Critical care in obstetrics: pregnancy-specific conditions

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This chapter summarizes the clinical presentation, pathophysiology, evaluation and management of six commonly encountered complications unique to pregnancy that require critical care management: obstetric haemorrhage; pre-eclampsia/HELLP (haemolysis–elevated liver enzymes–low platelets) syndrome; acute fatty liver of pregnancy; peripartum cardiomyopathy; amniotic fluid embolism; and trauma.

Key words: obstetric haemorrhage; trauma; pre-eclampsia/HELLP syndrome; acute fatty liver; peripartum cardiomyopathy; amniotic fluid embolism.

HAEMORRHAGE/DISSEMINATED INTRAVASCULAR COAGULATION

Haemorrhage is the second leading cause of pregnancy-related death in the USA1, and the leading cause of maternal death in developing countries, accounting for 25% of maternal deaths worldwide.2,3 Postpartum haemorrhage is defined as blood loss >500 mL at delivery3, and severe postpartum haemorrhage is defined as blood loss

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>1000 mL.4 Risk of haemorrhage-related maternal death increases with maternal age and is greater among African-Americans than among White Americans.5 Haemorrhage-related obstetric death is usually preceded by haemorrhagic shock and rapid cardiovascular collapse.6 In one developing world setting, 88% of deaths occurred within 4 h of delivery.7

**Aetiologies of obstetric haemorrhage**

Life-threatening obstetric haemorrhage may develop in the antepartum or the postpartum period. Antepartum haemorrhage is most often attributable to placental abruption or previa, whereas postpartum haemorrhage is most often associated with uterine atony.3 Other causes of postpartum haemorrhage include retained placenta, uterine inversion, placenta previa, placenta accreta, uterine rupture and genital tract trauma.3,6 Risk factors for postpartum haemorrhage include: pre-existing anaemia; obesity; chorioamnionitis; fetal macrosomia; prior caesarean section; and multiple gestation.6

**Aetiologies of coagulopathy/disseminated intravascular coagulation**

In the obstetric setting, disseminated intravascular coagulation (DIC) may develop due to the underlying shock process (abruption, amniotic fluid embolism)6 or due to dilutional effects of massive blood loss and fluid replacement in the setting of hypovolaemic shock.8 Bick defines DIC as ‘a systemic thrombohemorrhagic disorder seen in association with well-defined clinical situations and laboratory evidence of (1) procoagulant activation, (2) fibrinolytic activation, (3) inhibitor consumption and (4) biochemical evidence of end organ damage or failure’.9 Causes of DIC that are unique to pregnancy include retained fetus after in-utero fetal demise, placental abruption, severe pre-eclampsia/HELLP (haemolysis–elevated liver enzymes–low platelets) syndrome, and amniotic fluid embolism (AFE).9 DIC is always a secondary phenomenon, developing after procoagulant substances, such as collagen, tissue factor from tissue destruction, amniotic fluid, placental tissue, incompatible red blood cells or bacterial products, are released into the maternal circulation.8,10,11 This phenomenon leads to increased production and breakdown of coagulation factors, including increased conversion of fibrinogen to fibrin, platelet activation and consumption, activation of factors V and VIII, protein C activation, endothelial cell activation and fibrinolysis.12 Subsequent developments include increased intravascular fibrin deposition leading to thromboembolic complications.13 The consumption of platelets and coagulation factors leads to massive, and often life-threatening, haemorrhage. In the obstetric setting, increased circulating fibrin degradation products may decrease myometrial contractility, leading to worsening haemorrhage from uterine atony.8 Although haemorrhage is the immediate, life-threatening consequence of DIC, microvascular thromboses may lead to end organ damage or failure, and longer range morbidities.9,10,13

**Diagnosis of disseminated intravascular coagulation**

There are no agreed upon clinical criteria diagnostic for DIC. Signs of DIC may include persistent oozing from operative and venepuncture sites, ongoing postpartum haemorrhage with decreased clotting, acral cyanosis, purpura and petechiae.9 Bleeding
from unrelated sites is also typical. In the setting of massive haemorrhage, it is unwise and unnecessary to delay initiation of potentially life-saving therapies until laboratory results become available; however, many laboratory abnormalities can be seen and help with recognition of DIC. The prothrombin time and partial thromboplastin time are often elevated during DIC, but may be normal in up to 50% of cases. Fibrin degradation products and D-dimers are elevated in 85–100% and at least 93% of cases, respectively. However, both of these are commonly elevated in postpartum and/or postoperative patients and are therefore not diagnostic. Variable degrees of thrombocytopenia and hypofibrinogenaemia are also seen. A diagnostic scoring system combining clinical and laboratory manifestations of DIC has been proposed but is not in general use at this time.

**Management of obstetric haemorrhage**

The goals of managing life-threatening obstetric haemorrhage, with or without DIC, include controlling the source of blood loss, restoring adequate oxygen carrying capacity, and maintaining adequate tissue perfusion. Decreased cardiac output, hypotension and vasoconstriction may result in decreased end organ perfusion of vital organs including kidneys, heart and brain. In order to restore oxygen carrying capacity and maintain adequate tissue perfusion, fluid resuscitation should begin with volume expansion with crystalloid at a volume approximately three times that of the estimated blood loss. This should be followed immediately with replacement of packed red blood cells to restore oxygen carrying capacity, with the goal of maintaining haemoglobin at 7–10 g/dL. Lastly, clotting factors and platelets should be replaced in order to prevent or correct coagulopathy. This replacement should begin with fresh frozen plasma, followed by cryoprecipitate and platelets. In cases in which coagulopathy does not respond to these measures, administration of recombinant activated factor VII can be considered. In order to ‘fast-track’ availability of these blood products, some authors have suggested availability of a ‘massive transfusion’ protocol for hospitals providing obstetric services. One published protocol recommends that blood banks should provide massive transfusion packages containing red blood cells, fresh frozen plasma and platelets in a 6:4:1 ratio, which most closely approximates the composition of whole blood.

The source of bleeding may be controlled medically (with uterotonic drugs, such as oxytocin, methergine, prostaglandin E₂, prostaglandin F₂α and misoprostol), mechanically (with intra-uterine balloons or packs) or surgically. Surgical treatments include conservative measures such as hypogastric artery ligation, uterine artery ligation and arterial embolization by interventional radiology. Hysterectomy is carried out in the event of failure of these conservative measures. A recent Cochrane review concluded that there is currently insufficient evidence from appropriately powered randomized controlled trials to choose oxytocin/methergine over misoprostol as the first-line therapy for atony. Likewise, there are no randomized controlled trials comparing the effectiveness of mechanical and surgical measures to control severe postpartum haemorrhage. However, one recent systematic review evaluated 46 observational studies comparing the modalities intended to control severe postpartum haemorrhage after uterotonic medications have failed. These modalities include balloon tamponade, uterine compression sutures, internal iliac artery ligation or uterine devascularization, and arterial embolization. The reviewers found no significant difference in success rates among these four procedures. Balloon tamponade was successful in 84% of cases, uterine compression sutures were successful in 91.7%...
of cases, internal iliac artery ligation or uterine devascularization was successful in 84.6% of cases, and arterial embolization was successful in 90.7% of cases. Based on these findings, the authors suggest that balloon tamponade, the least invasive of these procedures, should be considered as the first-line approach, particularly after vaginal delivery.4

PRE-ECLAMPSIA, ECLAMPSIA AND HELLP SYNDROME

Classification

Obstetric patients who have high blood pressure, whether pregnant or post partum, can be classified into two categories: chronic hypertension or pre-eclampsia. Types of chronic hypertension include idiopathic or essential hypertension, secondary hypertension from renal disease, Cushing’s syndrome or pheochromocytoma. Pre-eclampsia is not a hypertensive disorder but a pregnancy-specific syndrome, with high blood pressure as one of the many possible symptoms.

Epidemiology

Pre-eclampsia is typically seen in the first pregnancy. The incidence of pre-eclampsia varies between 5% and 8% depending on the population being studied. In most Western cultures, morbidity and mortality associated with pre-eclampsia are low; however, in countries with less access to health care, pre-eclampsia/eclampsia and their associated morbidity and mortality for both mother and fetus remain significant clinical problems.

Pathophysiology

Recent discoveries have markedly improved our understanding of the pathophysiology of pre-eclampsia. It is hypothesized that an altered maternal immune response to antigens expressed on the invading trophoblast results in a premature halting of the trophoblastic invasion into the maternal (spiral) arteries. The lack of this invasion causes these maternal vessels to remain narrow and vasoreactive, thereby creating an increase in resistance and poor perfusion of the placenta. In an attempt to improve perfusion, the placenta releases factors into the maternal circulation.

Recent work has facilitated understanding of this process. The placentas of patients with pre-eclampsia produce angiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1), which binds to placental growth factor (PIGF) and vascular endothelial growth factor (VEGF). PIGF is important in angiogenesis of the placental vascular bed, and VEGF is essential in the stabilization of the maternal vascular endothelium. When sFlt-1 binds to PIGF and VEGF, these growth factors are no longer bio-available, resulting in decreased angiogenesis of the placenta, and destabilization and dysfunction of the maternal vascular endothelium. The clinical manifestations of pre-eclampsia, including hypertension, proteinuria, oedema, thrombocytopenia and activation of the coagulation cascade, reflect altered maternal vascular endothelial function.
Clinical management

Risk factors for pre-eclampsia include first pregnancy (85% of patients), multiple gestations and molar pregnancies. Patients with pre-existing maternal disorders involving the vascular endothelium, such as collagen vascular disease, diabetes mellitus, obesity and antiphospholipid syndrome, are at increased risk for pre-eclampsia. These disorders render the endothelium more susceptible to placental humoral factors.

Pregnant patients who present with new-onset hypertension, defined as systolic pressure >140 mmHg or diastolic pressure >90 mmHg, should be assumed to have pre-eclampsia. Clinicians should solicit symptoms of headaches and epigastric or right upper quadrant abdominal pain. Patients should have urine protein checked by dipstick. If positive, urine protein should be quantified by either a protein:creatinine ratio or 12- or 24-h urine collection. The degree of oedema is of little clinical value unless the patient presents with pulmonary oedema. Laboratory studies include complete blood count, platelet count, serum creatinine and uric acid, serum aspartate transaminase (AST) and alanine aminotransferase (ALT). Fetal wellbeing should be assessed. The patient is classified as having mild pre-eclampsia, unless any of the criteria listed in Table 1 are present.

Patients with mild pre-eclampsia can be managed expectantly if premature, twice-weekly assessment of mother and fetus are indicated. When the gestational age is ≥37 weeks or fetal lung maturity has been confirmed, delivery should be considered.

Patients with severe pre-eclampsia should be prepared for delivery. As described above, pre-eclampsia is a state of poor placental perfusion and altered maternal vascular endothelial function. Interventions are therefore focused on improving placental perfusion through improving cardiac output and peripheral vasodilation. The patient should be placed on her side (left or right) in a supine position. This will improve venous return, preload and cardiac output. In the authors’ experience, most pre-eclamptic patients are intravascular volume depleted and require some degree of volume resuscitation, which will result in improved cardiac output, improved placental perfusion and temporization of the disease process. If undelivered, continuous fetal monitoring is performed.

Magnesium sulphate seizure prophylaxis should be initiated in the severe pre-eclamptic, and there is great controversy regarding whether patients with mild pre-eclampsia should also receive magnesium prophylaxis. The authors use a loading dose of 4–6 g intravenously over 20 min, followed by a continuous intravenous drip at 2 g/h, which will maintain most patients in the therapeutic range of

<table>
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<th>Table 1. Criteria for severe pre-eclampsia.</th>
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<td>Sustained systolic blood pressure &gt;160 mmHg</td>
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<td>Sustained diastolic blood pressure &gt;110 mmHg</td>
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<tr>
<td>Pulmonary oedema</td>
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<td>Proteinuria &gt;5 g/24 h</td>
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<td>Oliguria &lt;500 mL/24 h</td>
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<td>Persistent headaches or scotomata</td>
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<td>Persistent right upper quadrant or epigastric pain</td>
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<td>Thrombocytopenia &lt;100 000/mm³</td>
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<td>Intra-uterine growth restriction &lt;10th percentile</td>
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4 mEq/mL. Blood pressure can be controlled with the judicious use of hydralazine or labetalol. The authors recommend target blood pressures of approximately 150 mmHg systolic and 100 mmHg diastolic. Rapid vasodilation should be avoided by adequate intravascular resuscitation in order to prevent further decrease in perfusion of the placenta.

At gestational ages <34 weeks, the administration of betamethasone should be considered and delivery delayed for 48 h if the maternal condition is stable. For patients with extreme premature gestational ages (<32 weeks), expectant management can be considered, particularly for those who are classified as severe based on isolated hypertension or proteinuria.

**Eclampsia**

Patients who develop seizures or who present after having had a seizure should be started on magnesium sulphate immediately (4–6 g intravenous loading dose, 2 g/h continuous intravenous infusion). A thorough neurological examination should be performed. The patient should be evaluated for other signs and symptoms suggestive of eclampsia. If the diagnosis of eclampsia is likely and the neurological examination is unremarkable, the patient is managed similarly as outlined for severe pre-eclampsia. If neurological deficits are present or other signs or symptoms of pre-eclampsia are not present, urgent central nervous system imaging and neurological consultation are indicated.

Pre-eclampsia is associated with an increased risk for both ischaemic and haemorrhagic stroke. Ischaemic stroke results from severe vasospasm, while haemorrhagic stroke is associated with uncontrolled hypertension. Clinicians must distinguish between eclampsia and primary intracranial pathologies which may also be associated with hypertension and seizures, such as stroke or neoplasm. This distinction may be difficult to make. Therefore, the authors recommend imaging studies in all patients who present with a new onset of seizure(s), particularly if the diagnosis of eclampsia is uncertain.

**HELLP syndrome**

Haemolysis should be demonstrated by either an elevation of lactate dehydrogenase of >600 IU/L, bilirubin level of >1.2 mg/dL or a peripheral blood smear showing the presence of schistocytes. Elevated liver enzymes are defined by either ALT or AST >72 IU/L. Low platelets is defined as <100 000/mm3.

If undelivered, patients with HELLP syndrome should be prepared for delivery and managed as outlined for severe pre-eclampsia.

The use of (high-dose) steroids in order to stabilize platelet values and speed up recovery has been suggested by some investigators. However, a recent randomized controlled trial does not seem to support the use of steroids for this indication.

Since pre-eclampsia, eclampsia and HELLP syndrome are caused by the placenta, the ultimate treatment requires delivery of the baby and the placenta. The mode of delivery is determined by the obstetric care provider. Many patients can be delivered safely vaginally and do not require a caesarean section. However, induction of labour remote from term is associated with high rates of failed induction. Importantly, one should only proceed with delivery after the maternal condition has been stabilized.
Chronic hypertension

The prevalence of chronic hypertension is low overall. However, as the number of older women having children increases, chronic hypertension will become more prevalent in pregnant patient populations.

Once pre-eclampsia has been excluded, the patient is managed as having chronic hypertension. A subgroup of these patients will have gestational hypertension, which will resolve within 6 weeks of delivery. It is critical to rule out other causes of hypertension including renal disease, primary hyperaldosteronism, collagen vascular disease and pheochromocytoma. The underlying disorder should be managed as appropriate; the authors recommend a continued blood pressure target of 140/90 mmHg.

Summary

Pre-eclampsia is a common complication of pregnancy associated with significant maternal and perinatal morbidity and mortality. The pathophysiology reflects poor placental perfusion, release of placental humoral angiogenic factors and subsequent maternal vascular endothelial dysfunction. Patients are classified as mild or severe. Mild pre-eclampsia may be managed expectantly, particularly if <37 weeks of gestation. Patients with severe pre-eclampsia should be stabilized, magnesium seizure prophylaxis initiated and prepared for delivery. Complications of pre-eclampsia include seizures (eclampsia), HELLP syndrome, renal failure and DIC. Fortunately, with the delivery of the placenta, these complications tend to be self-limiting.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy is a rare disorder with an incidence between one in 700 and one in 1300 deliveries. The disease is characterized by microvesicular fatty infiltration of the liver with hepatic failure, and usually presents clinically in the third trimester. Maternal and fetal/neonatal mortality estimates have ranged significantly over time, with two recent reviews revealing maternal mortality of 0–12.5% and fetal mortality of 15–66%.

Aetiology

While the aetiology of the disease is not currently understood, the pathology seen has long been likened to that of Reye’s syndrome and other inherited fatty acid oxidation disorders. As such, a link was made between mothers who developed acute fatty liver of pregnancy and those who have children with long-chain 3-ketoacyl-CoA dehydrogenate deficiency. One study evaluated 24 children with long-chain 3-ketoacyl-CoA dehydrogenate deficiency. Nineteen of them had a particular mutation (Glu474Gln), and of these, 79% of their mothers had developed acute fatty liver of pregnancy or HELLP syndrome. Of the five children who did not carry this particular mutation, none of their mothers had developed liver disease during pregnancy. It is thought that the combination of genetic and acquired factors can compromise intramitochondrial fatty acid oxidation significantly, and acute fatty liver can develop. The implications of this genetic link raise important perinatal and neonatal issues which will be discussed later.
Clinical presentation/diagnosis

As stated, the clinical presentation is usually in the third trimester, with an average gestational age of 35 weeks. Nausea and vomiting are the most common presenting symptoms, but malaise, epigastric or right upper quadrant pain, headache and fatigue are also seen. In two retrospective reviews, jaundice was seen at presentation in 37% and 100% of patients. Laboratory abnormalities overlap with abnormalities seen in HELLP syndrome (thrombocytopenia, elevated transaminases, hyperuricaemia and elevated creatinine), although the thrombocytopenia and elevations in transaminases may be mild to moderate (average platelets 151 000 and average AST/ALT 523/423 at presentation). Other abnormalities such as hyperbilirubinaemia, hypoglycaemia and hyperammonaemia can help to delineate the diagnosis. If the patient develops DIC, a deficiency of antithrombin III can be particularly prominent. While acute fatty liver is usually a clinical diagnosis, liver biopsy and imaging studies are sometimes performed in order to rule out other aetiologies for the presentation.

Clinical course/management

Prompt recognition, aggressive maternal stabilization and rapid delivery characterize the necessary treatment of this disease in order to minimize maternal and fetal morbidity and mortality. Hypoglycaemia and coagulopathy are seen in 40–50% of patients, and therefore, glucose infusion and aggressive resuscitation with blood products are common. Renal failure, encephalopathy and pancreatitis may also develop and need to be treated supportively. Most commonly, there is eventual resolution of the disease and recovery of organ systems involved, but this may require prolonged hospitalization (average stay in intensive care of 10.4 days, average hospitalization of 15.1 days). Liver transplantation is infrequent.

An important management issue is counselling with respect to subsequent pregnancy. Recurrence was first reported in 1991, and subsequently, a link has been established between development of acute fatty liver of pregnancy and mutation in genes related to fatty acid oxidation, most commonly in the gene for long-chain 3-ketoacyl-CoA dehydrogenase. As such, neonates born to mothers with acute fatty liver of pregnancy should be tested immediately for long-chain 3-ketoacyl-CoA dehydrogenase deficiency as well as other disorders of fatty acid oxidation. This is being done as part of the newborn metabolic screen in many regions. Counselling the patient regarding future pregnancy should include the option of testing for known mutations in the long-chain 3-ketoacyl-CoA dehydrogenase gene, as the presence of such a mutation increases the possibility of recurrence of acute fatty liver in subsequent pregnancies. Additionally, if such a mutation is found, there are important implications in terms of having an affected fetus (the disease state is inherited in an autosomal-recessive fashion). Ongoing research will aid understanding of the maternal–fetal interaction seen in this disease, and this will facilitate improved counselling for these patients.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy is a well-known but rare cause of heart failure associated with pregnancy. The National Institutes of Health have identified peripartum cardiomyopathy as a distinct clinical entity, occurring more often than idiopathic heart failure in non-pregnant women of the same age.
Four criteria have been developed to characterize peripartum cardiomyopathy: (1) development of heart failure within the last 4 weeks of pregnancy or within 5 months of delivery; (2) no pre-existing heart disease; (3) no other identifiable cause of heart failure; and (4) left ventricular systolic dysfunction.

The first two criteria are linked; the time constraints serve to minimize the possibility of pre-existing heart disease because the haemodynamic stresses of pregnancy in patients with pre-existing disease would likely lead to symptoms prior to the last 4 weeks of pregnancy. One study has questioned this component of the definition. This study included 100 women meeting the traditional definition of cardiomyopathy and 23 who differed in that they presented earlier than the last gestational month (but met the other criteria). This study found that there were no significant differences in the characteristics or clinical course between these two groups. From this, it was postulated that there may be a spectrum of disease which usually includes women characterized by the temporal characteristics described traditionally, but that also includes women with earlier presentation. Further research will be needed to clarify this issue.

Having no other identifiable cause of heart failure is the third part of the definition, and is important in that it distinguishes peripartum cardiomyopathy as its own clinical entity. Finally, although peripartum cardiomyopathy is a dilated form of cardiomyopathy, the definition also requires that systolic function be demonstrably impaired, in order to distinguish pathology from pregnancy itself which can lead to a dilated (but functional) left ventricle.

**Epidemiology**

The reported incidence of peripartum cardiomyopathy has varied greatly over time and worldwide. A recent review in a multi-ethnic community in the USA described an overall incidence of one in 4025 deliveries. The incidence was determined in Caucasians, African-Americans, Hispanics and Asians, and was highest in African-Americans (one in 1421) and lowest in Hispanics (one in 9861). The higher incidence in particular geographic/ethnic groups has been reported many times previously; the highest rates reported are one in 400 in Haiti. The risk factors are: age >30 years; multiparity; pre-eclampsia or hypertension; and long-term tocolytic therapy with beta-adrenergic medications.

**Aetiology**

The aetiology of peripartum cardiomyopathy is unknown; however, leading theories include damage caused by the release of inflammatory cytokines, viral or idiopathic myocarditis, abnormal immune response to fetal antigen, and maladaptive response to haemodynamic factors associated with pregnancy. Levels of inflammatory cytokines, such as tumour necrosis factor-alpha, interleukin-6 and Fas/APO-1 (an apoptosis-signalling surface receptor), have been shown to be significantly elevated in women with peripartum cardiomyopathy compared with healthy women. The possibility of postviral myocarditis or that seen as a result of an auto-immune aetiology has been explored and remains controversial.

**Clinical presentation/diagnosis**

Peripartum cardiomyopathy usually presents post partum. The diagnosis can be difficult due to the fact that many of the symptoms (such as dyspnoea, swelling and
fatigue) are common in the first postpartum month following a normal pregnancy. Patients most commonly present with dyspnoea, cough and orthopnoea. Other symptoms include fatigue, non-specific chest discomfort and abdominal pain. Rarely, a patient can present with systemic emboli as a result of the dilated, dysfunctional left ventricle, or with an acute myocardial infarction due to inadequate perfusion of the coronary arteries.

The physical examination will show signs typical of heart failure: hypoxia; jugular venous distention; S3 gallop; rales; and hepatomegaly. The chest x-ray will show cardiomegaly with pulmonary congestion and/or pleural effusions. The electrocardiogram can be normal, but may show left ventricular hypertrophy and/or dysrhythmias. In the initial evaluation, serum troponins may be useful to rule out myocardial infarction, although these elevations can occasionally be seen in peripartum cardiomyopathy as well. Ultimately, an echocardiogram is imperative for the diagnosis of peripartum cardiomyopathy; it will show a dilated left atrium and ventricle, left ventricular systolic dysfunction, and a diminished ejection fraction.

Management

In the acute setting, management begins with the ABCs (airway, breathing, circulation). Assessment of the airway is critical, as it can be suboptimal due to pregnancy or recent pregnancy with associated third spacing of excess intravascular volume. Breathing is addressed via continuous pulse oximetry and placement of the patient on supplemental oxygen. The circulation should be assessed with cardiac and blood pressure monitoring. Appropriate venous and/or arterial access should be obtained rapidly so that medications can be administered expeditiously and monitoring can be streamlined.

In antepartum patients, fetal heart rate monitoring should be obtained immediately. With impaired breathing and/or circulation, it is common to see heart rate tracing abnormalities. In this case, it is critically important to stabilize maternal status; this may result in resolution of fetal heart rate tracing abnormalities and will prevent haste in performing a caesarean delivery that may be poorly tolerated by the mother.

Maternal medical stabilization should then have three objectives: reduce preload; reduce afterload; and increase inotropy. This is done in order to achieve the goals of improving haemodynamics, minimizing patient symptoms, and optimizing long-term outcomes. Choice of medications requires consideration regarding whether the patient is still pregnant or breast feeding. Preload reduction is accomplished with nitrates, most of which are safe during pregnancy and breast feeding. Diuretics are also important, although caution is warranted in pregnant patients in order to avoid rapid changes in intravascular volume that can lead to decreasing the blood supply to the uterus. Afterload reduction can be achieved in the pregnant patient with vasodilators such as hydralazine. For the postpartum patient, angiotensin-converting-enzyme inhibitors are the preferred agents. To increase inotropy, beta-blockers are used and have been shown to improve survival in patients with dilated cardiomyopathy; however, it is important to note that these must not be initiated in the acute decompensated phase as they can decrease perfusion in this setting. Dopamine, dobutamine and digoxin are not contra-indicated in pregnancy, and are particularly useful in the case of acute decompensated heart failure with hypotension. Anticoagulation is an important adjunct to therapy due to the hypercoagulable state of pregnancy, as well as the stasis of blood seen with severe left ventricle dysfunction. Therapy is suggested with an ejection fraction <30%, and an agent other than coumadin (heparin, low-molecular-weight heparin) should be used when the

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patient is pregnant. Aggressive medical management of ventricular arrhythmias is recom-
mended, and 2–3% of patients will require implantable defibrillators/pacemakers. Treatment with immunosuppressive agents and intravenous immunoglobulin remain controversial at present. Left ventricular assist devices and heart transplant are reserved for the postpartum patient in whom other therapy is unsuccessful. According to one study, heart transplantation was necessary in 4% of patients.

**Prognosis/future pregnancy**

The prognosis of women with peripartum cardiomyopathy has varied greatly over time. Several current studies suggest that mortality and morbidity are significantly better with contemporary management than has been reported previously. Of these, one study followed 123 women and reported a mortality rate of 9% at a mean follow-up of 24 months. Another reported zero deaths in 55 women at a mean follow-up of 43 months. However, a study of a cohort of 29 African women reported eight deaths by 6 months following the diagnosis. These results suggest that although mortality rates have improved, mortality remains extremely high in a significant population of women.

With appropriate medical support, most patients will improve following their presentation. In one study, ejection fraction improved from 29% to 46% by 2 years, with most of the recovery occurring in the first 6 months. In the same study, 54% recovered fully (ejection fraction >50%). However, many patients will not improve and will go on to need further treatment (left ventricular assist devices, heart transplant). Several factors have been identified which are associated with these poorer prognoses: ejection fraction <30% at diagnosis; left ventricular end diastolic dimension >6 cm; elevated cardiac troponin T; and elevated sFas/APO-1.

Counselling women regarding the risks associated with subsequent pregnancy is difficult; however, studies have suggested that dividing women into two risk categories (recovered versus non-recovered left ventricle function) is most appropriate. In a study of 28 women with recovered left ventricle function who became pregnant, there were no deaths, but six women developed heart failure symptoms and six women had a reduction in ejection fraction >20%. In the same study, 16 women had persistent left ventricle dysfunction and subsequently became pregnant. Of these, four women underwent therapeutic abortion and 12 women continued their pregnancies. Among those continuing their pregnancy, three died, six developed heart failure symptoms and four had a reduction in their ejection fraction >20% (groups not mutually exclusive). With regard to neonatal outcomes, preterm delivery (between 30 and 36 weeks) was seen in 13% (three patients) of pregnancies in women with recovered left ventricle function and 50% (six patients) of pregnancies in women with persistent left ventricle dysfunction. There were no neonatal deaths. In summary, while some women will tolerate subsequent pregnancies, many will experience a decline in their left ventricular function. Furthermore, the subset of women with persistent left ventricular dysfunction has a significant risk of preterm birth and maternal death.

**AMNIOTIC FLUID EMBOLISM**

AFE is a rare, but often devastating, obstetric emergency. The patient typically presents with an acute onset of severe hypoxia, mental status changes, cardiovascular collapse and DIC. Mortality risk for the mother and baby is high, and survivors may have long-term clinical sequelae.
Epidemiology

There is a wide variation in the incidence of AFE, ranging from one in 8000 to one in 80,000. The incidence is reported as one in 20,000–30,000 in the USA, one in 27,000 in South-east Asia, and one in 80,000 in the UK. The clinical presentation is highly variable and milder cases may not be reported. The diagnosis of AFE is often made by exclusion, as there is no definitive diagnostic test. Although earlier publications reported maternal mortality as high as 86% in 1979 and 61% in 1995, more recent data from 1999 suggest a lower mortality rate of 26%. The UK AFE registry reported case fatality of 37% in 2005. Morbidity is also significant, but numbers vary largely between reports. In a retrospective review of 46 women, Clark et al reported that only 15% of the survivors were neurologically intact. The UK registry reports an incidence of poor long-term neurological outcome of 7%.

AFE most commonly occurs intra partum or immediately post partum. When AFE occurs prior to delivery, perinatal morbidity and mortality are also high. Clark et al reported a perinatal survival rate of 79% with 50% neurological morbidity. In the UK registry, 78% of infants survived, with 29% of these showing evidence of hypoxic ischaemic encephalopathy.

These data suggest that with improved diagnosis and medical intensive care, the maternal mortality rate has improved markedly but remains high at approximately 25–35%, with an estimated risk of 10–20% for long-term sequelae. Approximately 80% of infants will survive, with an estimated 30% risk for long-term morbidity.

Pathophysiology

Traditionally, AFE has been believed to be caused by the entry of amniotic fluid and its contents into the maternal venous blood stream. This sets off a chain of events in which the amniotic fluid travels to the pulmonary vasculature and causes a ‘massive, pulmonary embolism-like’ clinical presentation, including acute pulmonary vasospasm with severe hypoxia, pulmonary hypertension, right heart failure, cardiovascular collapse, mental status changes and often death. If the patient survives the initial event, she will often develop DIC and left ventricular heart failure. However, this classic theory remains controversial. The question remains whether it is the actual amniotic fluid, certain components within the amniotic fluid or an altered, immunopathological response to these components that sets off this chain of events.

Early autopsy studies in which amniotic fluid was described in the pulmonary vasculature provided evidence to support this theory. Later, Resnik et al identified mucin and fetal squamous cells in the pulmonary artery catheter aspirate of a patient who was diagnosed with AFE. James et al described gross enlargement of the right ventricle and pulmonary artery by transoesophageal echocardiography prior to the death of a 36-year-old patient with suspected AFE. Autopsy demonstrated extensive microvascular plugging of the pulmonary capillaries. However, the presence of fetal cells in the maternal circulation has also been described in patients without AFE.

Amniotic fluid is comprised of fetal urine and contains many cellular components, fetal hair, vernix and a variety of prostaglandins and leukotrienes. It may not be the actual presence of the amniotic fluid or its components, but the maternal (immune) response to these chemical mediators which ultimately determines whether the patient develops AFE. Clark described this as an ‘anaphylactoid’ reaction to amniotic fluid. Several publications posit a role for a number of vasoactive and inflammatory mediators including endothelin, histamine, serotonin, bradykinin, prostaglandins and...
leukotrienes. These mediators may play a causative role in the pathogenesis of AFE, or may only reflect components of the systemic maternal response. Well over 50% of patients with AFE will develop DIC, which may be the presenting or only symptom. The degree of consumptive coagulopathy appears to be disproportionate to the observed blood loss. It has been postulated that amniotic fluid activates factor X. Uszynski et al described the role of tissue factor and tissue factor pathway inhibitor in amniotic fluid and blood plasma as a possible mechanism.

Clinical presentation

AFE must be considered when a labouring or immediately postpartum patient presents with either one or a combination of the following primary symptoms: dyspnoea; coughing; severe hypoxia; profound hypotension; seizures; or mental status changes. Secondary symptoms may include fetal bradycardia and DIC.

The typical patient initially presents with coughing and complaints of shortness of breath, and then rapidly becomes hypoxic. If the patient is still pregnant, fetal bradycardia will develop. Pulmonary vasoconstriction leads to severe hypoxia, and is followed by the development of profound hypotension and systemic vascular collapse. Mental status changes may be seen at this point. The ‘second phase’ of the disease then evolves and is characterized by the development of left ventricular heart failure. This is due to poor diastolic filling as well as decreased cardiac contractility. The compromised filling is related to compression of the ventricle caused by increased volumes seen by the right heart, which are secondary to the impedance of flow caused by pulmonary vasoconstriction. The decreased contractility is felt to be secondary to a direct toxic effect on the myocytes. This combination leads to cardiac dysfunction which must be treated aggressively and monitored carefully. This ‘second phase’ is also commonly characterized by DIC, and seizure activity also been reported.

Importantly, patients with AFE may present with some but not all of these clinical findings, and the sequence of events may vary considerably. Ultimately, the diagnosis is based on the interpretation of the clinical presentation as well as the exclusion of other differential diagnoses, including pulmonary embolus, acute myocardial infarction, cerebral vascular accident, sepsis, placental abruption and uncompensated maternal blood loss (with or without consumptive coagulopathy). When the diagnosis remains unclear, some experimental assays (serum tryptase, serum sialyl Tn antigen levels and zinc coproporphyrin) have been proposed to be more specific and may be available in some centres.

Clinical management

The initial treatment begins with basic and advanced cardiac life support protocols. The need for an intensive care facility and personnel should be recognized and organized immediately. The patient should be intubated and mechanical ventilation initiated. High oxygen concentrations will be required in order to manage severe hypoxia. Adequate intravenous access needs to be established with large-bore catheters. Aggressive measures to maintain perfusion will be necessary (using crystalloid, blood products and vasopressors). Intra-arterial monitoring (with an arterial line and pulmonary artery catheter) are important tools to aid in this resuscitation. If the patient is still pregnant, the care team needs to assess whether the maternal condition is stable enough to proceed with an emergency delivery; if not, a decision may
be made not to intervene on behalf of the fetus. Concise communication between all participating care teams is critical.

After the initial stabilization and notification of care teams, communication with the blood bank is critical and the following serum studies should be obtained immediately: type and crossmatch; complete blood count with platelet count; coagulation profile (pro-time, partial thromboplastin time, fibrinogen, D-dimer, fibrin split products); and an arterial blood gas. Additionally, a chest x-ray, 12-lead electrocardiogram and cardiac echo (surface or transoesophageal) are needed.

When coagulopathy develops, significant resuscitation with blood products (packed red blood cells and fresh frozen plasma) will be required. Cryoprecipitate may be used when fibrinogen levels are low and administration of less volume is desired. Patients with DIC in the setting of AFE seem to require an unusually high amount of fresh frozen plasma in order to correct the coagulopathy. The administration of these blood products in this setting of impaired cardiac function requires particular attention to fluid balance, and tools to evaluate right and left cardiac dysfunction (pulmonary artery catheter; Swan-Ganz catheter) are advocated. When echocardiography is performed, it will reveal high pulmonary pressures and marked right ventricular dilation. As stated previously, the dilated right ventricle may prevent adequate diastolic filling of the left ventricle and worsen cardiac output. In this situation, nitric oxide has been reported to be beneficial.

After the acute coagulopathy is resolved, the use of prophylactic heparin (unfractionated or fractionated) should be considered in patients with AFE, as there is an increased risk for development of thrombotic complications. Supportive care is continued in intensive care until resolution of the disease process occurs.

Risk factors for AFE

A tumultuous labour pattern, particularly when oxytocin is used, has been postulated as having a causative relationship on the occurrence of AFE, although Morgan and Clark and Butt could not confirm any maternal risk factor related to AFE. The American College of Obstetrics and Gynecology (ACOG) and many textbooks reflect the opinion that oxytocin use is not associated with AFE. In the current setting of the increased use of prostaglandins, some feel that we may need to re-evaluate the association between uterine stimulation and AFE. One retrospective cohort study of risk factors for AFE found that medical induction of labour nearly doubled the risk of AFE, although the absolute risk (10 in 100 000) was still quite small. They also identified other risk factors including uterine rupture, placenta previa and abruptio placentae. There are published case reports of AFE after abdominal and surgical trauma, first- and second-trimester abortion, amniocentesis and removal of a cervical cerclage.

Summary

AFE is a rare but potentially catastrophic syndrome with an estimated incidence of one in 25 000 to one in 30 000. Mortality is high (30–40%) in those patients who exhibit the classic presentation of acute severe hypoxia, cardiovascular collapse, mental status changes, and DIC. Long-term neurological sequelae may persist in 10–20% of patients. If AFE occurs while the mother is still pregnant, immediate delivery of the fetus may result in good survival; otherwise, perinatal mortality and morbidity are high.

The pathophysiology of AFE remains controversial. There is clear evidence that amniotic fluid and its components enter the maternal venous circulation. This may result in mechanical obstruction in the pulmonary capillaries and/or incite
a systemic response by the mother which is similar to anaphylaxis or sepsis. The notion that labour induction or augmentation is not associated with AFE may need to be re-addressed. It may be that it is not the uterine tone or force that makes it more likely to ‘push’ amniotic fluid into the maternal circulation, but that the production of different mediators inciting AFE are associated with labour induction and augmentation.

Every obstetric care provider should be familiar with this clinical syndrome and consider the diagnosis early in its presentation. Early diagnosis and initiation of treatment are paramount. Treatment includes cardiovascular and respiratory resuscitation (with intubation/ventilation, crystalloids, vasopressors) in order to optimize cardiac output, and correction of coagulopathy.

TRAUMA IN PREGNANCY

Trauma during pregnancy is the leading non-obstetric cause of maternal mortality and is responsible for at least one million maternal deaths worldwide each year.\(^8^2\) Approximately 6–7% of pregnancies will be complicated by maternal trauma.\(^8^3\)–\(^8^5\) Motor vehicle accidents are the most common cause of maternal trauma (55%)\(^,\)\(^8^3\)\(^,\)\(^8^5\)\(^,\)\(^8^6\), followed by falls and assaults, both of which account for 22%.\(^8^6\)\(^,\)\(^8^7\) Traumatic injuries can be further classified as blunt (most frequently resulting from falls, motor vehicle accidents or partner violence) or penetrating (prevalent in high-crime settings).

Motor vehicle accidents

Motor vehicle accidents account for the largest number of trauma-related fetal deaths, accounting for 4000 fetal losses annually in the USA.\(^8^2\)\(^,\)\(^8^6\) Motor vehicle accidents fall under the general category of blunt injury.\(^8^2\) The risk that a motor vehicle accident will result in an obstetric complication is proportional to the speed at which the motor vehicle accident occurred and the severity of the injury.\(^8^2\) Although the risk of fetal loss is greatest after severe maternal trauma, even minor blunt abdominal trauma increases the risk for fetal loss compared with controls not experiencing trauma.\(^8^3\)

Approximately 70% of fetal losses resulting from maternal trauma are caused by placental abruption.\(^8^3\) Placental abruption complicates up to 40% of cases of severe maternal trauma and 1–5% of cases of minor maternal trauma.\(^8^8\) During blunt trauma, the myometrial tissue is able to respond to acceleration–deceleration forces by changing its shape. However, the placenta is relatively inelastic, and this mismatch between the myometrium and the placenta creates a shearing force which leads to placental abruption.\(^8^2\)\(^,\)\(^8^8\)

Partner abuse

Intimate partner violence is the most common cause of trauma-related maternal death during pregnancy, and maternal deaths due to homicide exceed those due to any obstetric cause.\(^8^9\) Between 6% and 22% of gravid women experience intimate partner violence during pregnancy and are at increased risk for violent assault compared with non-pregnant women.\(^8^9\) Kicks and punches to the abdomen are frequent types of intimate partner violence, and women who experience such violence are at increased
risk for miscarriage, preterm labour, premature rupture of membranes and low birth weight.  

**Falls**

Pregnancy may result in decreased postural stability and balance, leading to increased falls compared with the non-pregnant state.  The risk that a fall will result in fetal loss is low compared with other types of maternal trauma. In a recent prospective cohort study of minor trauma during the third trimester of pregnancy, there were no placental abruptions experienced among 153 women who presented for evaluation of falls.

**Penetrating trauma**

Gunshot wounds are the most frequent cause of maternal penetrating trauma, followed by knife wounds. Pregnant women are at decreased risk of death from penetrating abdominal trauma compared with non-pregnant women, owing to the protective effect of the gravid uterus. Conversely, penetrating injury to the maternal upper abdomen is associated with increased risk of bowel injury compared with the non-gravid state due to the upward displacement of the bowel by the uterus. However, penetrating abdominal trauma is associated with a very high risk of fetal death, ranging from 40% to 70%. In general, gunshot wounds are associated with a higher risk of fetal mortality than knife wounds.

**Direct fetal injuries**

Direct fetal injury is less common than indirect injury but can occur, particularly when the fetal head is engaged in the pelvis. These injuries, which complicate <1% of pregnancies affected by trauma, can result in fetal skull fractures, intracranial haemorrhage and cerebral oedema, all of which can lead to adverse neurological outcome. Advances in fetal imaging may lead to detection of more cases of direct injury.

**Evaluation and management**

Immediate response to suspected maternal trauma should include positioning the mother in the left lateral tilt position in order to displace the uterus from the inferior vena cava. Laboratory evaluation should include a complete blood count and platelet count, evaluation of coagulation and a Kleihauer-Betke (KB) test. The KB test, which detects the presence of fetal red blood cells in the maternal circulation, may be used to quantify the extent of maternal–fetal haemorrhage. ACOG advocates use of the KB test in order to identify those Rhesus-negative women who experience fetal–maternal haemorrhage >30 mL and who will require additional vials of RhoGam. In >90% of trauma cases, the feto–maternal haemorrhage will be <30 mL, and one vial of Rhesus immunoglobulin will be sufficient to prevent sensitization in Rhesus-negative women. KB testing may also be used as a screen for preterm labour in Rhesus-positive women. In one series of 71 pregnant women experiencing trauma, the KB test had 100% sensitivity for predicting preterm labour, correctly identifying all of the 25 women who developed preterm labour with a 4% false-positive rate. Based on these findings, the authors advocate KB testing in all pregnant trauma patients, regardless of Rhesus
status. However, these findings have not been duplicated by other authors and definitive recommendations await further studies.

Several authors recommend maternal/fetal assessment via the FAST (Focused Assessment with Sonography in Trauma) examination. The FAST examination consists of fetal position, fetal heart rate, gestational age assessment, biophysical profile, middle cerebral artery Doppler study, and evaluation of the placenta for abruption. Ultrasound assessment for maternal intraperitoneal haemorrhage can be performed at the same time. This evaluation has sensitivity of 80–83% and specificity of 98–100% for intraperitoneal haemorrhage.

**Fetal monitoring**

The fetal heart rate has been called the ‘fifth vital sign’ because of its role as a very early manifestation of maternal hypotension or hypovolaemia. Similarly, uterine activity may be a more sensitive indicator of placental abruption than ultrasound. As placental abruption has been observed up to 48 h after maternal trauma, a minimum of 4 h of fetal monitoring after trauma is advised, with 24 h of monitoring undertaken if frequent uterine activity is detected on initial screening.

**Diagnostic imaging**

Imaging with ultrasound is safe in all trimesters of pregnancy, and there are no known harmful effects of magnetic resonance imaging (MRI) during pregnancy. Some authors advise restricting MRI scanning to the second and third trimesters of pregnancy, owing to the relative scarcity of safety data concerning use in the first trimester. Computed tomography (CT) may be used during pregnancy when clearly indicated. Fetal exposure from CT scans not involving the abdomen or pelvis is low, and these scans may be performed safely in any trimester of pregnancy. CT scans of the abdomen and pelvis result in a maximum fetal dose of approximately 1–2 rad, well below the threshold dose of 10–20 rad for fetal loss or malformation; however, concerns regarding a small increased risk of childhood cancers in exposed infants have been raised.

In cases of penetrating trauma, management options include surgical exploration or conservative management, which consists of peritoneal lavage, ultrasound, contrast-enhanced CT scanning, local wound exploration and observation.

**Prevention**

Physician counselling for seatbelt use during prenatal care has been shown to increase seatbelt usage significantly. In primate (baboon) studies employing experimental crash injuries, Pearlman demonstrated that compared with two-point restraints, three-point restraints reduced fetal mortality from 100% to 40%. Based on these and other data, ACOG advocates prenatal education on proper placement of three-point restraints. Although concerns have been raised regarding the safety of airbag use, ACOG and the National Highway Traffic Safety Administration (NHTSA) do not recommend disabling airbags during pregnancy. However, NHTSA does recommend disabling airbags if the woman’s sternum or uterine fundus cannot be positioned at least 10 inches behind the centre of the airbag cover.
Practice points

- Approximately 70% of fetal losses complicating maternal trauma result from placental abruption. A minimum of 4 h of fetal monitoring following maternal trauma is advised.
- Providers of prenatal care should educate prenatal women on the proper use of three-point restraints.
- In the setting of massive haemorrhage, do not await laboratory confirmation of DIC before initiating resuscitation with blood products.
- Balloon tamponade is the easiest and least invasive therapy for postpartum haemorrhage when uterotonic medications have failed.
- An echocardiogram is the most useful diagnostic study for peripartum cardiomyopathy.
- AFE is a clinical diagnosis. Upon suspicion, presumptive treatment should be immediate and aggressive.
- Patients with persistent left ventricular dysfunction after peripartum cardiomyopathy should be strongly counselled against future pregnancies.
- Infants born to mothers with acute fatty liver of pregnancy should be tested for disorders of fatty acid metabolism.
- Serum glucose and ammonia are the most useful tests to help distinguish acute fatty liver of pregnancy from HELLP syndrome.
- Patients with mild pre-eclampsia may be managed expectantly, particularly when remote from term. Patients with severe pre-eclampsia should be prepared for delivery.

Research agenda

- Development and validation of a diagnostic scoring system for DIC.
- Review of outcomes and cost-effectiveness of current monitoring and evaluation of recommendations for fetal-placental surveillance after minor maternal trauma.
- More randomized controlled trials are needed to determine whether oxytocin plus methergine or misoprostol is the more appropriate first-line strategy for postpartum haemorrhage caused by uterine atony.
- Prior clinical trials have failed to find the benefit of a variety of treatments to prevent recurrent pre-eclampsia. Clinical trials to determine whether use of anticoagulants will prevent recurrent pre-eclampsia in patients with inherited thrombophilias are needed.

REFERENCES


