased contact with health-care professionals, provides an ideal opportunity to optimize asthma management. The drug treatment of asthma requires a short-acting symptom reliever and a long-term daily medication to address the underlying inflammation. All the drugs commonly used to treat asthma, including short- and long-acting β_2 -agonists, inhaled corticosteroids, and methyl xanthines are safe in pregnancy. Fluticasone may be used for those requiring high doses of inhaled corticosteroids.

Acute severe asthma is dangerous and should be vigorously managed in hospital. Treatment is no different from the emergency management of acute severe asthma outside pregnancy. Oxygen, nebulized β_2 -agonists, nebulized ipratropium, oral or intravenous corticosteroids, and in severe cases intravenous aminophylline or intravenous β_2 -agonists should be used as indicated. Provided abdominal shielding is used, a chest radiograph results in minimal exposure of the fetus to ionizing radiation, and if clinically indicated this investigation must never be withheld because the patient is pregnant.

Labour and delivery: acute attacks of asthma during labour and delivery are rare, and women should be reassured. Women may continue to use their regular inhalers throughout labour. Those taking oral corticosteroids (prednisolone, over 7.5 mg/day for more than 2 weeks) at the onset of labour or delivery should receive parenteral corticosteroids (hydrocortisone, 100 mg 6–8 hourly) during labour, and until they are able to restart their oral

medication. Prostaglandin E₂ used to induce labour, to ripen the cervix, or for early termination of pregnancy is a bronchodilator and is safe. Prostaglandin F_{2α}, indicated for severe post-partum haemorrhage should be used with caution because it may cause bronchospasm.

Asthmatic women may safely use all forms of pain relief in labour, including epidural analgesia and *Entonox*. In the unlikely event of an acute asthma attack, opiates should be avoided. If anaesthesia is required, women should be encouraged to have epidural rather than general anaesthesia because of the increased risk of chest infection and associated atelectasis. Ergometrine has been reported to cause bronchospasm, particularly in association with general anaesthesia, but this does not seem to be a practical problem when it is combined with oxytocin to prevent post-partum haemorrhage. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain relief following caesarean section. Women with asthma should be asked about any known aspirin or NSAID sensitivity before the use of these drugs.

Epilepsy

Epilepsy is the most common chronic neurological disorder to complicate pregnancy, affecting about 0.5% of pregnancies. Epilepsy is classified according to the clinical type of seizure, of which the most common are grand mal (tonic-clonic seizure), petit mal (absence seizure), and temporal lobe seizures (complex partial seizure). The term petit mal should be reserved for typical absences occurring almost exclusively in children and associated with 3 Hz spike and wave discharge on the EEG. Absence attacks occur in adulthood as a feature of partial seizures.

Most cases of epilepsy are idiopathic. Secondary epilepsy may be encountered in pregnancy in patients who have previously undergone surgery to the cerebral hemispheres or who have intracranial mass lesions. This should always be considered if the first fit occurs in pregnancy. Epilepsy may be a feature of antiphospholipid syndrome. Other causes of seizures in pregnancy include eclampsia, cerebral vein thrombosis, thrombotic thrombocytopenic purpura, cerebral infarction, drug and alcohol withdrawal and hypoglycaemia (complicating insulin-treated diabetes). Most women with epilepsy in pregnancy have already been diagnosed, but when a first fit occurs in pregnancy, having excluded pre-eclampsia, imaging with CT or MRI of the brain is appropriate.

Effect of pregnancy on epilepsy: in general, pregnancy does not affect the frequency of seizures. About 25% of women report improvement, and 10–30% experience an increased seizure frequency in pregnancy. Poorly controlled epileptics, especially those who fit more than once a month, are more likely to deteriorate in pregnancy. There is no relation to the seizure type or the course of epilepsy during previous pregnancies. Reasons for deterioration in seizure control during pregnancy are shown in Figure 4. There is no difference in the change of seizure frequency between trimesters, though the risk of seizures is greatest peripartum (see below).

Effect of epilepsy on pregnancy: most women with epilepsy have uncomplicated pregnancies with normal deliveries and healthy children. The fetus is relatively resistant to short episodes of

hypoxia, and there is no evidence of adverse effects of single seizures on the fetus. Some have documented fetal bradycardia during and after maternal convulsions, but cerebral damage in the long term is not a feature. Status epilepticus affects 1–2% of pregnant women with epilepsy; it is dangerous for both mother and fetus and therefore should be treated vigorously. In the Confidential Enquiry into Maternal Deaths in the UK (1994–1996) there were 19 deaths due to epilepsy. Most occurred antenatally with 10 in the third trimester. In 10 women the cause of death was aspiration. Five women had poorly controlled epilepsy, and two women died not having had a fit for the previous 2 years. However, epileptic seizures may be fatal, and there is a risk of sudden unexplained death in epilepsy even outside pregnancy, which has been estimated at 1/500 woman-years. Although some workers have suggested an increased risk of obstetric complications (e.g. miscarriage, pre-eclampsia, premature labour, ante-partum haemorrhage, caesarean section) most recent prospective studies have not indicated any increase in adverse pregnancy outcome.

The main concern in pregnancies complicated by epilepsy stems from the increased risk of congenital abnormalities. Even epileptics who are not taking anticonvulsants have a slightly increased risk (4%) compared with the general population (3%). The risk of the child developing epilepsy is also increased (4% compared with 1% background) if either parent has epilepsy. If there is a previously affected sibling the risk is 10%. If both parents have epilepsy the risk is 15–20%. The teratogenic risk for any one anti-epileptic drug is 6–7% (i.e. two to three times the background level). The risk increases with the number of drugs, so for those taking two or more anticonvulsants the risk is 15%, and for those taking the combination of valproate, carbamazepine, and phenytoin the risk is as high as 50%.

Management

Pre-pregnancy counselling: it should be assumed that all women of child-bearing age may become pregnant, therefore any opportunity to counsel such women should not be missed. Control of epilepsy should be maximized before pregnancy. For women still having seizures, the lowest dose of the most effective treatment that gives best control of seizures is appropriate. Polytherapy should be avoided. Sodium valproate therapy should be changed to a thrice daily regimen or modified-release preparation to lower peak concentrations and reduce the risk

Reasons for increase in seizures in pregnancy

- Poor drug compliance
- Nausea and vomiting
- Increased blood volume
- Changes in protein binding
- Increased drug clearance
- Lack of sleep
- Reduction of absorption of anticonvulsant drugs from the gastrointestinal tract during labour
- Hyperventilation during labour

of neural tube defects (the neural tube closes at day 26). For valproate there is evidence of a dose-dependent teratogenic effect. Thus, offspring of mothers using more than 1000 mg/day are at a six-fold increased risk of congenital malformations, particularly neural tube defects, compared with those exposed to less than 600 mg/day. Women who have been fit free for more than 2 or 3 years may wish to discontinue anticonvulsants at least pre-conceptually and for the first trimester. This should be an informed decision after counselling, concerning particularly the risk of losing a driving licence in the event of a seizure. The current recommendations are to stop driving from the commencement of the period of drug withdrawal and for a period of 6 months after cessation of treatment, even if there is no recurrence of seizures. All women taking anticonvulsant drugs should be advised to take folic acid (5 mg/day rather than 400 µg/day) for at least 12 weeks before conception and throughout the first trimester.

Ante-partum: folic acid should be continued throughout pregnancy because there is a small risk of folate deficiency anaemia. There is no need to change the anticonvulsant used in pregnancy if the woman is well controlled. Prenatal screening for congenital abnormalities with maternal serum screening or nuchal translucency and detailed ultrasound at 18–20 weeks should be offered. A repeat scan at 22 weeks is advisable if cardiac defects are suspected.

The altered pharmacokinetics (Figure 4) in pregnancy mean that drug levels are likely to change, and for most drugs, concentration of the free drug falls. This is because of the increased plasma volume and the enhanced renal and hepatic drug clearance. These effects are partially offset by decreased protein binding. In practice it is useful to have a baseline blood level early in pregnancy to confirm compliance, and to guide any necessary increases. If a woman is fit free there is no need to measure serial drug levels or adjust the dose. In women who have regular seizures, and who are dependent on critical drug levels, it is worth monitoring drug levels (preferably of the free drug) because they are likely to fall, and increasing doses of anticonvulsants should be guided by serum concentrations. The dose of anticonvulsant should be altered only on clinical grounds. Vitamin K, 10–20 mg orally, should be prescribed from 36 weeks' gestation because, in women taking hepatic enzyme-inducing drugs, vitamin K-dependent clotting factors in the fetus may be reduced, thus increasing the risk of haemorrhagic disease of the newborn.

Intra-partum: the risk of seizures increases around the time of delivery. 1–2% of women with epilepsy will have a seizure during labour, and 1–2% will fit in the first 24 hours post-partum. Caesarean section is required only for obstetric indications or if there are recurrent generalized seizures in labour.

Post-partum: epileptic patients require particular care in the immediate puerperium because of the increased risk of seizures. They should be supervised in the bath. Mothers with major seizures require advice regarding precautions such as bathing infants with somebody else around and changing nappies on the floor. The neonate should also receive vitamin K. All women with epilepsy should be encouraged to breast-feed.

Amniotic fluid embolism

Entry criteria for the amniotic fluid embolism register

- Acute hypotension or cardiac arrest
- Acute hypoxia (dyspnoea, cyanosis or respiratory arrest)
- Coagulopathy, disseminated intravascular coagulation or unexplained haemorrhage
- Onset during labour, caesarean section, uterine evacuation or within 30 minutes post-partum
- Absence of any other potential explanation of above symptoms and signs

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Amniotic fluid embolism is rare but it is associated with a mortality rate of about 80%. Despite a low incidence of 1/80,000 deliveries, amniotic fluid embolism was responsible for 17 confirmed and suspected cases of maternal death in the 1994–1996 UK triennial report. The anaphylactic-like reaction occurs as a result of passage of amniotic fluid and particulate debris into the maternal circulation. Associated maternal factors include multiparity, caesarean section, uterine stimulation, uterine manipulation and increased age. Fetal factors include large baby, polyhydramnios, intrauterine death, placental abruption and rupture of membranes. All but one case in the triennial report had one or more of these complications.

There is a national register for suspected amniotic fluid embolism set up in the UK and the USA. The criteria for entry are detailed in Figure 5.

Management: death usually occurs as a result of cardio-respiratory collapse or disseminated intravascular coagulation. The treatment of amniotic fluid embolism remains supportive and includes adequate oxygenation and ventilation, maintenance of cardiac output and correction of coagulopathy. Current studies are focused on the possible role of leukotrienes, histamine, bradykinin, cytokines, prostaglandins and thromboxane. ◆

FURTHER READING

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