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Peripartum Cardiomyopathy

Leonard TGA

Department of Anaesthesia, Chris Hani Baragwanath Academic Hospital,University of the Witwatersrand, South Africa
Corresponding author, email: tristanleonard@hotmail.com

Introduction

Maternal morbidity and mortality are a major issue in South Africa with the country currently reporting a maternal mortality rate of 132.9 deaths per 100 000 births. This far exceeds the target of 35 deaths per 100 000 as set out in the Millennium Development Goals. The top five causes of death are: non-pregnancy related infections, hypertension, haemorrhage, medical and surgical conditions, and pregnancy related sepsis.[1]

In the 2014 Saving Mothers report,[1] 11.4% of maternal deaths were due to medical or surgical conditions. Cardiac disease accounted for one-third of these deaths. While the exact number of patients who died due to cardiomyopathy is unclear it does remain a significant contributor towards maternal morbidity and mortality.

Definition

Peripartum cardiomyopathy (PPCM) has been defined by the Heart Failure Association of the European Society of Cardiology Working Group on PPCM[2] as: an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated but the ejection fraction is nearly always reduced below 45%.

The key features of this definition are that the presenting patient should have been previously well with new onset shortness of breath in the last month of pregnancy or up to 5 months postpartum with no other cause for the shortness of breath being found. Other causes of heart failure should be ruled out by an extensive history, physical examination and diagnostic testing.[3]

Epidemiology and risk factors of peripartum cardiomyopathy

The current incidence of PPCM around the world is not known and the data that does exist shows a wide variation in the incidence of PPCM. In the United States of America, the incidence of PPCM ranges from 1 in 1149 to 1 in 4350 live births. In South Africa the incidence of PPCM is 1 in 1000 births. There are also some countries that show a uniquely high incidence of PPCM with rates in Haiti of 1 in 299 live births and 1 in 100 deliveries in certain tribes in Nigeria.[3-5]

The large variation in the incidence of PPCM is due to many factors: genetic and geographical differences, reporting rates and access to diagnostic testing, as well as differences in cultural practices surrounding the peripartum period which may contribute to the development of PPCM. Indeed the practice of postpartum consumption of dried lake salt and lying on heated beds after delivery may contribute to the high incidence of PPCM in Nigeria.[4]

Risk factors for PPCM include: increased maternal age, multiparity, preeclampsia, multiple gestation, African descent, use of tocolytics, poverty, tobacco use, malnutrition and anaemia during the presenting pregnancy.[4]

Pathophysiology

The pathophysiology of PPCM is complex and multifactorial with a number of proposed theories. It is important to first understand the significant cardiovascular changes that occur during pregnancy and the stress that these changes cause to the myocardium.

The most important physiological changes during pregnancy are a combination of increased blood volume and decrease in systemic vascular resistance which lead to an increase in cardiac output. Vasodilation is mediated by the actions of oestrogen, progesterone and relaxin. This vasodilation causes the activation of the renin-angiotensin-aldosterone system leading to sodium and water retention. Cardiac remodelling occurs with an increase in left ventricular mass and increased angiogenesis.[6]

These changes are important in allowing the parturient to adapt to the metabolic needs of the foetoplacental unit as well as to prepare her for the upcoming labour and delivery. Failure or aberrations of these cardiovascular changes can lead to a variety of problems in the pregnancy, one of which is PPCM. The proposed contributory pathophysiological mechanisms will be discussed briefly.

Viral myocarditis

Viral infections have been proposed as the cause of PPCM in various investigations. Goulet et al.[7] and Melvin et al.[8] proposed it as the main mechanism for PPCM. Implicated viruses are parvovirus B19, cytomegalovirus, herpes virus 6 and Epstein-Barr virus.[4] However, the evidence is conflicting with myocarditis being found on endomyocardial biopsy in ranges of 9 to 62%.

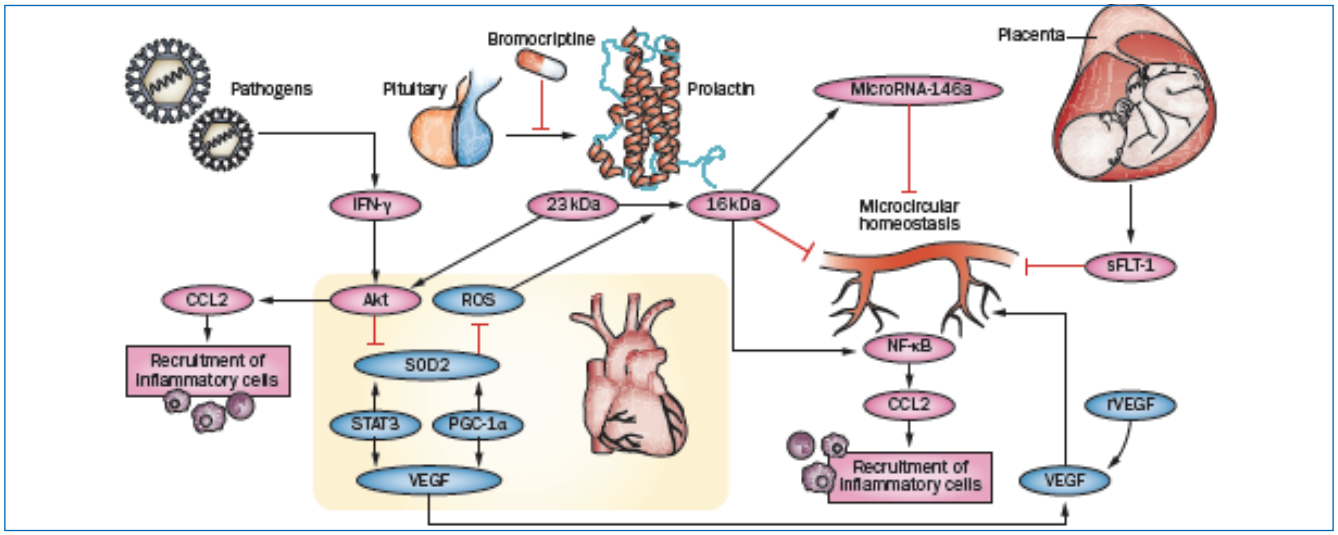

Figure 1. Pathophysiological mechanisms in PPCM[5]

Evidence of myocarditis has not been conclusively shown in the majority of women with PPCM.[4,9]

Oxidative stress and angiogenic imbalance

An imbalance between the production of reactive oxygen species and the ability of an organism to repair such damage leads to oxidative stress.[5] Mice that lack cardiac peroxisome proliferator-activated receptor gamma coactivator 1-alpha, a regulator of angiogenic vascular endothelial growth factor (VEGF), develop severe PPCM.[10] Toward the end of pregnancy the placenta secretes soluble fms-like tyrosine kinase (sFlt1) which inhibits VEGF. Higher levels of sFlt1 occur in women with preeclampsia and multiple gestations. This may explain the association between preeclampsia and multiple gestations with PPCM.[4,5]

Abnormal autoimmune response and inflammation

Circulating auto-antibodies to the myocardium have been reported in up to 50% of patients with PPCM. These auto-antibodies cause increased levels of cytokines such as tumour necrosis factor alpha, interleukin 6 and soluble Fas receptors, which may cause myotoxicity and myocarditis.[11] This auto-immune response may be due to previous exposure from a prior pregnancy or exposure to paternal major histocompatibility complex antigens.[4, 12]

Genetic susceptibility

The increased incidence of PPCM in certain geographical areas suggests a genetic predisposition to the disease and cases have been reported of multiple women in one family developing PPCM.[13] However, a conclusion by Hilfiker-Kleiner and Sliwa[5] is that most women with PPCM report no family history of cardiomyopathy. Mutations associated with dilated cardiomyopathy have been found in screening of relatives with PPCM and indeed the physiological stressors of pregnancy may reveal a dilated cardiomyopathy that is mistaken for PPCM.[4]

Prolactin and vasoinhibin

PPCM is a disease of late pregnancy and early postpartum and as such it is reasonable to assume that a factor specific to late pregnancy may be the cause. Prolactin is a hormone which is present in large quantities in late pregnancy and its role in the development of PPCM has gained traction in recent years.[4,9]

Prolactin is responsible not only for lactation but also has widespread effects on the cardiovascular system. It is associated with increased blood volume, decreased angiotensin responsiveness and a reduction in sodium and water retention. It also has effects on the endothelium and can exert various effects on angiogenesis depending on which form it is circulating in.[5,14]

Experimental evidence from Hilfiker-Kleiner et al.[14] demonstrated that in mice a deletion of STAT3 leads to enhanced expression of cardiac cathepsin-D, which promotes the cleavage of the normal 23kDa prolactin into a 16kDa fragment. This 16kDa prolactin, also called vasoinhibin, is potently antiangiogenic and proapoptotic.[5]

The formation of this 16kDa prolactin may be the central pathophysiological mechanism in PPCM. Unbalance oxidative stress from multiple sources leads to increased levels of cardiac cathepsin-D which leads to cleavage of the 23kDa prolactin. The subsequent increased levels of vasoinhibin cause damage to the cardiac microvasculature, reduce cardiac function and promote ventricular dilatation. It also inhibits the action of VEGF, induces apoptosis and impairs nitric oxide mediated vasodilatation.[4,6,14,15]

Further support for the prolactin model has come from the successful use of bromocriptine, which inhibits the actions of prolactin, in the treatment of PPCM.[3,15]

A pictorial summary of the pathophysiological mechanisms in PPCM is shown in Figure 1.

Presentation

Distinguishing true pathological symptoms from the normal symptoms of late pregnancy can be difficult. Mild oedema and shortness of breath are common in late pregnancy, as are mild ventricular dilatation and increased cardiac output, and as such

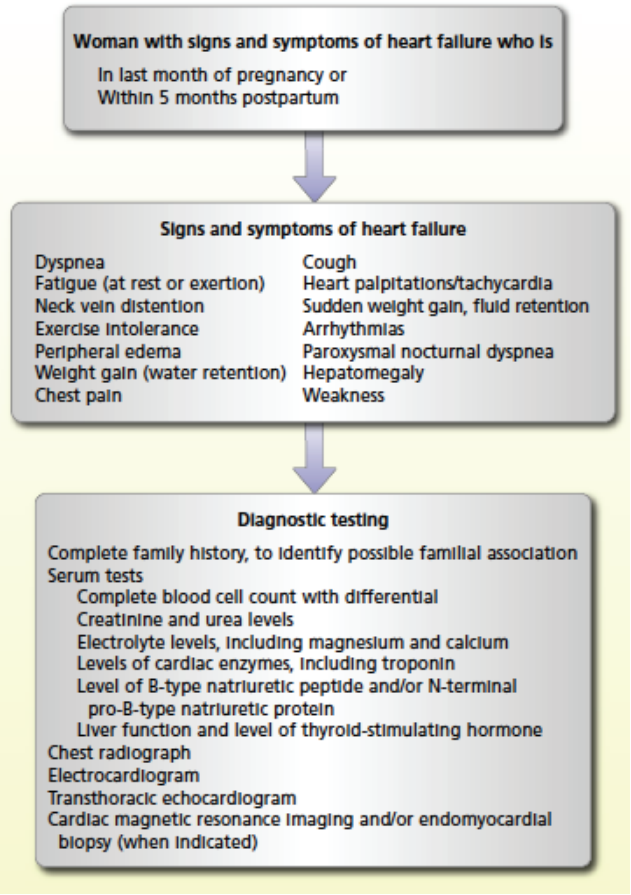

Figure 2. Evaluation of PPCM[9]

a high index of suspicion is required in the diagnosis of PPCM.[9] Particularly important is to ascertain the timing of symptoms and whether they are new onset.

Commonly reported symptoms that should warrant further investigation are dyspnoea (90%) which is typically New York Heart Association (NYHA) grade III or IV, fatigue (90%), palpitations (62%) and peripheral oedema (62%).[4] Persistent nocturnal cough, orthopnoea and paroxysmal nocturnal dyspnoea are also frequently reported.[16] Other symptoms such as dizziness, chest pain and abdominal discomfort have also been reported. Rarely, patients may present with acute cyanosis, thromboembolic events, liver failure and sudden cardiac arrest.[4]

In terms of signs, the presence of tachycardia is nearly universal, and it cannot be stressed enough how important accurately measuring the pulse rate is in these patients. Other signs are those consistent with heart failure: raised jugular venous pressure, third heart sound, displaced apex beat, new murmur of tricuspid or mitral regurgitation and evidence of pulmonary oedema.[16]

The blood pressure may be normal, increased or decreased. A patient presenting with low blood pressure and symptoms of heart failure may be in decompensated heart failure and should be treated as an emergency.[9] The presence of a high blood pressure does not rule out PPCM but should raise suspicion for another cause of cardiac dysfunction in pregnancy, namely preeclampsia.[6] Cardiac involvement in preeclampsia is common, with diastolic dysfunction and raised filling pressures but normal systolic function.[17] Echocardiography will allow the differentiation between PPCM and preeclampsia with cardiac dysfunction.

A proposed evaluation algorithm for PPCM by Johnson-Coyle et al.[9] is illustrated in figure 2.

In summary, it is vital that clinicians, including obstetricians and anaesthetists, look out for features of heart failure in late pregnancy and early postpartum.

Investigations

Routine laboratory investigations should include a full blood count, urea and electrolytes, calcium, magnesium and phosphate, liver function test, thyroid function test and markers of cardiac function (troponin and brain natriuretic peptide). These tests are to ascertain the patient's level of organ dysfunction as well as to exclude other causes of heart failure.

A 12-lead electrocardiogram (ECG) should be obtained in all patients with suspected PPCM. While no single ECG abnormality has been found to be pathognomonic for PPCM, a study in South Africa by Tibazarwa et al.[18] found that 96% of patients with PPCM had at least one ECG abnormality. The most common abnormalities were: T-wave changes, p-wave abnormalities and QRS-axis deviation. Thus the ECG is an important negative prediction tool in the investigation of PPCM and may reveal another diagnosis, such as myocardial infarction or pulmonary embolism.[4]

Echocardiography remains the most reliable and easiest diagnostic modality for PPCM and should be obtained urgently in suspected cases. The echocardiogram will show reduced left ventricular function with an ejection fraction of less than 45% in nearly all cases.[2] Fractional shortening of less than 30% and an end-diastolic diameter of more than 2.7 cm/m^2 are also diagnostic.[11] Other echographic findings are left atrial enlargement, left atrial or ventricular thrombus, dilated right ventricle and mitral and tricuspid regurgitation. The presence of pulmonary hypertension should be noted, if present.[4]

Chest radiography should be obtained with foetal shielding and will be able to detect the presence of cardiomegaly and pulmonary oedema. However, it is not an essential investigation in the diagnosis of PPCM.[4]

Other investigations such as cardiac magnetic resonance imaging, cardiac catheterization and endomyocardial biopsy are not routinely indicated. These are reserved for cases where the diagnosis is in doubt, especially if viral myocarditis or coronary artery disease are suspected.[4,9]

Management

The management of PPCM is similar to that for other forms of systolic heart failure, but should also take into account whether there is a need for operative delivery as well as the potential foetal side effects of therapy. A multi-disciplinary team of obstetricians, cardiologists, neonatologists, intensivists and anaesthetists should be involved. A clear plan for labour and delivery should

be established in advance and distributed to all persons who are likely to be involved in the case.[19]

The principles of treatment are to improve haemodynamic status, reduce preload and afterload, improve contractility, reduce symptoms and prevent thromboembolism. It is important to distinguish between compensated and decompensated heart failure as these will require different treatment as well as necessitate differences in the urgency of delivery.[9]

Patients with compensated heart failure who are antepartum should be commenced on beta-blockers and thiazide diuretics. The addition of hydralazine, digoxin and loop diuretics should also be considered based on symptoms and response to treatment. Low molecular weight heparin should be started in patients with an ejection fraction of less than 35%. The pregnancy should be allowed to continue as long as the patient is stable and there is no obstetric indication for delivery. Once the patient has delivered, she should be started on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker and spironolactone. Heparin can then be changed to warfarin.[9]

Table 1: Management of compensated heart failure in peripartum cardiomyopathy[9,20]

Non-pharmaceutical therapies
Low sodium diet: limit of 2 g sodium per day
Fluid restriction: 2 L/day
Light daily activity
Oral pharmaceutical therapies
Antepartum management of peripartum cardiomyopathy
Beta-blocker
Vasodilator
Digoxin
Thiazide diuretic
Low molecular weight heparin if ejection fraction < 35%
May consider loop diuretic with caution
Postpartum management of peripartum cardiomyopathy
Angiotensin converting enzyme (ACE) inhibitor
Angiotensin-receptor blocker (ARB)
Consider nitrates or hydralazine if woman is intolerant to ACE and ARB
Loop diuretic
Aldosterone antagonist
Beta-blocker
Warfarin if ejection fraction is less than 35%

Decompensated heart failure should be managed as a medical emergency with advanced cardiac life support principles. These patients should be managed in a high care or intensive care unit. The airway should be secured in patients who are severely distressed with the initiation of positive pressure ventilation. Supplemental oxygen should be provided to all other patients and non-invasive ventilation can be considered to reduce left ventricular afterload. Circulatory support is required in patients who are hypotensive, the agents of choice are milrinone and dobutamine. Levosimendan can also be considered. Invasive haemodynamic monitoring should be inserted, and foetal monitoring must be obtained. Preload reduction is obtained with the use of diuretics and vasodilators. Anticoagulation must also be commenced.[4,9] Delivery for these patients is urgent to reduce the myocardial strain caused by pregnancy.[19]

Table 2: Management of decompensated heart failure in peripartum cardiomyopathy[9,20]

Airway
Intubate promptly upon distress for increased work of breathing to prevent complications with difficult airway later in treatment
Breathing
Provide supplemental oxygen
Maintain continuous pulse oximetry
Measure arterial blood gases every 4-6 hours
Circulation
Start cardiac and blood pressure monitoring
Insert arterial catheter
Insert central venous catheter
In antepartum women, obtain foetal monitoring
Intravenous loop diuretic
Intravenous vasodilator
Positive inotropic agent
Avoid beta-blockers in the acute phase as they may decrease perfusion
Heparin, alone or with oral warfarin therapy
If no improvement clinically:
Consider cardiac magnetic resonance imaging
Perform endomyocardial biopsy
Assist devices:
Intra-aortic balloon pump
Left ventricular assist device
Extracorporeal membrane oxygenation
Transplantation
Consider bromocriptine therapy

Bromocriptine

Since the discovery of an inflammation induced increase in cathepsin D and the production of 16kDa prolactin as a pathophysiological process in PPCM, the use of bromocriptine to block the production of prolactin has gained interest. A pilot study by Sliwa et al.[21] in 2010 demonstrated an improvement in left ventricular ejection fraction, improvement in NYHA class and fewer deaths when bromocriptine was added to standard heart failure treatment.

Analysis of the German PPCM registry from 2013 demonstrated a beneficial effect of bromocriptine therapy.[3] Significantly higher numbers of patients treated with bromocriptine were classified as improvers. Subsequent to this a multicentre randomized study was conducted by Hilfiker-Kleiner et al.[15] in Germany comparing 1 week of bromocriptine therapy with 8 weeks of bromocriptine therapy, in addition to standard heart failure therapy. It was considered unethical to have a control group. Bromocriptine therapy was associated with an improvement in left ventricular function and low morbidity and mortality. There was no significant difference in treatment outcome between 1 week and 8 weeks of therapy, however there was a trend toward better recovery in patients with a very low ejection fraction (< 30%) in the 8-week group. The proposed scheme of the actions of bromocriptine is depicted in Figure 3. The authors recommend large prospective registries be developed in countries to allow

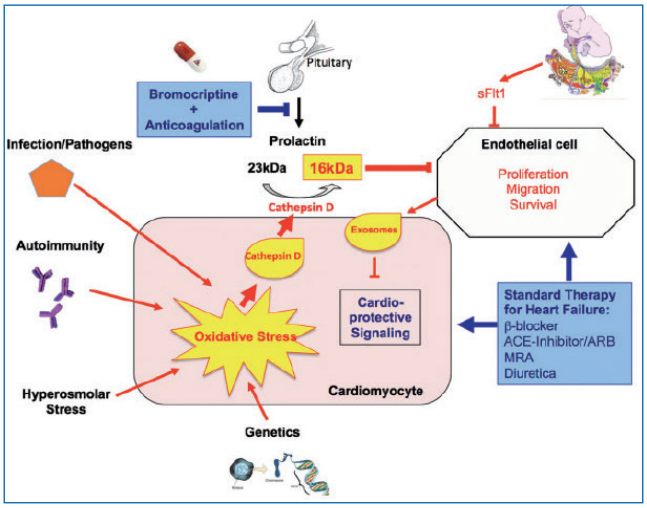

Figure 3. Disease specific therapy with bromocriptine[15]

for greater knowledge on the effects of bromocriptine therapy in large numbers of patients.[15]

Based on the above evidence the Hannover Medical School recommends the use of bromocriptine in patients with PPCM whose ejection fraction is less than 35%.[3]

Anaesthetic management of PPCM

Hilfiker-Kleiner and Sliwa report that 43% of patients with PPCM in South Africa will present in the antepartum period.[5] Many of these patients will require anaesthetic intervention for both normal vaginal delivery and caesarean section. It is important for anaesthetists to be involved in the multi-disciplinary management of such patients.[19,22] It is also vital that the decision for the method of delivery be a multi-disciplinary one. In general, patients who are stable may be allowed progress to spontaneous labour provided there is no deterioration, while patients in decompensated heart failure should have urgent operative delivery.[4,22]

Preoperative assessment

The preoperative, or pre-anaesthetic assessment of patients with PPCM should focus on determining the severity of the patient's condition and whether heart failure is compensated or decompensated. Specific warning symptoms are: NYHAIII/IV and an inability to lie flat. Careful attention should be paid to the respiratory and pulse rate, blood pressure, the presence of a third heart sound and clinical features of pulmonary hypertension.[19,23] The ECG and echocardiogram should be reviewed with specific emphasis on the ejection fraction and left ventricular end-diastolic volume.[22]

Labour analgesia

The provision of adequate labour analgesia is beneficial in achieving the haemodynamic goals required in PPCM. These are specifically a reduction in afterload and maintenance of contractility. The functional sympathectomy from a carefully titrated labour epidural can achieve these goals. The patient's anticoagulation status should be checked prior to the insertion of any neuraxial blockade. It is prudent to institute invasive blood pressure monitoring before any intervention and the patient should be in a high care environment. The epidural should be inserted early in labour with very slow, careful titration so as not to drop the preload or afterload too drastically. These patients will be unable to compensate for hypotension with an increase in cardiac output.[19,22,23]

A controlled second stage of labour with forceps or vacuum delivery is advised to reduce the straining and pushing efforts of the mother.[22] Careful attention should be paid to the fluid management during labour as the patients tolerate hypovolaemia poorly, but are also at risk for fluid overload. The use of oxytocin in the active management of the third stage of labour should be carefully considered and boluses should be avoided, with the use of an infusion if required.[19]

Intraoperative management

While spontaneous vaginal delivery is preferred for patients with stable PPCM, some of these patients will require operative delivery for an obstetric indication. Unstable patients will require urgent caesarean section to reduce maternal cardiovascular strain and possibly prevent foetal loss. An experienced anaesthetist and surgeon should be present.[4,9]

Stable patients presenting for caesarean section are ideally managed with regional anaesthesia with invasive blood pressure monitoring as for those receiving labour analgesia. The theatre should be fully prepared for any complication that may arise intraoperatively. This includes the availability of inotropic agents dobutamine, milrinone and levosimendan and dilator drugs such as nitrocine or nitroprusside.

The choice of anaesthetic technique is varied, and many approaches have been used successfully and include epidural anaesthesia, combined spinal epidural and continuous spinal anaesthesia. George et al.[24] describe the use of epidural anaesthesia over 6 hours to achieve adequate anaesthesia. This may not be practical in many instances. Schnaider et al.[25] prefer the use of a combined spinal epidural due to a lower failure rate, better patient satisfaction and superior haemodynamic profile. The key principles of all these techniques is the avoidance of large single boluses and the maintenance of cardiovascular stability. A single shot spinal is not advised due to the sudden reduction in preload and afterload associated with the rapid sympathectomy.[22]

A novel technique described by Tiwari et al.[26] is the "epidural volume extension" technique. They describe a case series of five patients with PPCM presenting for caesarean section. These patients had a lumbar epidural catheter placed preoperatively that was not activated. After the institution of invasive monitoring the patients underwent a single shot spinal of 1 ml of 0.5% bupivacaine. They were then laid supine and had 8 ml of normal saline injected into the epidural. The theory of this technique is that the epidural expansion will allow surgical anaesthesia with a smaller volume of local anaesthetic. All patients achieved a dermatome level of anaesthesia of T4 with haemodynamic stability and uneventful intraoperative course.

Unstable patients with decompensated heart failure are best managed under general anaesthesia due to the ability to titrate anaesthesia to haemodynamic stability as well as the benefits of positive pressure ventilation in reducing left ventricular afterload. The insertion of an arterial and central venous line should be done prior to the induction of anaesthesia and inotropic and vasodilator infusions should be prepared. Cardiac output monitoring is ideal, and the availability of a transoesophageal echo can provide invaluable information.[23]

The actual choice of anaesthetic technique is depended on the patient's haemodynamic status and anaesthetic experience. A modified rapid sequence technique must be employed balancing the risk of maternal aspiration against haemodynamic stability. A high dose opioid technique will provide maximum haemodynamic stability, but must be weighed against the possible need for maternal postoperative ventilation and foetal respiratory depression. Other techniques include the use of etomidate, remifentanil and volatile anaesthetics. Total intravenous anaesthesia with propofol and remifentanil has been described in one case report, but this should be viewed with extreme caution due to the risk of vasodilation with propofol and the reduction in heart rate from remifentanil that may significantly impair cardiac output.[19,22,23]

Acidosis, hypercarbia and anaemia should be avoided. Careful titration of fluids to maintain preload but not over distend the myocardium is essential. A single dose of furosemide may assist in countering the autotransfusion following delivery of the foetus. Meticulous attention must be paid to blood loss as these patients tolerate hypovolaemia poorly. Syntocinon should be administered via small boluses titrated slowly to response and ergometrine should be avoided.[22]

Postoperative

These patients should be monitored in a high care or intensive care unit postdelivery with continuous invasive monitoring as there are ongoing haemodynamic changes in the postpartum period.[9] Positive pressure ventilation may be required for patients with decompensated heart failure or those who have received a high dose opioid anaesthetic. Heart failure treatment should be continued with the introduction of drugs that were contraindicated in the antepartum period, particularly ACE inhibitors.[4,25]

Prognosis and outcome

Left ventricular recovery is common in PPCM with reported rates of 45 to 78% at 6 months postpartum. Mortality rates vary between 0 and 19%. Overall predictors of mortality are left ventricular ejection fraction of less than 30%, higher maternal age, black race and multiparity.[4] Blauwet et al.[27] analysed predictors of outcome in 176 South African patients and identified increased left ventricular end-systolic diameter, lower body mass index, and lower serum cholesterol as independent predictors of poor outcome.

Patients should be monitored for at least 12 months postpartum and be counselled on the risk of relapse in subsequent pregnancy. They should be provided with effective contraception.[4]

Conclusion

PPCM remains a significant cause of maternal morbidity and mortality as well as a diagnostic challenge. All clinicians involved in the management of pregnant women should maintain a high index of suspicion for PPCM. Management is as for other forms of systolic heart failure with cognizance of the physiological changes and demands of pregnancy and the puerperium. The use of bromocriptine has been shown to improve outcome.

Anaesthetists should be part of the multi-disciplinary team when PPCM is diagnosed antepartum and may be called upon to provide labour analgesia and administer anaesthesia for operative delivery. Anaesthetic goals are to provide cardiovascular stability, reduce preload and afterload and maintain contractility. Where possible, anaesthetists experienced in cardiac and obstetric anaesthesia should be called upon to manage patients with PPCM.

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