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Review Article

Update in Perioperative Maternal Intensive Care

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Abstract

Critical illness in pregnancy is relatively uncommon but it carries a significant amount of morbidity and mortality when it does occur. The majority of patients admitted to the intensive care unit will be admitted in the postpartum period and patients are admitted with mixture direct and indirect causes. Managing this unique cohort of patients is challenging and requires an in depth knowledge of the maternal physiological adaptations to pregnancy and how these may affect the course of the patients illness. This review aims to review the recent updates with regards to pregnancy specific causes of critical illness. Recent advances in the management of common causes of maternal critical illness will be presented and the evidence associated with each intervention discussed.

Keywords: *Maternal critical care; High risk pregnancy; Post partum haemorrhage; Preeclampsia; Eclampsia; Thromboembolism; Amniotic fluid embolism; Post partum cardiomyopathy; HELLP syndrome; Sepsis; Septic shock*

Introduction

Maternal critical care describes the multi-disciplinary care of the pregnant or postpartum woman who finds themselves facing a critical illness which may be as a result of:

1. Exacerbation of a previous illness that is worsened during pregnancy.
2. Pregnancy specific illness that affects the woman.

Because of maternal physiological adaptations to pregnancy (Table 1) the critically ill obstetric patient who requires admission to an intensive care unit (ICU) presents a unique and difficult challenge to the intensives. Here we present recent updates in the care of pregnant and postpartum women whose pregnancies are complicated by the major causes of maternal morbidity and mortality with specific reference to the management of: Preeclampsia and Eclampsia, hemorrhage, thromboembolism, amniotic fluid embolism, cardiomyopathy, liver diseases of pregnancy and sepsis.

System	Changes in Pregnancy
Respiratory system	Increased minute ventilation
	Increased O_2 consumption
	Reduced FRC
	Respiratory alkalosis
Cardiovascular system	Increased cardiac output
	Increased circulating and plasma volume
Gastrointestinal	Reduced lower oesophageal tone
	Increased metabolism
	Hypergylcaemia

Renal	Increased renal blood flow
	Increased GFR
	Reduced serum urea & creatinine
	Mild proteinuria
Haematological	Physiologic anaemia
	Elevated leucocyte count
	Reduced platelet count
	Hypercoaguolpathy

Table 1: *Physiologic changes in various systems during pregnancy.*

Materials and Methods

Preeclampsia is a significant cause of maternal and foetal morbidity and mortality in both developed and developing countries, complicating between 5-6% of pregnancies [1]. Recent reviews have identified preeclampsia and eclampsia as one of the leading causes of ICU admissions in both developed and developing countries [2]. Despite a better understanding of its pathophysiology and some improvements in the ability of monitoring the hemodynamic alterations in this population, the only curative treatment remains delivery of the fetus and placenta. Medical treatment aims at avoiding maternal complications such as seizures, haemorrhagic stroke, renal failure, or pulmonary oedema.

Management

a) Preeclampsia

The most important treatment goals for severe pre-eclampsia are the prevention of eclampsia and lowering maternal blood pressure.

The landmark MAGPIE trial [3] evaluated the effectiveness of Magnesium sulphate in the prevention of seizures. When administered as a bolus and an infusion the risk of eclampsia is halved. For this reason Magnesium has become the cornerstone in the treatment of preeclampsia.

Hypertension in best managed using agents such as Labetalol, Methyldopa, Nifedipine and Hydrazaline. There is insufficient evidence currently to recommend one agent over another although with a recent Cochrane review concluding there did not appear to be one particular antihypertensive agent that is preferable in lowering blood pressure for the mother or the foetus. A clinical trial [4] is currently underway to evaluate if there is any clinical difference between Nifedipine and Labetalol as antihypertensive treatment in pregnancy. Agents that should be avoided in pregnancy include ACE inhibitors and the alpha blocker Atenolol.

Regarding timing of delivery in parturient with preeclampsia evidence from the HYPITAT trial [5] suggests that in women with non-severe pre-eclampsia, induction of labour after 37 weeks gestation is associated with a significant reduction in adverse maternal outcomes, without a difference in neonatal outcomes or an increase in Caesarean section rates. Consideration should be given to induction of labour in this situation.

Future treatments will likely focus on ameliorating early onset preeclampsia. Aspirin, Pravastatin and antioxidents are such treatments currently under investigation [6-8]. Biomarkers such as placental growth factor (PGIF) are allowing earlier detection and treatment of this disease [9].

b) Eclampsia

Eclampsia is a medical emergency complicating 1% to 2% of pre eclamptic pregnancies. Magnesium sulphate is the treatment of choice for both treatment and prevention of further seizures [3]. A loading dose of 4g should be given intravenously over 5 minutes, followed by an infusion of 1 g/hour maintained for 24 hours. Recurrent seizures should be treated with a further dose of 2-4g given over 5

minutes. Other treatments such as phenytoin have been investigated but proved to be non inferior to magnesium [10]. If seizures are not controlled by repeat magnesium boli, benzodiazepines may be added. Once the patient is stabilized and the maternal and foetal effects of the seizure have subsided, delivery must occur. Monitoring absolute serum levels of magnesium is not regularly required but monitoring of respiratory rate, urine output and tendon reflexes should be frequently undertaken to assess for toxicity. In the event of repeated seizure activity other causes should be out ruled and a CT brain may be warranted if seizures persist.

Haemorrhage

Obstetric haemorrhage is a significant cause of maternal mortality worldwide accounting for up to 35% of maternal deaths in some developing countries [11], while in the UK it accounts for approximately 10% of all direct maternal deaths [12]. It is also a significant cause of maternal morbidity. Postpartum haemorrhage affects up to 13% of all maternities and major obstetric haemorrhage (blood loss ≥ 2500 ml, or blood transfusion ≥ 5 unit's red cells or treatment for coagulopathy) affects approximately 0.6% of maternities [12]. Internationally the incidence of postpartum haemorrhage is increasing [12].

Management

a) Fibrinogen

The role of Fibrinogen in Obstetric haemorrhage has undergone recent scrutiny in the literature. The role of Fibrinogen in obstetric haemorrhage was evaluated in the PITHAGORE6 study [13], which aimed to determine whether the fibrinogen level at diagnosis of postpartum hemorrhage (PPH) is associated with the severity of bleeding. This study suggested that a low fibrinogen level (< 3g litre^{-1}) at PPH diagnosis is associated with a higher risk of severe PPH, independently of the other laboratory indicators. The recent FIB-PPH trial [14] which looked at pre-emptive treatment with fibrinogen concentrate for postpartum hemorrhage showed no benefit for the use of 2g fibrinogen as pre-emptive treatment for severe PPH in patients with normal fibrinogenemia. It is worth noting that patients included in this trial had a mean fibrinogen concentration of 4.5g litre^{-1}. Current best practice recommends keeping fibrinogen levels ideally between 3-4g litre^{-1} in the setting of PPH.

b) Transexamic acid

The recent CRASH-2 trial [15] examined the role of TXA on death and transfusion requirement in bleeding trauma patients. Results of this trial showed all-cause mortality at 28 days was significantly reduced by TXA when compared with placebo. The risk of death due to bleeding was significantly reduced in those patients who received TXA also. There was no increase in thrombotic events in these patients.

There have been a number of small trials of TXA in obstetric bleeding [16], most of which show a decrease in blood loss but the quality of the trials is poor and none are large enough to assess the effect of TXA on maternal outcomes. As pregnant women have a heightened risk for thrombosis compared with the general population it is important to assess the efficacy and associated risks of tranexamic acid in this group in this group. This is the basis of the WOMAN Trial [17] that is currently underway. Results of this trial will help determine if TXA should be routinely used in patients at risk of PPH.

c) Cell Salvage

The use of intra-operative cell salvage (IOCS) is well established in many types of surgery such as aortic surgery, spinal surgery and cardiac surgery where it has shown to reduce the need for allogeneic blood transfusions. The role of IOCS is less defined in Obstetric practice. Fears of amniotic fluid and red cell contamination have resulted in a reluctance of its routine use. The use of a leucocyte depletion filter in the circuit seems to protect the mother against the risk of amniotic fluid embolus and red cell contamination and large case series in the literature support its safe use in obstetric practice. The routine use of IOCS in women at risk of haemorrhage is currently under investigation in a multi-centre trial known as the SALVO trial [18] which aims to reliably measure the difference, evaluate cost effectiveness and address concerns of adverse effects of IOCS in obstetric practice.

d) Factor VIIa

The use of rFVIIa in Obstetric practice has never undergone any clinical trials and so its use is limited to case reports and case series only [19]. Thrombosis is a major concern when using rFVIIa and giving a drug that is known to cause thrombosis to pro-thrombotic patients is a major safety worry. Case series would suggest rFVIIa is safe to use in PPH but caution must be exercised when interpreting case series and reports.

e) Ratio of products

Earlier transfusion with higher blood product ratios (plasma, platelets, and red blood cells), defined as damage control resuscitation, has been associated with improved outcomes in the setting of trauma. The results of the recent PROPPER trial [20] defined the optimal ratio of product transfusion. Although this trial was in trauma patients its results can be extrapolated to the Obstetric setting. The results of this trial showed that patients who received red blood cells, plasma and platelets in a 1:1:1 ratio compared to a 1:1:2 ratio achieved haemostasis quicker and exsanguination was significantly less.

f) Interventional Radiology

The role of Interventional Radiology (IR) in controlling bleeding is gaining popularity among many surgical specialities so it is no surprise it is fast becoming popular in the management of PPH. IR may be used in the elective setting in women at risk of PPH but also in the emergency setting to help control PPH. In both the elective setting and emergency setting both vascular occlusion balloons or selective arterial embolization or coiling may be undertaken. Although there are no clinical trials supporting its use, there is a growing body of case reports and case series [21] highlighting how effective this intervention can be. Specific targets for embolization include the uterine and vaginal arteries that are anterior divisions of the internal iliac artery and also the ovarian artery that branches off the abdominal aorta. If successful surgery can be avoided in these patients reducing the morbidity associated with it but it also saves the uterus and adnexal organs, thus preserving fertility.

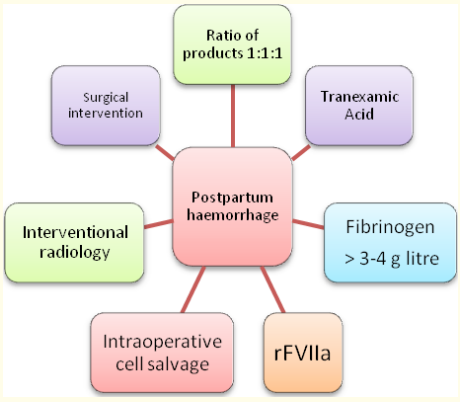

Figure 1: *Management of PPH.*

Venousthromboembolism

Venous thromboembolism (VTE) remains a significant cause of maternal mortality in the developed world [12]. VTE is 10 times more common in the pregnant population and the greatest risk occurs during the puerperium. This condition is often under diagnosed in pregnancy as the scoring systems used to identify VTE in the non-obstetric population have no validation in the obstetric setting. Pregnancy potentiates all three components of Virchow's triad putting pregnant women at increased risk. Women who developed a pulmonary embolism should be stratified as stable or unstable and treated accordingly.

Management

Management of unstable PE in the pregnant woman is supportive and based on maintaining;

1. Haemodynamic stability
2. Oxygenation

Specific treatment with thrombolysis is documented in case reports only. Published data on 28 pregnant women treated with thrombolytic agents suggest that the risk of complications for the mother may be similar to that in the non-pregnant population [22]. Thrombolysis may also be considered in patients with evidence of myocardial strain as seen by a rise in cardiac specific biomarkers such as Troponin and evidence of right heart strain on echocardiography. Dose of thrombolytic used should not differ between the non-pregnant population. Considering that thrombolytic agents do not cross the placenta and taking into account that the complication rates do not exceed those of large randomised controlled trials thrombolytic therapy should not be withheld in pregnant patients in case of life-threatening or potentially debilitating thrombembolic disease. If bleeding is a major concern local delivery of the thrombolytic agent using a pulmonary artery catheter may be considered.

Future treatment may see mechanical thrombectomy devices been used to decrease the time taken for thrombus removal. As the technology around these devices improves their use will become more widespread.

Amniotic fluid embolism

Amniotic fluid embolism (AFE) is a rare and often it is a fatal complication, characterized by sudden cardiovascular collapse, altered mental status, and disseminated intravascular coagulation (DIC). Diagnosis is often made on clinical grounds and is essentially a diagnosis of exclusion. The presence of foetal squamous cells in the maternal circulation is considered suggestive but not diagnostic of AFE syndrome since these cells can also be found in the circulation of laboring patients who do not develop the syndrome. Although our understanding about the pathophysiology of AFE has increased in recent years the exact mechanism of injury remains unclear although several risk factors exist (Table 2). There's currently no curative treatment for AFE and care is mainly supportive.

1. Advanced maternal age
2. Precipitous labor
3. Medically induced labor
4. Instrumental or caesarean delivery
5. Cervical lacerations
6. Placenta previa and abruption
7. Polyhydramnios
8. Grand multiparity

Table 2: *Risk factors for Amniotic fluid embolism (AFE).*

Management

The management of AFE is supportive and directed towards the maintenance of:

1. Oxygenation
2. Cardiac output
3. Blood pressure
4. Correction of the coagulopathy

Novel approaches to the management of AFE have only been reported in case reports but should be considered. These include inhaled nitric oxide [23], a selective pulmonary vasodilator, in the treatment of acute right ventricular failure and pulmonary hypertension, cardiopulmonary bypass, extracorporeal membrane oxygenation and intra-aortic balloon counter pulsation for treating left ventricular failure unresponsive to medical therapy [24]. With improvements in treatments been offered to this cohort of patient's outcomes seem to be also improving and this condition is now not considered as uniformly lethal.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is defined as an idiopathic cardiomyopathy that develops towards the end of pregnancy or in the months following delivery. Characterised by left ventricular systolic dysfunction with an ejection fraction of less than 45%. Although there's no clear etiology for PPCM a number of factors have been linked (Figure 2) and the exact cause is likely multifactorial.

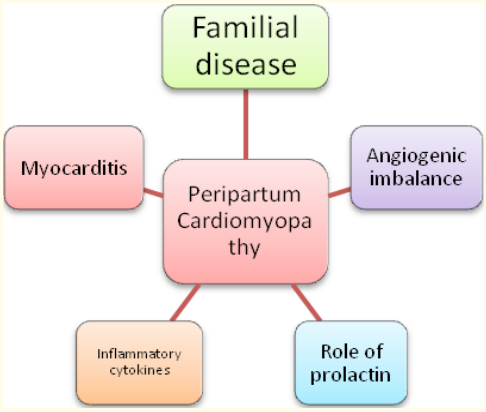

Figure 2: *Postulated causes of PPCM.*

Management

The majority of women who develop PPCM respond well to treatments such as those used for congestive cardiac failure with the exception of ACEi's being ommited given their teratogenicity. ACEi's can be replaced with hydralazine and nitrates.

Those patients who present with severe PPCM pose a greater challenge to the intensives. Inotropic agents are all generally all safe to use during pregnancy. Although lacking an evidence base other therapies have proved useful in treating patients with PPCM. These include the use of immune modulators such as immune glogulin [25], inhibition of cytokines with agents such as Pentoxifylline [26] and also the use of the prolactin inhibitor Bromocriptine [27].

Mechanical assist devices such as IABP, ventricular assist devices or ECMO may be considered in extreme cases as a treatment option and also bridge to transplant. A recent case review series that looked at six PPCM patients requiring mechanical support. All required IABP support while four required LVAD support and one needed ECMO support. Three LVAD patients were successfully transplanted while one remained on that waiting list. IABP was safe and efficient as a bridge to recovery or as a bridge to LVAD. ECMO provided temporary support as a bridge to LVAD, while the newer continuous-flow LVADs offered a safe bridge to transplant.

Liver diseases in pregnancy

Liver diseases in pregnancy encompass:

1. Acute Fatty Liver of Pregnancy
2. HELLP Syndrome

Although both are rare and arise from different etiologies they both result in acute liver failure and carry a high incidence of maternal and foetal morbidity and mortality. Differing features of the two disease processes include would include the absence of thrombocytopenia and hypertension in patients with AFLP.

Management

Early recognition is pivitol for improving patient outcomes. Delivery of the foetus should occur as soon as possible in patients who are acutely unwell. Coagulopathy and hypertension should both be treated aggressively. Patients who become encephalopathic may

require intubation for airway protection. Specific treatments that may be considered include the use of dexamethasone [28] to improve platelet count and maternal and neonatal outcomes in HELLP syndrome and also the use of plasma exchange therapy [29] in AFLP. Although the evidence for such interventions is limited to case reports and series results have been promising. Albumin liver dialysis in the form of Molecular adsorbent recirculating system (MARS) is again a therapy that is reported to have been used successfully in the literature [30] and may be considered in the most extreme of cases.

Sepsis

Sepsis may occur at any stage during pregnancy, although it is more common in the postpartum period. Bacteraemia in pregnancy is relatively common, but progression to severe sepsis and septic shock is a rare event, however it does carry significant mortality when it does occur [31-35]. Pregnancy predisposes women to an increased incidence of endometritis, pyelonephritis, choriomnionitis and pneumonia. Infections may be Gram-negative, Gram-positive or rarely anerobic in etiology. The most commonly isolated organsims are Lancefield group A beta-haemolytic Streptococcus and *E. Coli* [36,37]. Mixed infections with both Gram-positive and Gram-negative organisms are common, especially in chorioamnionitis. Coliform infection is particularly associated with urinary sepsis, preterm premature rupture of membranes, and cerclage [36]. Anaerobes such as Clostridium perfringensare less commonly seen nowadays, with Peptostreptococcus and Bacteroides spp. predominating. Caesarean section is the leading risk factor for puerperal sepsis, however other risk factors such as retained products of conception, episiotomy and prolonged rupture of the amniotic membranes may also play a role. Infant mortality in affected pregnancies is high at up to 50% [38] with group A streptococcal infection accounting for the majority of these deaths.

Management

Sepsis in the pregnant patient can often have an insidious and deceptive onset but fulminant course. Early and appropriate recognition and intervention is required to reduce morbidity and mortality. The signs and symptoms of sepsis in pregnant women may be less distinctive than in the non-pregnant population and are not necessarily present in all cases; therefore, a high index of suspicion is necessary. The patient typically has a temperature of 38°C during the period from the end of the first to the end of the 10th day after childbirth or abortion. Purpurafulminans may be associated with GAS infection. Physicians must have a high index of suspicion for sepsis in any peripartum patient who presents with fever and evidence of organ dysfunction: confusion, oliguria, tachycardia, and so on. Treatment is based around the surviving sepsis guidelines [39], and includes adequate fluid resuscitation, empiric antibiotic therapy, and source control. Noradrenaline appears safe to use in pregnancy with no adverse affects on foetal well-being. Organ support is initiated as required. Empirically, broad spectrum antimicrobials active against Gram-negative bacteria, and capable of preventing exotoxin production from Gram-positive bacteria, should be used according to local microbiology policy, and therapy narrowed once the causative organism(s) has been identified. Tetracycline and quinolone antibiotics should be avoided in early pregnancy. Penicillins, macrolides, and cephalosporins appear relatively safe within normal dosage range.

Conclusion

Acute life threating events in pregnancy are rare but result in significant morbidity and potentially mortality when they do occur. First and foremost treatment should be aimed at treating the mother and this is often beneficial to the foetus. Often expediant delivery of the foetus is required to hasten the effects of the critical illness encountered by the mother. Careful consideration to physiologic changes associated with pregnancy must be taken into consideration. A multidisplinary team input is paramount in order to improve outcomes in these patients.

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