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Recognition and management of maternal cardiac disease in pregnancy

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Heart disease is a leading cause of maternal death. The aim of this study is to review the most common causes of cardiac disease, highlight factors that should be recognized by the clinician, and address recent advances in the anaesthetic management of these patients. Incipient cardiac disease, including peripartum cardiomyopathy, myocardial infarction and aortic dissection, accounts for approximately one in six maternal deaths. The keys to successful diagnosis and management of incipient disease are: a high index of suspicion, particularly in women with known risk factors for cardiovascular disease; a low threshold for radiological investigations; early cardiology input; and invasive monitoring during labour and delivery. Echocardiography is a safe, non-invasive test, under-used in pregnancy. Management of pregnant women with pre-existing cardiac problems should be undertaken by multidisciplinary teams in tertiary centres. In women with pre-existing cardiac disease wishing to proceed to term, cardiac status must be optimized preoperatively and planned elective delivery is preferable. Vaginal delivery is preferable, and with careful incremental regional anaesthesia is safe in most women with cardiac disease. The presence of adequate systems for early detection, appropriate referral to specialist centres, and timely delivery with multidisciplinary support can minimize the serious consequences of poorly controlled heart disease in pregnancy.

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Heart disease is a leading indirect cause of maternal death in the UK, accounting for 35 (16.5%) of all maternal deaths over the period 1997–99,[18] and equalled only by the number of deaths due to thromboembolism. The relative incidences of various types of cardiac disease as a cause of maternal death are listed in Table 1. Three of these deaths were attributed to deviations from standard practice.[18] Less than standard care is not easy to determine and is often complex in aetiology but the recurring themes are: failure of communication between members of multidisciplinary teams; lack of clear policies for the management of cardiac problems; and failure of individual clinicians to diagnose cardiac problems accurately or to appreciate the severity of these conditions when identified. The purpose of this article is to review the clinical features of incipient maternal cardiac disease that should be recognized by the anaesthetist, and address recent advances in the management of these patients, and to consider the management of pregnant women known to have cardiac disease before delivery.

Incipient maternal cardiac disease

In the event that a pregnant woman presents with acute-onset cardiorespiratory symptoms, the anaesthetist is frequently consulted early in the course of the patient's management. The main differential diagnoses for acute cardiovascular deterioration in pregnant women include thromboembolism, pre-eclampsia, haemorrhage, cardiac disease and sepsis.[83] Perhaps the least expected of these diagnoses in a young mother is underlying heart disease.

Peripartum cardiomyopathy

Peripartum cardiomyopathy is a poorly understood condition, with an incidence of 1:1500 to 1:4000 live births. It has been defined clinically as the onset of cardiac failure with no identifiable cause in the last month of pregnancy or within 5 months after delivery, in the absence of heart disease before the last month of pregnancy.[23] It is associated with older maternal age, greater parity, black race and multiple gestations.[96]

Table 1 Maternal deaths due to cardiac disease:[18] UK, 1997–99. The pattern of heart disease has changed over the last 50 yr because of the dramatic reduction in rheumatic heart disease, now largely confined to recent immigrants to the UK. Peripartum cardiomyopathy is currently the most common cause of cardiac-related deaths; with myocardial infarction and aortic dissection, incipient cardiac disease accounts for almost half of all deaths. Pulmonary hypertension remains an important cause of morbidity and, in particular, Eisenmenger's syndrome secondary to congenital heart disease has a high mortality. Endocarditis is largely, although not exclusively, associated with congenital disease or previous cardiac surgery

Cause of death	Deaths	%
Puerperal cardiomyopathy	7	20
Myocardial infarction	5	14
Aortic dissection	5	14
Cardiomyopathy and myocarditis	5	14
Secondary pulmonary hypertension	4	11
Primary pulmonary hypertension	3	9
Endocarditis	3	9
Heart failure, cause unknown	2	6
Dysrhythmia	1	3

Table 2 Clinical definition of peripartum cardiomyopathy[40]

1. Heart failure within last month of pregnancy or five months postpartum
2. Absence of prior heart disease
3. No determinable cause
4. Strict echocardiographic indication of left ventricular dysfunction:
   Ejection fraction <45%
   and/or
   Fractional shortening <30%
   End-diastolic dimension >2.7 cm per m^2 body surface area

Terbutaline tocolytic therapy has also been suggested as a factor; four of 15 women in one case study having received prolonged terbutaline therapy.[47] However, β-agonists may simply unmask clinical heart disease rather than inducing cardiomyopathy, and an association between tocolytic therapy and peripartum cardiomyopathy remains unproven. Viral myocarditis and an abnormal immune response to pregnancy have been implicated in the pathogenesis, but the aetiology of peripartum cardiomyopathy remains unclear.[9 76]

The diagnosis of peripartum cardiomyopathy presents a challenge because many normal women in the last month of a normal pregnancy experience dyspnoea, fatigue and pedal oedema; symptoms identical to early congestive cardiac failure. Symptoms and signs that should raise the suspicion of heart failure include paroxysmal nocturnal dyspnoea, chest pain, nocturnal cough, new regurgitant murmurs, pulmonary crackles, elevated jugular venous pressure and hepatomegaly. A high index of suspicion and a low threshold for echocardiography in patients with these symptoms and signs are essential. The differential diagnosis includes myocardial infarction, sepsis, severe pre-eclampsia, amniotic fluid embolism and pulmonary embolism. The electrocardiogram usually demonstrates normal sinus rhythm or a sinus tachycardia but dysrhythmias may also be present. Left ventricular hypertrophy, inverted T waves, Q waves and non-specific ST segment changes have also been reported.[9] Diagnosis rests on the echocardiographic identification of new left ventricular systolic dysfunction during a limited period around parturition, when other causes of cardiomyopathy have been excluded (Table 2). All patients usually exhibit cardiomegaly on chest X-ray. Endomyocardial biopsy demonstrates myocarditis in up to 76% of patients,[59] and may be necessary where the diagnosis is unclear.

Treatment of peripartum cardiomyopathy involves salt restriction, and the use of diuretics to decrease pulmonary congestion and volume overload. In patients with systolic dysfunction, afterload is usually reduced with vasodilators.

The use of angiotensin-converting enzyme inhibitors during pregnancy is contraindicated because of the risk of teratogenicity, neonatal anuric renal failure and neonatal death.[54] Hydralazine is the drug of choice prepartum, in addition to nitrates or amlodipine. Other calcium channel blockers may be associated with a negative ionotropic effect and should be avoided.[73] Angiotensin-converting enzyme inhibitors are the mainstay of treatment post-partum, even in mothers who are breast feeding. The β-blocker, carvedilol, has been shown to improve overall survival in pregnant women with dilative cardiomyopathy.[72] However, whether this also applies specifically to those with peripartum cardiomyopathy is unclear. More recently, immunosuppressive therapy has been used in the treatment of peripartum cardiomyopathy with mixed success. Administration of pooled polyclonal human antibodies resulted in improvement in recovery of left ventricular function in a cohort of patients with peripartum cardiomyopathy compared to unmatched controls.[7] Atrial arrhythmias should be treated with digoxin, which may also be used for its positive inotropic effect.[80] Class 3 (amiodarone) and class 4 (verapamil) agents are to be avoided because of their side-effects: fetal hypothyroidism and premature delivery, fetal bradycardia, heart block and hypotension respectively.[74] Patients with poor cardiac function, as evidenced by an ejection fraction <35%, are at risk of thromboembolism and anticoagulation is indicated.[76] Unfractionated or low-molecular weight heparins are the choice during pregnancy, and warfarin or a suitable oral alternative is safe in the postpartum period.[77]

When cardiomyopathy occurs during pregnancy, delivery of the fetus reduces the haemodynamic stresses on the heart. As cardiomyopathy manifests in the final trimester, the fetus is usually mature and can be delivered safely before or at the time of commencement of medical therapy. The mode of delivery for patients with peripartum cardiomyopathy is generally based on obstetric indications. After stabilization of the mother's symptoms by the cardiologist and obstetric physician, in most cases induction and vaginal delivery can be attempted in consultation with consultant obstetrician and anaesthetic staff.[33] The advantages of vaginal delivery are minimal blood loss, greater haemodynamic stability, avoidance of surgical stress, and less chance of postoperative infection and pulmonary complications. Effective pain management is a necessity to avoid further increases in cardiac output from pain and anxiety. The use of local infiltration anaesthesia in combination with bilateral ilio-inguinal nerve block has been described.[58] However, regional anaesthesia has the additional

advantages of reducing preload and afterload, and minimizes the fluctuations in cardiac output associated with labour. Regional anaesthesia is contraindicated in anticoagulated patients.[37 42] Caesarean delivery is reserved for indications such as fetal distress or failure to progress.[33] For Caesarean section, regional or general anaesthesia can be used, and this is often determined by the patient's anticoagulation status. In patients undergoing general anaesthesia, the principles of anaesthetic management are as for any patient with cardiac failure: maintenance of normal to low heart rate to decrease oxygen demand, and prevention of large swings in blood pressure. The hypertensive response to intubation can be obtunded by, for example, the use of alfentanil 1–2 mg before careful titration of the induction agent. Thereafter a nitrous oxide–volatile–relaxant technique is suitable. Kaufman and colleagues[45] described an uneventful Caesarean delivery under general anaesthesia using sufentanil 50 μg, thiopental 100 mg and lidocaine 100 mg as induction agents with succinylcholine 200 mg as relaxant during intubation. Anaesthesia was maintained with isoflurane 0.4% in oxygen 100% and muscle relaxation was maintained with rocuronium.

Careful monitoring of fluid balance is obligatory and arterial and CVP lines are recommended. Early critical care referral is essential for unstable patients and critically ill patients with pulmonary oedema, hypoxia, mental obtundation, hypotension, refractory oliguria or acidaemia will require Swan–Ganz monitoring, artificial ventilation and ionotropic support. The phosphodiesterase inhibitor enoximone 0.5–3 mg kg^{-1} loading dose and maintenance infusion of 5–20 μg kg^{-1} min has been used to good effect in such patients.[81] For patients with severe myocardial dysfunction, the use of an intra-aortic balloon pump or a left ventricular assist device may be needed as a bridge until myocardial recovery or cardiac transplantation is performed.[17 48]

Outcome is dependent on the ejection fraction and left ventricular end-diastolic volume at diagnosis, response to medical therapy, and normalization of left ventricular function within six months of pregnancy.[29] Reported mortality rates range from 18 to 56%.[9] Persistent cardiomegaly on chest X-ray is associated with 85% mortality.[23]

Myocardial infarction

Ischaemic heart disease in pregnancy is uncommon, occurring in an estimated 1 in 10 000 deliveries.[38] Myocardial infarction is more common during the third trimester or puerperium of either the first or second pregnancies. If myocardial infarction occurs within 2 weeks of labour or delivery, mortality may be as high as 45%.[38] Patients typically present with ischaemic chest pain in the presence of an abnormal ECG and elevated cardiac enzymes. Symptoms may often be masked or unclear during labour and delivery, and the ECG and cardiac enzymes can be insensitive. Cardiac specific troponin I greater than 0.15 ng ml^{-1} is a more sensitive indicator of myocardial infarction than creatinine kinase muscle–bone serum concentrations, which increase during normal labour.[86] The differential diagnosis of ischaemic chest pain must include haemorrhage, sickle crisis, pre-eclampsia, acute pulmonary emboli and aortic dissection.

Management of myocardial infarction must involve early coronary angiography. In the immediate postpartum period, spontaneous coronary artery dissection is the most common cause of myocardial infarction. The pathophysiological mechanisms responsible in the coronary arteries are similar to those responsible for aortic dissection, although the exact pathogenesis remains unclear. Seventy-eight per cent of women with peripartum coronary artery dissection have no risk factors for coronary artery disease and 84% of lesions involve the left anterior descending artery.[57] Successful treatments include coronary stenting and emergency coronary artery bypass grafting.[41 48] Twenty per cent of women with peripartum myocardial infarction have angiographic evidence of atherosclerosis or intracoronary thrombus. Increasing maternal age, prevalence of type II diabetes and the incidence of smoking in young women may cause this figure to rise. Individual cases in this category have been managed successfully by coronary stenting[90] or the administration of tissue plasminogen activator (TPA) 100 mg over 90 min to lyse intracoronary thrombus.[84] TPA has a large molecular weight and theoretically should not cross the placenta, making it eminently suitable for thrombolysis.[84] The use of TPA is contraindicated in the early postpartum period because the risk of haemorrhage outweighs the risk of treatment with angioplasty and stenting. Concomitant or recent use of anticoagulants and antiplatelet drugs will affect the choice of anaesthesia for labour or Caesarean delivery.[37 42]

The administration of intramuscular or intravenous ergometrine to induce uterine contraction after delivery is associated with myocardial infarction due to coronary artery spasm.[65 90 95] Women with underlying ischaemic heart disease are particularly at risk and the administration of ergometrine should be contraindicated in these patients. If ergometrine is given to patients at risk of ischaemic heart disease, it is advisable to administer it either intramuscularly or intravenously in incremental, divided doses. The mode of action is rapid with myocardial ischaemia observed within 2 min of intravenous administration.[95] If coronary vasospasm is suspected, the immediate administration of a nitrate such as glyceryl trinitrate (GTN) 10–400 μg min^{-1} intravenously or 300 μg sublingually may prevent infarction. If this is ineffective, supportive therapy and immediate coronary angiography with intracoronary injection of GTN or aspiration of associated thrombus may be effective.[95] Myocardial infarction has also been reported with the use of nifedipine therapy for preterm labour.[70] The possible aetiology of this rare complication is that systemic hypotension in combination with a reflex tachycardia after nifedipine therapy may result in myocardial ischaemia.

Aortic dissection

Acute aortic dissection may occur in pregnancy in association with severe hypertension due to pre-eclampsia, coarctation of

the aorta, or connective tissue diseases such as Marfan's syndrome.[79] [105] Although rare, aortic dissection occurring during pregnancy accounts for 50% of all dissections in women under 40 yr.[44] The mother typically presents with severe chest or interscapular pain associated with end-organ ischaemia (myocardial, renal, cerebrovascular, limb ischaemia) and/or acute heart failure secondary to acute aortic incompetence or haemopericardium and tamponade. Diagnosis is made by computed tomography or trans-oesophageal echocardiography. In the presence of aortic dissection, outcome is poor with maternal mortality as high as 25% and fetal mortality higher still.[49] [105] The ultimate goal is to save both mother and fetus, and the decision to repair the dissection is often determined by the clinical state of the patient and fetal gestation. Some patients, predominantly those with dissection limited to the descending aorta (Stanford type B), can be managed successfully to term and surgery performed postpartum. Before 28 weeks gestation, aortic repair with the fetus kept *in situ* is warranted, given the high mortality (80%) of non-operative treatment in this setting.[100] [105] The use of cardiopulmonary bypass in the first trimester is associated with congenital malformations, and the procedure is safer during the second and third trimesters. If the fetus is viable (after 32 weeks gestation), primary Caesarean section with concomitant or staged surgical repair is indicated,[49] [55] [105] although successful vaginal delivery under regional anaesthesia has been described at this stage.[49] Between 28 and 32 weeks gestation there is a dilemma, with the management strategy determined by the maternal and fetal status. In patients with cardiovascular instability or signs of end-organ or uterine ischaemia and fetal distress, immediate Caesarean section and operative repair are justified.

In the presence of aortic dissection, the aims of anaesthetic management during delivery are to reduce the effect of cardiovascular lability on the dissected or abnormal aorta. Epidural anaesthesia effectively reduces the increase in vessel shear stress (cardiac output) and wall tension (mean arterial blood pressure, MABP) associated with labour.[12] In addition, an infusion of the combined α- and β-blocker labetalol $1-10$ μg kg^{-1} min^{-1} can be titrated to allow rapid control of MABP during labour and delivery. The medical management of patients with Marfan's disease often involves the administration of longer acting oral β-blockers, e.g. atenolol $25-100$ mg/day, that have been shown to reduce the rate of aortic dilatation. The use of regional anaesthesia in patients with Marfan's disease can be associated with marked hypotension and there is a potentially increased risk of epidural haematoma due to increased fragility of the epidural veins. The best method of anaesthesia for Caesarean section remains controversial. General anaesthesia may be necessary in anticoagulated patients, but the hypertensive response to intubation and surgical stimulation may increase cardiovascular stress, promoting rupture or progression of a pre-existing dissection.

Acute chronic cardiac disease

Many cardiac problems can be identified or optimized in the preconception or antenatal period, particularly in those patients with congenital heart disease, prior cardiac surgery, or cardiac-related problems in previous pregnancies.[50] Preconception and antenatal counselling offers women information regarding the risks of pregnancy to both mother and fetus, permits assessment of their functional status, and should involve referral to a cardiologist for optimization of their condition. Subsequently, a plan of care in pregnancy should be formed,[50] and in some conditions, for example pulmonary hypertension or Eisenmenger's syndrome,[98] this may include consideration of early termination of pregnancy. Antenatal care is complex and should involve early referral to specialist centres where appropriate multidisciplinary expertise is available. The centres should be staffed at consultant level by physicians with relevant specialized medical experience and knowledge of obstetrics.[18] Close cooperation between the cardiologist, obstetric physician, obstetrician and anaesthetist is essential for a successful pregnancy, labour, delivery and puerperium. Before conception, New York Heart Association (NYHA) functional class (Table 3) does not always predict how the patient will cope with pregnancy and therefore regular clinical assessment using echocardiography and electrocardiograms may be required in addition to regular fetal monitoring.[66] An agreed care plan should be written in the patient's case notes to pass this information on to colleagues. Consultant delivery with high-dependency care, permitting invasive monitoring and intensive therapy where appropriate, should be planned. The most suitable location for delivery is case-dependent. Women with severe or life-threatening structural abnormalities, such as aortic or coronary dissection or severe aortic stenosis, may benefit from delivery near a cardiothoracic surgical unit. Those with conditions unlikely to benefit from or require urgent surgical intervention do not. Whilst planned multidisciplinary care is preferable, it is often the women at greatest risk from cardiac disease, such as recent immigrants or those from lower socioeconomic groups, that are also more likely to receive suboptimal care. Such women are disproportionately represented among women dying from cardiac disease in pregnancy.[18] The rationale may be an overriding desire,

Table 3 New York Heart Association functional classification of heart failure[92]

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause fatigue, palpitations, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in an inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency may even be present at rest. If any physical activity is undertaken, discomfort is increased.

particularly in some ethnic groups, to produce children and consequent under-reporting of cardiac symptoms, or language difficulties and late presentation to antenatal services. In these cases, the anaesthetist may be presented with a patient suffering from undiagnosed or poorly controlled cardiac disease during labour or immediately after delivery. Early recognition, accurate assessment and optimal treatment, with appropriate involvement of senior medical staff, have been highlighted as a potential means of reducing mortality in these patients.[18]

Idiopathic dilative and hypertrophic cardiomyopathy

Idiopathic dilative cardiomyopathy
Idiopathic dilative cardiomyopathy occurring during pregnancy is very rare (5–8/100 000 live births per yr).[103] The clinical characteristics of idiopathic (primary) dilative cardiomyopathy and peripartum cardiomyopathy are similar and the echocardiographic definitions are the same. The diagnosis is reserved for those patients with dilative cardiomyopathy of unknown cause that do not meet the diagnostic criteria for peripartum cardiomyopathy (Table 2). The onset is not restricted to the peripartum period and can occur in the second trimester. In such cases, optimization of their condition using medical therapy until the fetus becomes deliverable (approximately 32 weeks) is an important part of management. In almost every other respect, management is as for peripartum cardiomyopathy. Idiopathic cardiomyopathy has the worse long-term outcome.[30]

Hypertrophic cardiomyopathy
Hypertrophic cardiomyopathy (HCM) is a genetically transmitted cardiac disease with a broad clinical and morphological spectrum, which is generally characterized by left ventricular hypertrophy and reduced left ventricular size and compliance. In general, HCM is well tolerated in pregnancy and most patients can undergo successful vaginal delivery.[4] The haemodynamic state of HCM is strongly influenced by loading conditions, especially in patients with ventricular outflow obstruction. Reduction of preload and afterload results in an increase of outflow gradient and reduction of left ventricular filling. Regional anaesthesia is therefore relatively contraindicated, although there are reports of successful use of epidural anaesthesia for Caesarean section in these patients,[3] as well as for assisted vaginal delivery.[61] Careful invasive monitoring is required and great care must be taken during drug titration and in the management of hypotension, avoiding large fluctuations in afterload. Phenylephrine, a pure α-adrenergic vasoconstrictor without inotropic effects, is the preferred choice for treatment of hypotension.[3 22] It has the added advantage of slowing the heart rate in some patients, thereby improving perfusion to the hypertrophied ventricle. Unlike other cardiac diseases, in HCM the ability to tolerate pregnancy correlates closely with preconception NHYA functional status (Table 3). In a retrospective cohort study of pregnant women, deterioration of symptoms during pregnancy occurred in 4% of those with preconception NYHA class I symptoms and 42% of those patients with HYHA class III and IV symptoms.[4] In this series, HCM-related morbidity and mortality were restricted to those patients with a large ventricular mass, ventricular outflow obstruction (hypertrophic obstructive cardiomyopathy) or recurrent ventricular dysrhythmias.[4]

Congenital heart disease
Congenital heart disease, whether surgically corrected or not, is increasingly prevalent in women of child bearing age, due in large part to advances in the diagnoses and treatment of these conditions in recent decades.[56] In most of these cases however, the underlying condition is not associated with increased maternal or fetal mortality, and mode of delivery is determined by obstetric indications. Acyanotic conditions such as atrial and ventricular septal defects or persistent ductus arteriosus with small or moderate left to right shunts are well tolerated,[102] as is prior surgical repair of a coarctation of the aorta.[56 64] Ebstein's anomaly, a condition in which the tricuspid valve is displaced apically and is usually incompetent, is also well tolerated,[20 25] although in cases where it is associated with an atrial septal defect or Wolf–Parkinson–White syndrome cyanosis or arrhythmias may occur.

Cyanotic conditions that have been corrected surgically are not associated with increased risk to either mother or fetus. Total repair of the tetralogy of Fallot relieves the cyanosis and the outflow obstruction of the right ventricle and, in the absence of major residual defects, pregnancy can proceed without risk to mother or child.[56 67 87] A successful outcome to pregnancy has also been reported after surgical correction of transposition of the great arteries,[14 19] and even after the Fontan repair of a functionally single left ventricle.[10] The success of pregnancy is determined by the functional status of the right ventricle in the former and the single ventricle in the latter. The major problems arising in pregnant women with congenital heart disease occur in the presence of pulmonary hypertension or Eisenmenger's syndrome. These are considered in more detail below. Specific aspects of the anaesthetic management of patients with congenital heart disease have been reviewed comprehensively elsewhere.[26]

Pulmonary hypertension
Pulmonary hypertension that is secondary to cardiac disease is usually reversible upon treating the cause; for example, mitral valvotomy for mitral stenosis. Pulmonary vascular disease, however, is associated with a substantially increased risk of maternal death. Primary pulmonary hypertension is a rare disease that particularly affects young women of child-bearing age. It is associated with a reduction in vascular nitric oxide and prostacyclin synthesis together with an increase in endothelin and thromboxane production, and is characterized histologically by medial thickening and intimal fibrosis. It is

Table 4 Causes of secondary pulmonary hypertension. ASD = atrial septal defect; VSD = ventricular septal defect; PDA = patent ductus arteriosus; HIV = human immunodeficiency virus

Cardiac diseases
  Congenital: left-to-right shunts, e.g. ASD, VSD and PDA
  Acquired: left ventricular failure, mitral valve disease, left atrial thrombus or tumour
Respiratory diseases
  Chronic obstructive, e.g. chronic bronchitis, emphysema, asthma, bronchiectasis
  Chronic parenchymal, e.g. pulmonary fibrosis, pneumoconiosis, extrinsic allergic alveolitis
  Cystic fibrosis
  Obstructive sleep apnoea
  Thoracic cage abnormalities
Pulmonary thromboembolism
Pulmonary vasculitides, e.g. systemic lupus erythematosus, scleroderma, rheumatoid disease
Hyperviscosity syndromes, e.g. myeloma
Infection, e.g. HIV, schistosomiasis
Portal hypertension
Cirrhosis
Drugs, e.g. oral contraceptives, crotalaria teas, appetite suppressants, amphetamines
Primary pulmonary hypertension

defined clinically by a persistently elevated pulmonary artery pressure (PAP), mean pressure >25 mm Hg at rest, without an obvious aetiology.[32] The mortality of mothers with primary pulmonary hypertension in pregnancy is thought to be as high as 30%.[101] Secondary pulmonary hypertension (Table 4) has a reported 60% perinatal mortality and any parturient with this condition should be regarded as critically ill.[101]

Pulmonary hypertension is tolerated badly during pregnancy because of insufficient adaptation of the right heart to increases in cardiac output, in association with a poorly compliant pulmonary vasculature. Pregnancy causes an increase in cardiac output of 30–50%, an increase in blood volume of 40–50% and an increase in oxygen consumption of 20%. An impaired right ventricular reserve can be pushed into failure by these increased gestational demands, and by the increases in cardiac output and potential intravascular volume injections of up to 500 ml per uterine contraction during labour. Postpartum intravascular volume shifts resulting from haemorrhage or diuresis are particularly poorly tolerated. The greatest risk occurs in the peripartum period and most deaths occur between 2 and 9 days postpartum.[52] Right ventricular decompensation presents clinically as increasing dyspnoea, cyanosis, chronic cough, haemoptysis, early fatigue and syncope. Death results from irreversible right ventricular failure or arrhythmias. Pulmonary embolism is an important differential diagnosis. Ventilation perfusion scans, computed tomographic pulmonary angiography or right heart catheterization and digital subtraction pulmonary angiography can be used to confirm the diagnosis in patients with echocardiographic evidence of right heart failure: a hypertrophic and dilated right ventricle, tricuspid regurgitation, and right-to-left septal shift.

Specific drug management of the pregnant patient with pulmonary hypertension is as for the non-pregnant patient.

Treatment includes the use of pulmonary vasodilators such as nifedipine 20–80 mg/day, or parenteral vasodilators such as prostacyclin and nitric oxide,[27] in addition to anticoagulation because of the increased risk of thromboembolism. Premature spontaneous delivery is common and therefore delivery is usually planned for 32–34 weeks gestation. The principles of management in the peripartum period are the avoidance of increases in pulmonary vascular resistance (PVR), and maintenance of right ventricular preload, left ventricular afterload and right ventricular contractility.[52] In general, better results can be achieved by avoiding increases in PVR due to hypothermia, acidosis, hypercarbia, hypoxia, high ventilation pressures, and sympathetic agents such as epinephrine and norepinephrine. Mode of delivery, type and technique of anaesthesia and the manner of maternal monitoring have each been shown to be significant risk factors for poor outcome in pregnant women with pulmonary hypertension.[98] Most reports have recommended vaginal delivery under epidural anaesthesia, thereby reducing pain, oxygen consumption and the haemodynamic consequences of labour.[82 88] Other techniques described include intrathecal opiates with pudendal block, the combination of intrathecal opiates followed by low-dose epidural infusion, continuous low-dose epidural local anaesthetic and opiate infusions, and double epidural catheter techniques, without a demonstrable advantage of any one technique.[82] Oxytocin has been used in several reports to induce labour as well as to increase uterine tone after delivery without haemodynamic consequence.[46 62] An infusion of oxytocin can lower systemic vascular resistance (SVR) as well as elevate PVR, resulting in a drop in cardiac output; care must be taken during its administration.[69] Prostaglandin $F_{2\alpha}$ causes pulmonary vasoconstriction and must be avoided.

Multivariate analysis shows that operative delivery is associated with increased mortality in women with pulmonary hypertension.[101] This may be due to the likelihood that Caesarean section is more often performed in those with severe cardiovascular instability. However, alternatively, the increased cardiovascular instability associated with an abdominal procedure may increase morbidity. The correct choice of anaesthetic technique for Caesarean section is unclear and should be matched to the individual patient.[16 69 71] The high, dense regional block required for operative delivery is potentially hazardous as it can result in a considerable reduction in right ventricular preload.[89] In addition, general anaesthesia may permit effective control of right ventricular preload, enable better control of PAP responses to surgical stimulation, and permit administration of inhaled or nebulized pulmonary vasodilators in a controlled fashion.[46] An opioid-based technique minimizes increased pulmonary pressures during laryngoscopy and avoids the excessive negative ionotropic effects of inhalational agents.[12 97] Nitrous oxide increases pulmonary vascular resistance and is to be avoided.[62] Care must also be taken to minimize reduction of venous return by positive pressure ventilation.

Pulmonary vasodilators

Inhaled nitric oxide (iNO) is a potent selective pulmonary vasodilator, used successfully in the treatment of the non-pregnant patient with pulmonary hypertension. There are a number of reports of its successful use in labour and the peripartum period.[21 46 62] Administration via facemask or nasal cannula is possible, with iNO concentrations administered to achieve an estimated final alveolar concentration of 5–40 p.p.m. For longer-term administration, insertion of a tracheal cannula under local anaesthesia may be required.[51] Inhaled nitric oxide must be delivered close to the patient's airway to limit any chemical reaction with oxygen resulting in toxic nitrogen dioxide (NO_2) production that can, at high concentrations, produce a pneumonitis. Continuous supervision of tidal iNO and NO_2 concentrations using electrochemical monitors is therefore required during labour to allow control of variations in iNO delivery with minute volume, and to prevent iatrogenic injury to the pulmonary tract from high concentrations of NO_2.[28 51] In the awake patient, this may be accomplished via a pharyngeal catheter connected to the monitoring device. Nitric oxide scavenging is not possible in the awake patient, and care must be taken to avoid accumulation of potentially hazardous gases in the immediate patient environment, especially in rooms with poor ventilation.[28]

Side-effects of iNO treatment are an increase in bleeding time due to impaired platelet activation, tachyphylaxis, and methaemoglobin formation. Postpartum haemorrhage not responsive to Syntocinon, may respond to an alternative pulmonary vasodilator.[62] Impaired platelet activation may be beneficial, given the significant risk of thromboembolism in patients with pulmonary hypertension. Tachyphylaxis, seen in some patients, resolves with temporary cessation of therapy. Methaemoglobin can be transmitted to the fetus, where it is associated with tissue hypoxia. Fetal concentrations are usually minimal at final maternal alveolar concentrations of iNO <100 p.p.m.[31] Goodwin and colleagues[36] reported significant methaemoglobinaemia (6.4 g dl^{-1}) with iNO concentrations of 80 p.p.m. Maternal methaemoglobin concentrations must be measured regularly during treatment, as frequently as hourly during labour or when iNO doses are high, to maintain concentrations <5 g dl^{-1}.[54] Fetal blood concentrations must also be measured postpartum. High concentrations may be treated with intravenous methylene blue (2 mg kg^{-1}).

Prostacyclin (epoprostenol, PGI_2), a naturally occurring prostaglandin, acts as a potent vasodilator as well as having an inhibitory effect on platelet aggregation. Prostacyclin infusions of 0–10 ng kg^{-1} min^{-1} [69 89] effectively reduce PVR but also can also reduce SVR and right ventricular preload to a significant degree. The significant impairment of platelet activation and the systemic side-effects of headache, flushing, nausea and abdominal cramps are disadvantages of prostacyclin. Iloprost, its synthetic analogue, has superior metabolic and chemical stability with effects lasting up to 60–120 min. It decreases PVR, increases cardiac output,

and has a minimal effect on SVR. These drugs can also be administered with nebulizers, thereby reducing the systemic effect. Iloprost 20 µg is given diluted in NaCl 0.9% 2 ml up to six times daily[100] and prostacyclin 60 µg h^{-1}.[69] They reduce PAP in patients with pulmonary hypertension more effectively than either intravenous prostacyclin or iNO.[60] Both prostacyclin and iloprost may have adverse effects on uterine blood flow and, in rats, have caused fetal abnormalities.[6] Their successful use in the antenatal and peripartal care of women has been described without adverse effects, however.[62 69 89] The use of GTN infusions to reduce PVR has also been described. There may be difficulties controlling PVR with this drug in the presence of an oxytocin infusion, where prostacyclin has been found to be more effective.[69]

Monitoring

The effect of pulmonary vasculature dilators on PAP must be monitored to confirm their effectiveness. The use of pulmonary artery catheters is controversial, some studies suggesting that they have a significant detrimental effect on patient outcome.[101] The placement of a pulmonary artery catheter enables more accurate and frequent monitoring of PAP, PVR, SVR and cardiac output than can be ascertained by serial transthoracic echocardiography performed during labour or postpartum. A pulmonary artery catheter can also be used to deliver pulmonary vasculature dilators directly to the pulmonary vascular bed. In addition, if pulmonary artery occlusion pressure is not measured, procedural risk is reduced.

In reality, the small number of patients reported in the literature prevents the development of a consensus regarding the best management of these patients. The optimal treatment, including the need for a pulmonary artery catheter, should therefore be considered for each individual case.

Eisenmenger's syndrome is the final stage of pulmonary hypertension at a systemic level with a reversed or bidirectional shunt. It is usually associated with congenital abnormalities but can also occur as a consequence of pulmonary hypertension secondary to any aetiology. In these conditions, the systemic and pulmonary circulations are in open communication, such that if the SVR falls or PVR rises the lungs may be bypassed with fatal consequences. Systemic vasodilatation may be followed rapidly by cyanosis, hypotension, bradycardia and death, even in monitored patients. It is a rare condition with a reported mortality of 36% in pregnancy.[98] The primary anaesthetic goal is to avoid haemodynamic changes that might increase the right-to-left shunt and thereby increase hypoxaemia. The principle involves lowering PVR and maintaining cardiac output and SVR. General anaesthesia with operative delivery has been recommended traditionally because of the risk of a sudden increase in the right-to-left shunt associated with the sympathectomy of regional, and especially spinal, anaesthesia. Regional techniques for both vaginal (epidural) and operative (spinal) delivery have been described,[16 36] with the emphasis on careful incremental increases in drug administration in addition to

low doses of systemic vasoconstrictors (ephedrine),[16] and pulmonary vasodilators (NO and prostacyclin).[51] The estimated incidence of perinatal maternal mortality in association with labours where regional techniques have been employed is 24%.[53]

Valve disease

In general, pregnant women tolerate valvular incompetence better than stenosis. This is because the reduced SVR improves forward flow and limits the effects of regurgitation. Stenosis, in contrast, creates a fixed impediment to the increase in cardiac output that accompanies pregnancy and labour, possibly precipitating heart failure and arrhythmias. The incidence of valve disease in pregnant women in the UK has decreased in recent decades with the decline in rheumatic fever. The incidence remains high in developing countries and therefore pregnant women who are recent immigrants to the UK should be screened for valvular stenosis. The mitral valve is most commonly affected by rheumatic heart disease, the aortic valve much less so. In the UK, calcific degeneration of congenital bicuspid aortic valves is the leading cause of stenosis encountered in pregnancy.[93] All pregnant women with heart valve disease require antibiotic prophylaxis because of the serious consequence of endocarditis.

Mitral valve

In mitral stenosis, a gradient develops across the valve between the left atrium and ventricle, the magnitude of which depends on the severity of the stenosis and the flow across the valve. In non-pregnant patients, symptoms correlate closely with the size of valve area. NYHA class I and II symptoms compare with a valve area of $1.4–2.5\ cm^2$, and NYHA class IV symptoms with severe stenosis ($<1\ cm^2$). The increased cardiac output of pregnancy can exacerbate this situation, precipitating heart failure and ventricular arrhythmias in the final stages of gestation, labour and the postpartum period, and an associated high risk of acute decompensation, pulmonary oedema and cardiovascular collapse. In patients with severe mitral stenosis, mortality can be as high as 5%.[91] Echocardiography is the investigation of choice in the diagnosis of mitral stenosis and can be used to assess the suitability of the patient's valve for commissurotomy.

Prenatal management is directed towards avoiding cardiac decompensation, with regular assessment for volume overload and pulmonary oedema. Treatment involves bed rest, oxygen therapy and diuretics. In severe cases, balloon mitral valvuloplasty is the treatment of choice, with excellent results. Patel and colleagues[75] reported a clinically significant improvement in functional class and reduction in valve gradient in 18 patients undergoing antenatal balloon mitral valvuloplasty.

Most women with mitral stenosis can undergo vaginal delivery with epidural anaesthesia unless obstetrically contraindicated.[24] Tachycardia, secondary to labour pain, increases flow across the mitral valve, producing sudden rises in left atrial pressure and potentially leading to acute pulmonary oedema. This tachycardia is relieved by epidural analgesia without significantly altering patient haemodynamics.[13 40] By means of invasive haemodynamic monitoring, sudden drops in SVR in the presence of a fixed cardiac output can be prevented by small bolus doses of phenylephrine, with volume expansion when necessary.[39] Ziskind and colleagues[106] used epidural anaesthesia and a variable Trendelenburg position to maintain a pulmonary capillary wedge pressure of 25 mm Hg for Caesarean section in seven women with severe mitral stenosis.

Aortic stenosis

Although the symptoms of aortic stenosis can be masked by left ventricular hypertrophy, preconception functional class provides a good estimate of the patient's ability to tolerate pregnancy. Women asymptomatic before conception will in general tolerate pregnancy, whilst those with symptoms or severe stenosis (valve area $<0.5\ cm^2\ m^{-2}$, gradient >60 mm Hg) are at risk of acute left ventricular failure.[66] Together with clinical symptoms, echocardiographic estimation of valve area rather than pressure gradient has been shown to be a better guide to the severity of disease in pregnancy, where the hyperdynamic flow can overestimate the valve gradient.[43] Patients with severe stenosis do not tolerate blood loss, tachycardia and central neural blockade or vena caval compression. The main objective is to avoid fluid depletion and hypotension. Early placement of arterial and central venous lines, maintenance of left uterine displacement and Caesarean delivery under general anaesthesia are recommended. Intravenous oxytocin at delivery can cause severe intractable hypotension and preplanning to avoid its use in these patients is prudent.[104] Phenylephrine to restore coronary perfusion pressure has no adverse effect on left ventricular function[35] and filling dynamics[34] in patients with valvular aortic stenosis under general anaesthesia, and has also been used uneventfully in cases with severe stenosis.[94] In patients with less severe disease, whilst single shot spinal anaesthesia is contraindicated, Caesarean delivery has been successfully managed by invasively monitored, incremental regional analgesia/anaesthesia using both epidural[8 15] and subarachnoid catheters.[78] Balloon valvuloplasty is possible in pregnant patients, but the risk of severe regurgitation is high. Antenatal aortic valve replacement has also been described, with a reported operative maternal mortality of 11%.[100]

Valve prosthesis

Women with prosthetic heart valves who are asymptomatic or mildly symptomatic before conception tolerate pregnancy well. Infection, thromboembolism, particularly with older metal valves (Starr Edwards), and haemorrhage as a consequence of anticoagulation are all recognized complications of prosthetic valves in pregnant women.[68 100] The possibility of teratogenicity, central nervous system abnormalities and

Table 5 Major findings of this review

1. There should be a low threshold for echocardiography in women with cardiorespiratory symptoms in the peripartum period.
2. Coronary angiography and computed tomography may be necessary in the assessment of pregnant women with incipient, life-threatening, cardiac disease.
3. Ergometrine must be used with caution. It is contraindicated in women with underlying ischaemic heart disease.
4. Management of pregnant women with known cardiac disease should be undertaken by multidisciplinary teams in tertiary centres.
5. In women wishing to proceed to term, cardiac status must be optimized preoperatively and planned elective delivery is preferable.
6. Invasive monitoring is frequently required in the management of pregnant patients with cardiac disease.
7. Vaginal delivery is preferable, and carefully titrated regional anaesthesia is safe in most women with cardiac disease.

increased fetal bleeding precludes the use of oral anticoagulants for women with mechanical valve prostheses during the first trimester of pregnancy.[77] Subcutaneous heparin or low molecular weight heparin can be administered to maintain the activated partial thromboplastin time ratio at 2.5–3 times normal. Higher levels (3–4 times normal) are required for older valves.

Cardiac transplantation

Women who have undergone heart transplantation tolerate pregnancy well provided the function of the transplant was stable before pregnancy.[2] Complications in such pregnancies are related to the immunosuppressive therapy and include hypertension, pre-eclampsia, infections and episodes of acute rejection in the mother, and low birth weight and pre-term birth in the infant.[63 85] A transplanted heart is denervated, although it retains its own conducting system; it is devoid of functional autonomic innervation. The transplant therefore responds to pregnancy-related haemodynamic changes through atypical adaptive mechanisms. The increased central venous pressure and cardiac preload associated with the increased blood volume result in an increase in stroke volume through the Frank–Starling mechanism. Physical exercise or other stress produces a delayed increase in cardiac output through a rise in heart rate and contractility when circulating catecholamines released from the adrenal medulla reach myocardial cells.[1] The transplanted heart also tolerates well the haemodynamic changes induced by labour and delivery.[1] The choice between spontaneous delivery and Caesarean section is based on obstetric indications; spontaneous delivery is preferred. In a series of 22 pregnancies occurring in heart-transplanted women, 16 pregnancies progressed to live births, of which 10 were by vaginal delivery and six by Caesarean section.[63] Four Caesarean sections were performed for obstetric reasons, one for fetal distress and one for maternal pre-eclampsia and renal insufficiency associated with fetal intrauterine growth retardation. Regional anaesthesia (epidural or spinal) was used in five Caesarean and four vaginal deliveries (including two operative vaginal deliveries). There were no maternal or infant deaths. Caesarean

section is associated with an increased risk of infection in the immunosuppressed patient,[5] and antibiotic prophylaxis is mandatory in the case of operative delivery.

Conclusions

A summary of the major findings of this review is listed in Table 5. The presence of adequate systems for early detection, appropriate referral to specialist centres and timely delivery with multidisciplinary support can minimize the serious consequences of poorly controlled heart disease in pregnancy. In some cases, the individual clinician may be faced with a patient who has received inadequate antenatal care. A high index of suspicion along with an awareness of the need for the appropriate anaesthetic technique, in combination with adequate and, where necessary, invasive monitoring, are important in these cases.

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